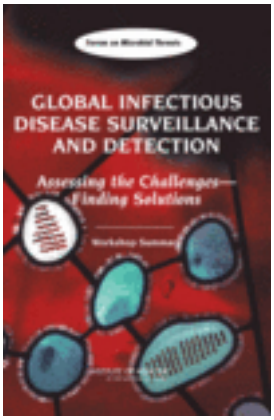

Global Infectious Disease Surveillance and Detection: Assessing the Challenges -- Finding Solutions, Workshop Summary

Forum on Microbial Threats, Stanley M. Lemon, Margaret A. Hamburg, P. Frederick Sparling, Eileen R. Choffnes, and Alison Mack, Rapporteurs

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Global Infectious Disease Surveillance and Detection: Assessing the Challenges—Finding Solutions

Workshop Summary

Rapporteurs: Stanley M. Lemon, Margaret A. Hamburg, P. Frederick Sparling, Eileen R. Choffnes, and Alison Mack

Forum on Microbial Threats
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Willing is not enough; we must do."
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PHIL HOSBACH, New Products and Immunization Policy, Sanofi Pasteur, Swiftwater, Pennsylvania

JAMES M. HUGHES, Global Infectious Diseases Program, Emory University, Atlanta, Georgia
STEPHEN A. JOHNSTON, Arizona BioDesign Institute, Arizona State University, Tempe
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RIMA F. KHABBAZ, National Center for Preparedness, Detection and Control of Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
LONNIE J. KING, Center for Zoonotic, Vectorborne, and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
GEORGE W. KORCH, U.S. Army Medical Research Institute for Infectious Diseases, Fort Detrick, Maryland
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BRIAN J. STASKAWICZ, Department of Plant and Microbial Biology, University of California, Berkeley
TERENCE TAYLOR, International Council for the Life Sciences, Washington, DC

Staff

EILEEN CHOFFNES, Forum Director
ALLISON BRANTLEY, Senior Program Assistant*
SARAH BRONKO, Senior Program Assistant†
ALISON MACK, Science Writer
KATE SKOCZDOPOLE, Research Associate

*Ending June 2007.
†Beginning June 2007.

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

John Besser, Public Health Laboratory, Minnesota Department of Health
R. James Cook, Department of Plant Pathology, Washington State University
Charlotte A Gaydos, Division of Infectious Diseases, The Johns Hopkins University and International STD Reference Laboratory

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Melvin Worth,** Scholar-in-Residence, Institute of Medicine. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

The Forum on Emerging Infections was created by the Institute of Medicine (IOM) in 1996 in response to a request from the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH). The purpose of the Forum is to provide structured opportunities for leaders from government, academia, and industry to meet and examine issues of shared concern regarding research, prevention, detection, and management of emerging or reemerging infectious diseases. In pursuing this task, the Forum provides a venue to foster the exchange of information and ideas, identify areas in need of greater attention, clarify policy issues by enhancing knowledge and identifying points of agreement, and inform decision makers about science and policy issues. The Forum seeks to illuminate issues rather than resolve them; for this reason, it does not provide advice or recommendations on any specific policy initiative pending before any agency or organization. Its value derives instead from the diversity of its membership and from the contributions that individual members make throughout the activities of the Forum. In September 2003, the Forum changed its name to the Forum on Microbial Threats.

ABOUT THE WORKSHOP

Early detection is essential to the control of emerging, reemerging, and novel infectious diseases, including agents of bioterrorism. Containing the spread of such a disease in a profoundly interconnected world requires *active* vigilance for signs of an outbreak, rapid recognition of its presence, and diagnosis of its microbial cause, as well as strategies and resources for an appropriate and efficient response. While often viewed in terms of public health, the challenges

of detecting natural and intentionally introduced disease outbreaks are equally shared by the plant and animal health communities.

Currently, disease surveillance and detection relies heavily on the astute individual: the clinician, veterinarian, grower, livestock manager, or agricultural extension agent who notices atypical or suspicious symptoms and brings them to the attention of public health, veterinary medicine, or agricultural officials—including academicians and zoological parks. While most developed countries have a surveillance system in place and the ability to detect and diagnose human, animal, and plant diseases, many developing countries—where most of the global population resides—may not have the resources or infrastructure to support such activities. Under such circumstances, disease detection occurs on the local level and depends entirely on the early recognition of both known and novel infectious diseases.

Technological advances in disease surveillance and detection such as regional syndromic surveillance, bioinformatics, and new rapid diagnostic methods have the potential to improve infectious disease control and prevention efforts. Further improvements are likely to result from ongoing innovations in infectious disease diagnostics, reporting, and surveillance. However, a number of challenges remain to be met before deployment of rapid, low-cost, sensitive, and specific point-of-care disease diagnostics become a reality.

The Forum on Microbial Threats of the Institute of Medicine hosted a public workshop in Washington, DC, on December 12 and 13, 2006, to consider the scientific and policy issues—some of them long standing, others more recently arisen—relevant to the practice of disease surveillance and detection. Through invited presentations and discussions, participants examined current and emerging methods and strategies for the surveillance and detection of human, animal, and plant diseases, and assessed the resource needs and opportunities for improving and coordinating infectious disease surveillance, detection, and reporting.

ACKNOWLEDGMENTS

The Forum on Microbial Threats and the IOM wish to express their warmest appreciation to the individuals and organizations who gave their valuable time to provide information and advice to the Forum through their participation in this workshop. A full list of presenters can be found in Appendix A.

The Forum is indebted to the IOM staff who contributed during the course of the workshop and the production of this workshop summary. On behalf of the Forum, we gratefully acknowledge the efforts led by Eileen Choffnes, director of the Forum, and Kate Skoczdopole, research associate, for dedicating much effort and time to developing this workshop's agenda and for their thoughtful and insightful approach and skill in translating the workshop's proceedings and discussion into this workshop summary. We would also like to thank the following IOM staff and consultants for their valuable contributions to this activity: Patrick

Kelley, Alison Mack, Sarah Bronko, Bronwyn Schrecker, Allison Brantley, Lara Andersen, and Laura Penny.

Finally, the Forum wishes to recognize the sponsors that supported this activity. Financial support for this project was provided by the U.S. Department of Health and Human Services: National Institutes of Health, National Institute of Allergy and Infectious Diseases, Centers for Disease Control and Prevention, and Food and Drug Administration; U.S. Department of Defense: Global Emerging Infections Surveillance and Response System, Walter Reed Army Institute of Research, and Defense Threat Reduction Agency; U.S. Department of Veterans Affairs; U.S. Department of Homeland Security; Lawrence Livermore National Laboratory; American Society for Microbiology; Sanofi Pasteur; Burroughs Wellcome Fund; Pfizer; GlaxoSmithKline; Infectious Diseases Society of America; and the Merck Company Foundation. The views presented in this workshop summary report are those of the workshop participants and rapporteurs and are not necessarily those of the Forum on Microbial Threats or its sponsors.

Stanley M. Lemon, *Chair*
Margaret A. Hamburg, *Vice-chair*
P. Frederick Sparling, *Vice-chair*
Forum on Microbial Threats

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Summary and Assessment

GLOBAL INFECTIOUS DISEASE SURVEILLANCE AND DETECTION: ASSESSING THE CHALLENGES—FINDING SOLUTIONS

Early detection is essential to the control of emerging, reemerging, and novel infectious diseases, whether naturally occurring or intentionally introduced. Containing the spread of such diseases in a profoundly interconnected world requires active vigilance for signs of an outbreak, rapid recognition of its presence, and diagnosis of its microbial cause, in addition to strategies and resources for an appropriate and efficient response. Although these actions are often viewed in terms of human public health, they also challenge the plant and animal health communities.

Surveillance, defined as "the continual scrutiny of all aspects of occurrence and spread of a disease that are pertinent to effective control" (IOM, 2003; Last, 1995; WHO, 2000), involves the "systematic collection, analysis, interpretation, and dissemination of health data" (WHO, 2000). Disease detection and diagnosis is the act of discovering a novel, emerging, or reemerging disease or disease event and identifying its cause. Diagnosis is "the cornerstone of effective disease control and prevention efforts, including surveillance" (IOM, 2003).

Disease surveillance and detection relies heavily on the astute individual: the clinician, veterinarian, plant pathologist, farmer, livestock manager, or agricultural extension agent who notices something unusual, atypical, or suspicious and brings this discovery in a timely way to the attention of an appropriate representative of human public health, veterinary medicine, or agriculture. Most developed countries have the ability to detect and diagnose human, animal, and plant diseases

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The Forum's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop.

and have some type of active or passive surveillance for many well-characterized agents. However, many developing countries—where most of the global population resides—lack the resources or infrastructure to support such activities.

One way to close this gap in infectious disease surveillance and detection may lie with the dispersion of technological advances such as regional syndromic surveillance, bioinformatics, and rapid diagnostic methods. Such tools and approaches have already made important contributions to infectious disease control and prevention efforts, albeit mainly in the developed world. Further improvements are expected to result from ongoing progress in infectious disease awareness and reporting, and from the continued development and deployment of efficient, low-cost diagnostic platforms. A major challenge to global disease surveillance and detection, and to this workshop, is not only the detection and reporting of well-characterized "known" infectious diseases, but also the ability to detect novel, emerging, or reemerging infectious diseases in relatively low-tech environments. There is a corresponding need to also develop redundant/complimentary systems for infectious disease detection that go beyond the yield of the more traditional surveillance systems and approaches.

The Institute of Medicine's (IOM's) Forum on Microbial Threats convened a workshop addressing *Global Infectious Disease Surveillance and Detection: Assessing the Challenges—Finding Solutions* on December 12 and 13, 2006, to consider these and other scientific and policy issues relevant to the practice of disease surveillance and detection. To adequately cover a broad range of topics related to global infectious disease surveillance and detection, the Forum had to be selective in prioritizing the challenges and exploring solutions to disease detection and surveillance.

While the workshop *did* explore a variety of conventional and novel approaches for disease surveillance and detection, the workshop organizers did not attempt to critique standard domestic disease detection approaches nor did the workshop make recommendations about what an "optimal" or "desirable" disease surveillance and detection system would look like. Workshop participants examined current and emerging methods and strategies for the surveillance, detection, and diagnosis of human, animal, and plant diseases in order to assess resource needs and opportunities for improving and coordinating global infectious disease surveillance, detection, and reporting.

Organization of Workshop Summary

This workshop summary was prepared for the Forum membership in the name of the rapporteurs and includes a collection of individually authored papers and commentary.[1] Sections of the workshop summary not specifically attributed

[1]The individually authored papers and commentaries of the speakers and participants at this workshop reflect their appreciation of disease detection and surveillance. As such, we have limited control over how the experts defined disease surveillance and detection. For our purposes, surveillance is defined on page 1.

to an individual reflect the views of the rapporteurs and not those of the Forum on Microbial Threats, its sponsors, or the IOM. The contents of the unattributed sections are based on the presentations and discussions at the workshop.

The workshop summary is organized into chapters as a topic-by-topic description of the presentations and discussions that took place at the workshop. Its purpose is to present lessons from relevant experience, to delineate a range of pivotal issues and their respective problems, and to offer potential responses as described by workshop participants.

Although this workshop summary provides an account of the individual presentations, it also reflects an important aspect of the Forum philosophy. The workshop functions as a dialogue among representatives from different sectors and presents their beliefs about which areas may merit further attention. The reader should be aware, however, that the material presented here expresses the views and opinions of the individuals participating in the workshop and not the deliberations and conclusions of a formally constituted IOM study committee. These proceedings summarize only what participants stated in the workshop and are not intended to be an exhaustive exploration of the subject matter or a representation of consensus evaluation.

Surveillance Strategies

The practice of infectious disease surveillance is no longer restricted to its original role in recognizing outbreaks of feared human diseases. Workshop presentations reflected diverse goals, approaches, and methodologies for disease surveillance in humans, animals, and plants. To place these presentations and ensuing discussions in context, we begin by briefly describing the multiple purposes served by public health surveillance, as well as current disease surveillance practices in animals and plants.

Surveillance Purposes and Practices

Public Health Surveillance

In the United States, public health surveillance for infectious disease is conducted through a variety of state and federal programs (GAO, 2004). Health-care providers and others report cases of "notifiable" infectious disease (as defined by local and state health codes) to health departments; health department officials verify disease reports, monitor disease incidence, identify possible outbreaks, and forward their findings to the Centers for Disease Control and Prevention (CDC). CDC and other federal agencies, including the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and the Department of Defense (DoD), independently gather and analyze information for disease surveillance. In addition, these agencies fund domestic and international networks of disease surveillance laboratories that develop diagnostic tests and conduct disease

diagnostic research. Although the CDC has provided guidelines for surveillance systems funded by the federal government, evaluation is generally lacking. Furthermore, as noted by Forum member Edward McSweegan, little evidence has been provided on the cost-effectiveness of massive federal public health surveillance investments (see also Eban, 2007).

Early Warning

Some surveillance systems are designed to provide early warning of a disease threat by detecting the mere presence of potentially infectious microorganisms. The federal BioWatch program, for example, uses a network of aerosol sampling stations to monitor major U.S. population centers for a range of potential biological agents, such as anthrax, plague, and tularemia (the entire list of pathogens is not publicly available) (Shea and Lister, 2003; OIG, 2005). The goal of this program is to detect biological agents within 36 hours of release, allowing federal, state, and local officials to organize a timely response (OIG, 2005).

Surveillance also extends to symptoms indicative of infectious disease. Syndromic surveillance[2]—the real time monitoring of nonspecific, prediagnostic indicators for disease outbreaks—has been widely adopted by cities, states, and the federal government as a means to provide early warning of infectious disease outbreaks (Sosin, 2003; Stoto, 2005). Several syndromic surveillance systems are currently operational. The Real Time Outbreak and Disease Surveillance System (RODS) is used by several states to gather data on the symptoms of emergency room patients (GAO, 2004). The RODS laboratory at the University of Pittsburgh also created the National Retail Data Monitor (NRDM) to examine sales of over-the-counter health-care products.[3] The Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE), operated by DoD, allows epidemiologists to track, in real-time, syndromes reported in daily data feeds from regional hospitals and clinics in the National Capital area (GAO, 2004). The federal BioSense program—in which the United States has invested an estimated $230 million since its 2004 inception—aggregates data relevant to bioterrorism and other public health threats from numerous electronic sources

[2]The term "syndromic surveillance" applies to surveillance using health-related data that precede diagnosis and signal a sufficient probability of a case or an outbreak to warrant further public health response. Though historically syndromic surveillance has been used to target investigation of potential cases, its utility for detecting outbreaks associated with bioterrorism is increasingly being explored by public health officials (CDC, 2006a).

[3]The National Retail Data Monitor (NRDM) is a public health surveillance tool that collects and analyzes daily sales data for over-the-counter health-care products. NRDM collects sales data for selected over-the-counter health-care products in near-real time from more than 15,000 retail stores and makes them available to public health officials. NRDM is one of the first examples of a national data utility for public health surveillance that collects, redistributes, and analyzes daily sales-volume data of selected health-care products, thereby reducing the effort for both data providers and health departments. For further information on the NRDM, see Wagner et al., 2004.

(GAO, 2004; Eban, 2007). Despite the considerable investments that have been made in domestic syndromic surveillance systems, many workshop participants noted, their promise remains largely unproven (Descenclos, 2006; Bravata et al., 2004; Reingold, 2003; RAND Corporation, 2004; Stoto, 2005; Sosin, 2003).

Situational Awareness

Surveillance approaches are also used to monitor the progress and outcome of an intervention to mitigate or stop the progression of a communicable disease, as during the recent severe acute respiratory syndrome (SARS) pandemic (IOM, 2004; Heymann and Rodier, 2004) and in the campaigns to eradicate smallpox (Henderson, 1999) and polio (WHO, 2006). The broad and multifaceted use of surveillance to describe and inform response over the entire course of an outbreak, known as "situational awareness," was a central topic of workshop discussion, as noted below.

Animals

The practice of surveillance is not limited to human diseases. Some surveillance systems protect economically and ecologically important animal or plant species; others are designed to detect transmission of a zoonotic disease among animal and human populations over space and time, and to predict future transmission patterns.

Within the complex network of federal agencies that govern animal health, separate—and in some cases, parallel—surveillance programs are conducted by USDA, Department of Homeland Security (DHS), DoD, Department of Health and Human Services (HHS), the Department of the Interior (DoI), and Department of Commerce (NRC, 2005). As noted in the recent National Research Council report, *Animal Health at the Crossroads*, "whether due to historic structures or functions of . . . related federal, state, and local governments, or because of changes and challenges in funding and resources, there is an apparent disconnect between [animal health] agencies that should function in partnership" (NRC, 2005). A further element of disintegration is introduced through the practice of disease-specific surveillance at both federal and state levels.

Technological advances in disease detection that have benefited public health surveillance—such as rapid, automated, sensitive, and portable sampling and assay systems and DNA-based diagnostic tools—remain to be adapted to track animal diseases (NRC, 2005). Such tools could have significantly reduced the severe burden of recent outbreaks such as exotic Newcastle disease (END) among chickens in the United States and foot-and-mouth disease (FMD) among cattle in the United Kingdom; a recent analysis supports the use of polymerase chain reaction (PCR) to screen bulk milk for the FMD virus (Thurmond and Perez, 2006). Other early warning technologies with potential application to animal

disease surveillance include embedded monitoring chips to measure temperature and other physiological states, gene-based pathogen assays, and biosensors.

Plants

Plant disease surveillance occurs at several levels: through growers, who monitor crops for signs of disease; at the local and regional levels, by private crop consultants and USDA cooperative extension agents who diagnose disease and provide advice to growers on outbreak management; at the national level, through programs such as the National Plant Diagnostic Network (NPDN; see subsequent discussion) and BioWatch; and at the international level through collaborative research organizations such as the Consultative Group on International Agriculture Research (CGIAR) (Fletcher, 2005; Stack et al., 2006).

In recent years, a broad range of molecular techniques, including PCR-based and immunological assays and DNA arrays, have been adapted to detect and track the spread of plant pathogens (Alvarez, 2004; Schaad et al., 2003). Although routine diagnosis of many crop diseases can now be made within a day by real-time PCR, there is further need to develop same-day, onsite protocols for identifying plant pathogens, as well as standardized procedures to validate diagnostic protocols (Schaad et al., 2003). In theory, earlier detection of plant pathogens could be achieved through the capture of molecular signals from pathogens *in situ*; however, this and related technologies are likely to be first applied to detect animal and human pathogens (Cook, 2005; Schaad et al., 2003).

Public Health Surveillance: A Local Perspective

The traditional model of infectious disease surveillance remains essential to public health practice, particularly at the local level. Speaker Marci Layton, of the New York City Department of Health and Mental Hygiene (DOHMH), emphasized the importance of reports—of both routine and unusual findings—by health-care providers to local health departments. The interpretation and investigation of such reports by DOHMH officials supports the identification and control of infectious disease in one of the world's largest and most cosmopolitan cities (see Chapter 1 overview). These efforts have been boosted in recent years by the introduction of electronic reporting for laboratory results and web-based reporting by health-care providers. An alert system has also been established to inform area health-care providers of public health emergencies.

Because of the high risk for disease importation into New York City, DOHMH officials stay abreast of international infectious disease trends, ramping up surveillance and alerting health-care providers in response to threatened outbreaks. The city has also invested federal funding to improve the ability of hospital triage systems to identify and appropriately treat patients who show symptoms associated with an emerging infectious disease. This is crucial, Layton observed,

because New York City "could be the next Toronto, with an unrecognized SARS outbreak from overseas."

Syndromic Surveillance

Layton noted that many infectious disease threats (e.g., influenza, SARS, and viral encephalitis, as well as potential bioterrorism agents such as anthrax and smallpox) manifest as syndromes with nonspecific symptoms ("influenza-like symptoms"). In the case of a rapidly spreading, emerging infectious disease, laboratory diagnosis may be impossible. Under these circumstances, she said, syndromic surveillance systems can alert public health authorities to an outbreak before it is revealed in reports from health-care providers.

Keynote speaker Patrick Kelley, director of the Institute of Medicine's Board on Global Health, and presenter Michael Stoto, of the Georgetown University's School of Nursing and Health Studies, reviewed the theoretical underpinnings and historical development of syndromic surveillance (see Kelley, Stoto in Chapter 1). When people first develop symptoms, following an exposure or first contact with a novel or rapidly emerging infectious disease, they may be much more likely to attempt to treat themselves and stay home from work or school rather than seeking care from a health-care provider to obtain a clinical or laboratory diagnosis (Stoto, 2005). Syndromic surveillance systems monitor existing descriptive data of these behaviors (e.g., school and work absenteeism, sales of over-the-counter medications, illness-related 911 calls, emergency room admissions for symptoms indicative of infectious disease) for patterns or clusters of behaviors suggestive of an illness outbreak. The concept of syndromic surveillance is doubly attractive because in addition to its potential to increase the speed and effectiveness of the public health response to natural or deliberate disease outbreaks, it costs far less to implement than traditional, labor-intensive approaches to disease surveillance (Stoto, 2005). However, the ability of syndromic surveillance to reduce disease-related morbidity and mortality remains to be demonstrated, as does its cost-effectiveness (Bravata et al., 2004; Reingold, 2003; RAND Corporation, 2004; Stoto, 2005; Sosin, 2003). Although rigorous evaluations of syndromic surveillance in general may be impossible, individual systems can be assessed under a variety of circumstances (Reingold, 2003). Moreover, because syndromic surveillance systems are warning devices, it will be critical to determine their utility within the context of health systems that respond to both "true" and "false" alarms (Pavlin, 2003; RAND Corporation, 2004).

Global Syndromic Surveillance

In parts of the world where clinicians are in short supply, syndromic surveillance offers a promising model for disease detection, Kelley observed (see

Chapter 1). Infectious disease is a major cause of morbidity and mortality in low-resource populations, and such environments frequently provide amplifying conditions for emerging pathogens. Recognition of this threat has spurred the World Health Organization (WHO) to revise the International Health Regulations (IHRs)—the legal framework for international cooperation on infectious disease surveillance. Once limited to a trio of internationally notifiable diseases (plague, cholera, and yellow fever), as of June 15, 2007, the revised IHRs became the "world's first legally binding agreement in the fight against public health emergencies of international concern" (WHO, 2007). Reporting of new and reemerging diseases with epidemic or pandemic potential, as well as diseases associated with acute chemical or radionuclear events, will be mandatory regardless of their origin or source (WHO, 2007).

"The mandate for general global public health surveillance is moving beyond named diseases to encompass a global responsibility to detect and report in a timely manner internationally important disease events, whether they are individual cases or clusters, whether they are well-defined diseases or ill-defined diseases," Kelley explained. Syndrome detection is central to this new paradigm, and should be viewed as one of a collection of approaches to global surveillance for infectious diseases, he said. However, he also noted considerable challenges in moving syndromic surveillance from theory to practice.

Syndromic Surveillance by Design

Kelley emphasized that a key step in developing effective syndromic surveillance systems—and one that has frequently been overlooked—is the precise definition of system capabilities. While considerable effort has been applied to the development of syndromic definitions (e.g., for flu-like illnesses that may indicate bioterrorism), far less attention has been paid to identifying robust detectors of those conditions, he said. Moreover, rather than formulate clear and specific questions and design systems to answer them, he observed that developers of syndromic surveillance systems have too often created systems based on opportunistic datasets.

In addition to appropriate data to answer essential questions, a system for public health surveillance requires powerful analytical tools, as well as technically proficient analysts to use them and accurately interpret the findings, Kelley said. He added that these considerations are equally applicable to domestic surveillance programs that, due to their complexity, might be fruitfully developed through academic partnerships with individual communities. Kelley also advocated strengthening the epidemiological capacity at the local level in order to inform the interpretation of syndromic findings in light of "local epidemiological peculiarities," as well as to ensure a rapid response to syndromic alerts.

From Syndromic Surveillance to "Situational Awareness"

Syndromic surveillance systems are handicapped by their very nature. Not only must they obtain relevant and accurate data quickly and from a variety of sources, but they must also be tuned to recognize unusual trends against a highly variable background; otherwise, syndromic surveillance systems may either miss an important event or generate unacceptable levels of false positives (see contributions by Kelley, Stoto in Chapter 1). Indeed, Stoto explained, according to the syndromic detection algorithm, it is impossible to increase the sensitivity, specificity, or timeliness of syndromic detection without reducing the other two attributes. This point is illustrated by a recent model of outbreak detection for inhalational anthrax by Buckeridge and colleagues (2006), who concluded that "when syndromic surveillance was sufficiently sensitive to detect a substantial proportion of outbreaks before clinical case finding, it generated frequent false alarms" (Buckeridge et al., 2006).

Stoto explored several additional examples of this dilemma, all of which support his contention that traditional, statistics-based syndromic surveillance systems are unsuited to the detection of rare, small-scale events such as a localized biological attack or the initial cases of a newly imported or emerging disease. He suggested, rather, that syndromic surveillance was most likely to be valuable in detecting potentially large-scale, natural disease outbreaks (e.g., seasonal and pandemic influenza, foodborne disease) for which the useful "detection window" is relatively broad.

Case-Finding by Syndrome

Instead of bypassing health-care providers, Stoto said that syndromic surveillance technology could be used to "arm astute physicians and health departments with modern approaches to finding small numbers of cases" and allow health professionals to identify them before they are formally diagnosed. Such "case-finding" surveillance systems currently in operation include the Syndromic Reporting Information System (SYRIS) (ARES, 2007; Mandl et al., 2004; CDC, 2006b), Rapid Syndrome Validation Project (RSVP) (Zelicoff et al., 2001), and Lightweight Epidemiological Advanced Detection Emergency Response System (LEADERS) (Green and Kaufman, 2002). Because case-finding syndromic surveillance requires early reporting of symptoms, it can only succeed in "an atmosphere that doesn't penalize people for getting it wrong," Stoto said (and, as other participants noted, for getting it right, that is, for being the bearer of bad news). Under enabling conditions, he said, case-finding syndromic surveillance could build the kind of strong relationships between public health and health-care providers that are critical to effective outbreak response.

"Like any alarm system, [syndromic surveillance is] only as good as what happens when the bell rings," Stoto concluded. "It must be followed with active

surveillance and epidemiological investigation, and with policy decisions regarding intervention." Speaker Joseph Lombardo, of the Johns Hopkins University Applied Physics Laboratory, further advised that syndromic surveillance systems be designed to meet the specific needs of epidemiologists and public health analysts. "The tools need to be built to support those individuals, and I believe public health informatics has a tremendous role in doing that," he said.

Situational Awareness

Several workshop participants described the use of syndromic surveillance data beyond the mere detection of behavioral "signals" of an outbreak. Kelley noted that syndromic data could support efforts to characterize infectious diseases, help target outbreak response, and inform risk communication. Lombardo distinguished between syndromic surveillance, which he defined as an automated detection and alarm system, and "situational awareness," a term long used by DoD that encompasses disease classification, tracking, response, and outcome monitoring, in addition to detection. Viewed through the lens of situational awareness, syndromic surveillance provides a rapid means to obtain descriptive data throughout the course of an infectious disease outbreak. Epidemiologists and others who monitor surveillance findings represent "the most important component of an advanced disease surveillance system," Lombardo insisted. "They cannot be replaced by statistics."

Real-Time and Batched Reporting

In addition to collecting strategic data, well-designed public health surveillance systems incorporate appropriate mechanisms to process information and deliver it to users. The computational performance of these tasks may occur in "real time" or it may be "batched," according to Lombardo, who explained the implications of these descriptions for infectious disease surveillance (see Chapter 1).

Real-time computing methods (presently used in video games and automotive safety systems) permit an immediate response to surveillance data, Lombardo said. Batching may occur at any of several junctures along the path from data collection to reporting, he explained; the term "batched reporting" may therefore reflect the simultaneous collection of multiple data points, or the contemporaneous processing of data collected at different times, or the reporting, at regular intervals, of the outcome of sequentially processed data. Batched health data may be reported to users as soon as it is processed, at regular intervals, or accessed on demand.

Breaking the electronic surveillance process into a series of steps, Lombardo compared the potential and consequences for real-time and batched reporting. Only certain syndromic surveillance data are available in real time, he noted.

For example, while cash registers transmit medication purchases immediately, schools report absenteeism on a daily basis. Moreover, he observed, "the benefits of real-time data collection are only realized if the other components of a surveillance system are real-time as well."

Data may be continuously communicated for processing via a virtual private network (used in some hospitals), or it may be sent by file transfer protocol as batched files in intervals of seconds to hours. At the data processing step, the distinction between real time and batched may not be meaningful if computation is complex and therefore time consuming, Lombardo observed. For example, a spatial analysis of disease phenomena across a series of ZIP codes could take a long time to process; however, surveillance systems can allow analysts selectively to invoke certain processes in real time in order to monitor a potentially urgent situation.

Surveillance reports can be delivered in real time, in the form of automatic alerts, but Lombardo described considerable problems with this feature. As previously noted, many reports that are based on syndromic data represent false positives and will therefore require an epidemiologist's attention and expertise to discern a true signal among considerable background noise. This can take time.

Unless surveillance reports are subject to continuous analysis, it makes no sense to invest resources in providing them on a real-time basis, Lombardo concluded. "Getting information several times an hour should be more than adequate for public health needs," he said. To provide for public health emergencies, he envisioned two modes of operation for advanced disease surveillance systems: batched reporting for routine analysis, and real-time reporting, which would be based on case definition and used for more focused surveillance during a crisis.

Animal Disease Surveillance

Two important factors contribute to the proliferation of zoonotic diseases: the explosive growth of human and domestic animal populations, and the increasingly close physical proximity within which humans and domestic and wild animals live (Karesh and Cook, 2005; NRC, 2005). Infectious diseases primarily affecting animals can have both direct and indirect impacts on humans (Table SA-1), including significant economic consequences (Figure SA-1). Therefore it is widely acknowledged that the timely identification of future emerging microbial threats (on the order of SARS, West Nile virus, or H5N1 avian influenza) will require an integrated international approach to disease surveillance. Progress toward this goal has been hampered by a variety of economic and political factors, most notably the threat of trade embargoes against countries that voluntarily report livestock or wildlife disease outbreaks.

Although they share comparable objectives, the U.S. animal health community lags far behind its public health counterpart in terms of surveillance infrastructure and technology (NRC, 2005). These deficits were raised in several

TABLE SA-1 Animal Diseases Associated with Direct and Indirect Human Impacts

Infectious Disease	Affects Wildlife	Affects Domestic Animals	Affects Humans Directly	Affects Humans Indirectly
Brucellosis	X	X	X	X
Canine Parvovirus	X	X		
Chagas	X	X	X	
Distemper	X	X		
Foot-and-mouth disease	X	X		X
Leishmania	X		X	
Leptospirosis	X	X	X	
Rabies	X	X	X	X
Scabies	X	X	X	
Toxoplasmosis	X	X	X	

SOURCE: WCS (2007).

workshop discussions, and particularly in comments from veterinary pathologist Tracey McNamara of the Wildlife Conservation Society (WCS). In 1999, McNamara linked the presence of dead birds on the grounds of two New York City zoos with the first human cases of West Nile encephalitis in the United States. Thereafter, she led the effort to create a national surveillance network for the disease involving more than 35 zoos (Watanabe, 2002). A far more comprehensive and integrated strategy is needed for the surveillance of zoonoses, McNamara said. She noted that there is no provision for veterinarians who routinely diagnose infectious disease in zoo animals and wildlife to report unusual findings or send samples to public health authorities for testing, as physicians are required to do. "Zoos are the most overlooked long-term epidemiological monitoring stations in the United States and in the world today," she concluded.

As part of their overall mission, WCS conducts routine surveillance for a wide variety of infectious diseases in animals around the world, including the 20,000 residents of zoological parks in the New York City area. In his presentation, William Karesh, director of the Society's Field Veterinary Program, described ongoing programs to monitor two important zoonoses: Ebola virus and avian influenza (see Karesh in Chapter 1).

Ebola Virus Surveillance in Central Africa

In a reversal of standard public health thinking, WCS views humans as a worrisome source of diseases that infect great apes. To protect endangered gorillas in central Africa from the Ebola virus, WCS has supported human disease surveillance among the underserved populations that live in close contact with the gorillas by training local people in simple data collection, syndromic surveil-

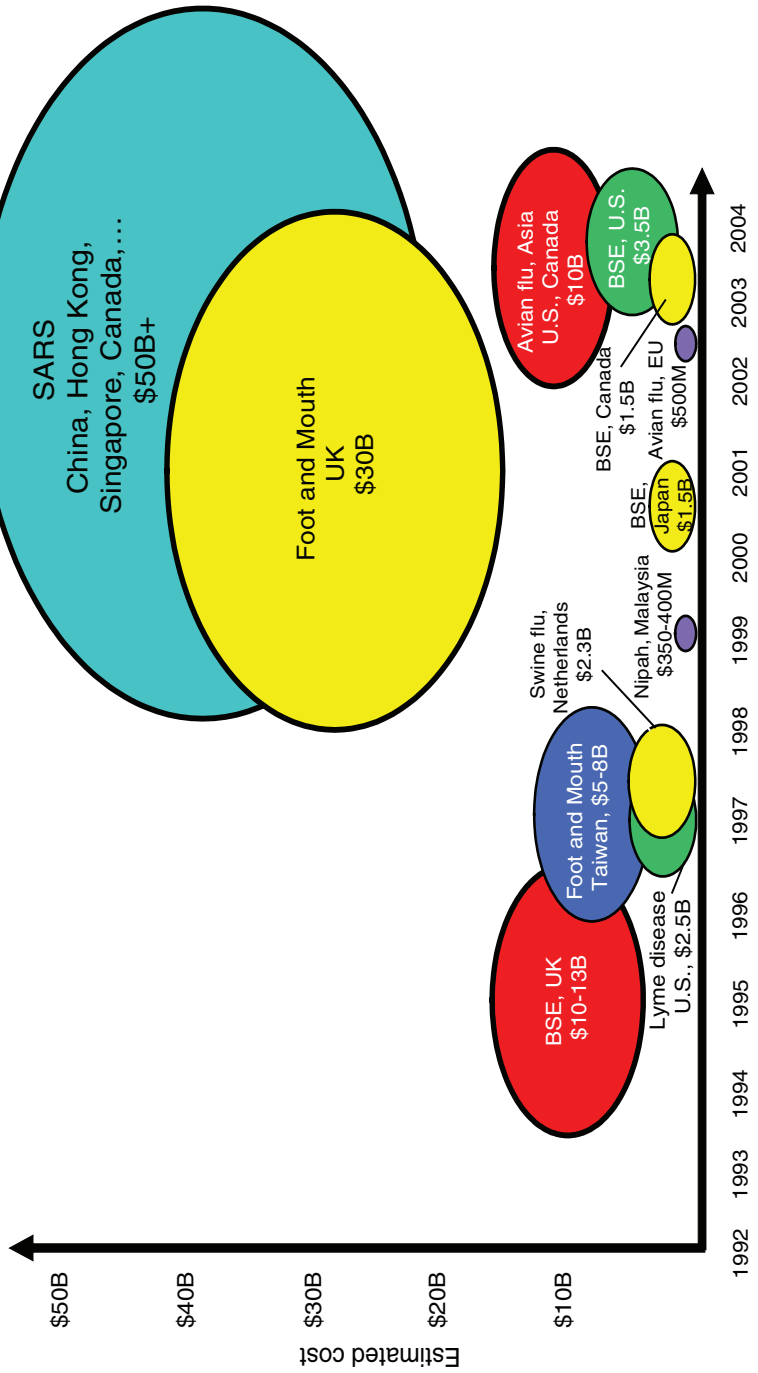

FIGURE SA-1 The economic impact of selected infectious diseases.
SOURCE: Karesh (2006). Reprinted with permission from Bio-era. Copyright 2007.

lance, and basic laboratory diagnosis. These efforts, which helped to identify the link between human outbreaks of Ebola virus and the consumption of gorilla and chimpanzee meat (Leroy et al., 2004), now enable community members to avoid infection with the virus by providing early warning of outbreaks in animals. Current surveillance is also directed toward evaluating the effectiveness of human Ebola vaccine candidates in wildlife.

In addition to their efforts on behalf of gorillas, WCS has sought to teach people in central Africa how to avoid getting Ebola through basic hygiene measures such as hand washing and cooking meat thoroughly. These lessons have afforded opportunities to improve overall food safety in communities, Karesh observed.

Global Surveillance for Avian Influenza

Over the course of several years, WCS has worked with individual governments to conduct surveillance for avian influenza in wild birds. This typically involves basic epidemiology and viral sample collection and characterization (by CDC); in some instances, birds are tracked with radio transmitters. In Mongolia, such a program has provided a candidate virus for development of a human influenza vaccine, Karesh said. More recently, these individual efforts have been combined into the Global Avian Influenza Network for Surveillance (GAINS). The program seeks to expand international surveillance for influenza in wild birds and promote the dissemination of surveillance information to governments, international organizations, the private sector, and the public.[4] With support from USDA, the U.S. Agency for International Development (USAID), and the Food and Agriculture Organization of the United Nations (FAO), GAINS trains individuals and organizations to collect samples for analysis by a network of diagnostic labs, the results of which are disseminated through a common, open-access database. Participants in the program, which currently reaches 24 countries, include hunters, birdwatchers, and other members of the public, as well as animal health professionals. Karesh acknowledged that GAINS raises privacy concerns in the United States. ("Who wants to say they have a sick bird on their property?"), but he also observed, "the rest of the world doesn't seem to have that problem."

Indeed, as Karesh notes in Chapter 1, the early success of GAINS has led to an expansion of the program to address a broader range of infectious diseases and species. The Wildlife Global Animal Information Network for Surveillance (Wildlife GAINS) aims to establish "a comprehensive worldwide wildlife health surveillance system to enhance preparedness for and awareness of emerging infectious diseases," he reports.

[4]See http://www.gains.org.

Plant Disease Surveillance and Detection

While plant health programs address many of the same challenges (e.g., globalization, biosecurity) and use similar tools and approaches as their animal and public health counterparts, the near impossibility of preventing the global spread of plant pathogens orients surveillance and detection toward preparedness for disease. Agricultural production in the United States is especially vulnerable because it encompasses vast areas, observed speaker Jacqueline Fletcher of the University of Oklahoma (see Fletcher and Stack in Chapter 1).

Considerable time often elapses between the introduction of an agricultural pathogen and its detection; therefore, federal programs such as the aforementioned NPDN focus on the early detection of plant diseases to minimize economic losses. Because it would be too expensive to eradicate the more than 50,000 plant diseases currently in the United States, the typical strategy is to minimize the economic impact of each disease, Fletcher explained. However, given sufficient warning prior to the introduction of a new plant disease threat, researchers can reduce the impact of disease by identifying chemical control measures or by breeding resistant crop varieties.

National Plant Diagnostic Network

Early detection, aimed at reducing the economic impact of plant diseases, is the central mission of NPDN, according to speaker James Stack of Kansas State University (see Stack and Fletcher in Chapter 1). Created in 2002 by the U.S. Secretary of Agriculture, NPDN links plant disease and pest diagnostic facilities at land grant universities in order to provide rapid detection and accurate diagnosis of important plant pathogens and pests (Stack et al., 2006). These efforts received further federal support in 2004, under a Homeland Security Presidential Directive (HSPD-9), which "establishes a national policy to defend the agriculture and food system against terrorist attacks, major disasters, and other emergencies." HSPD-9 mandates the development of a national agricultural biosecurity initiative that would expand capacity for disease detection and diagnosis (White House, 2004).

According to Stack, NPDN is currently pursuing a range of passive and active disease surveillance strategies. These include sentinel surveillance for specific pathogens (e.g., soybean rust, introduced to the United States by hurricanes in 2004); random surveys for plant disease conducted by specialists throughout the country; strategic and bidirectional surveillance, which attempt to locate the source of disease outbreaks; syndromic surveillance (also for soybean rust); and biosensors (for toxin-producing pathogens in stored grains and seeds). While mandatory reporting of high-consequence pathogens and pests has been instituted in some circumstances, Stack noted that the considerable disincentives to do so probably lead to high rates of noncompliance.

NPDN has also undertaken several projects intended to maximize the productivity of shrinking numbers of plant scientists trained in diagnosing disease, Stack said. These include the creation of a curriculum to teach agricultural workers to recognize signs of important plant diseases, and the development of diagnostic databases and a "telemedicine" system that links state agricultural labs to diagnostic experts.

National Center for Plant Biosecurity

Fletcher discussed a proposal for a comprehensive National Center for Plant Biosecurity that has been endorsed by a broad coalition of scientific societies with a common interest in crop protection. It is envisioned that the center, modeled on CDC, would coordinate plant disease information at the national level and collect and disseminate knowledge on plant-disease management and agricultural biosecurity. The center's mission would be fundamentally different from that of USDA, which is driven by the needs of agribusiness and focused on near-term profitability, Stack explained. "We need another group that can step back from that and look at our plant-based systems from a strategic standpoint," he said.

Although the threat of agricultural bioterrorism provided the impetus for proposing the center's creation, Fletcher said, its benefits would be substantial in the absence of such crises. This is particularly true because former USDA functions, such as the Animal and Plant Health Inspection Service (APHIS) and the Plum Island Animal Disease Center, were subsumed by DHS, Stack observed. That move has diminished attention to the specific missions of these agencies, which represent "a first pair of eyes for what is coming into the country," he said. "If they don't know what they are looking for, then that's wasted time."

Surveillance Networks

In traditional public health surveillance (based on reports from medical practitioners, as described in the previous section), information travels up or down the public health hierarchy, from the local to the international level and vice versa. According to Forum member Stephen Morse, this seemingly orderly scenario tends to produce surveillance that is patchy and erratic due to differing priorities at various levels of the public health system, and information that is too often focused on "diseases of the moment." By contrast, electronic network surveillance systems have the potential to recognize any outbreak, including that of an emerging or otherwise unexpected disease, on a global scale.

The presentations and discussions summarized below demonstrate the power of electronic networks to collect and integrate information on infectious disease from a variety of sources and the ability of networks to disseminate such intelligence widely and rapidly to the user community. Participants also noted several

limitations of disease surveillance networks and—much as they had done for syndromic surveillance systems—urged the creation of network surveillance technologies that address specific public health needs and strengthen connections between "astute clinicians" and public health practitioners.

ProMED-Mail

The first disease surveillance network, ProMED-mail (PMM), began in 1994 as a project of the Federation of American Scientists' Program for Monitoring Emerging Diseases (ProMED) (Madoff and Woodall, 2005). Morse, a founding member of both ProMED and PMM, recounted that the network was initially intended to enhance communication between working group members; however, the listserv's potential as an outbreak reporting system was quickly recognized and expanded (see Morse in Chapter 2). Now sponsored by the International Society for Infectious Diseases, PMM is a free, nonprofit, noncommercial, moderated e-mail list that serves in excess of 37,000 subscribers in more than 150 countries, as well as anyone with access to the website.[5]

As illustrated in Figure SA-2, traditional public health reporting follows a linear "bottom-up" process, beginning with an ill person presenting to a local doctor, where they may receive medical tests. If the doctor or laboratorian finds evidence of a "reportable" disease, or merely something unusual, he or she reports the discovery to local health officials. If the apparent threat is severe, local health officials report it to the national ministry or department of health, which forwards the report to international health organizations ("world bodies") if the case is of global concern.

Figure SA-3 depicts the nonhierarchical ProMED network, which fosters the exchange of information on reported diseases among a variety of sources.

In addition to volunteer "rapporteurs," who provide information on possible infectious disease outbreaks specific to their geographic area, PMM receives information from subscribers (who may report firsthand or from other sources) and from staff-conducted searches of the Internet, media, and various official and unofficial websites (Madoff, 2004). Moderators assess these reports for plausibility (via established rumor verification protocols and private query to experts), edit them as necessary, and often add comments or context before posting. Furthermore, because PMM aggregates reports from various locations, it can reveal the geographical extent of an outbreak. Morse noted that this system has resulted in several emerging disease reporting "firsts," including outbreaks of Ebola virus in Zaire (1995), West Nile virus in the United States (1999), SARS in China (2002), and H5N1 avian influenza in Indonesia (2003).

[5]See http://www.promedmail.org.

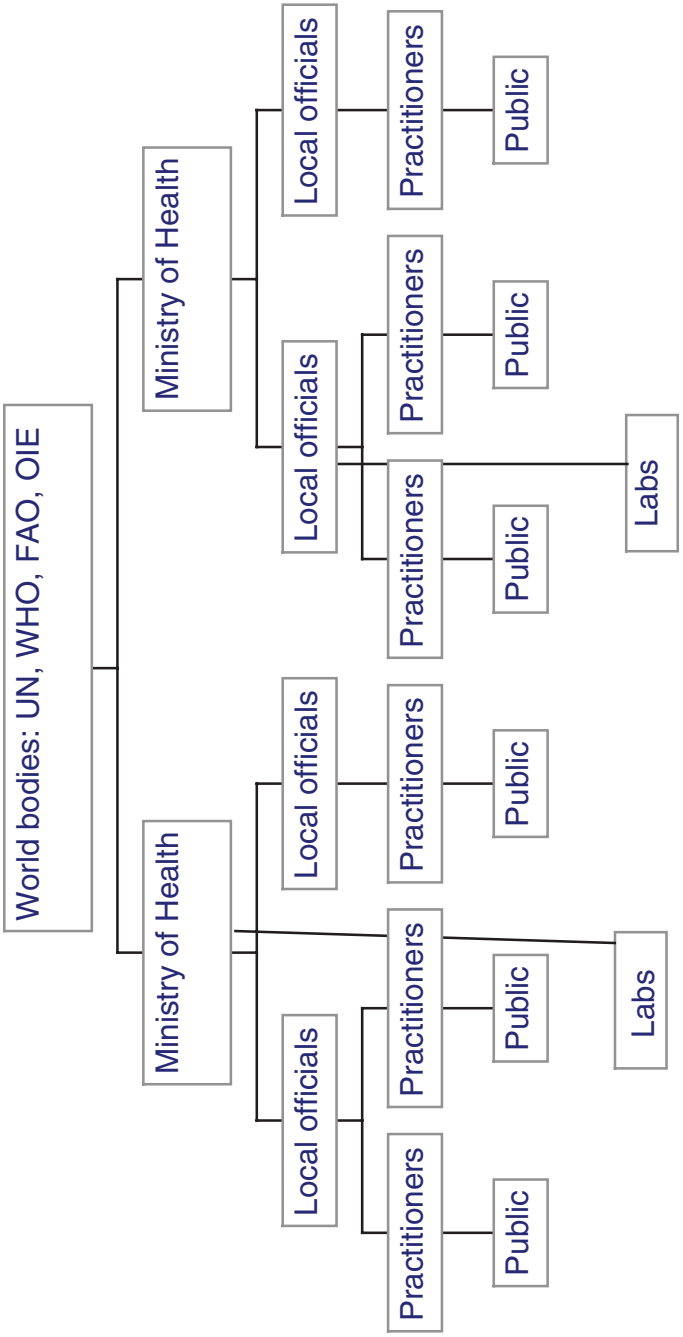

FIGURE SA-2 Traditional public health reporting.
SOURCE: Figure courtesy of Dr. Larry Madoff.

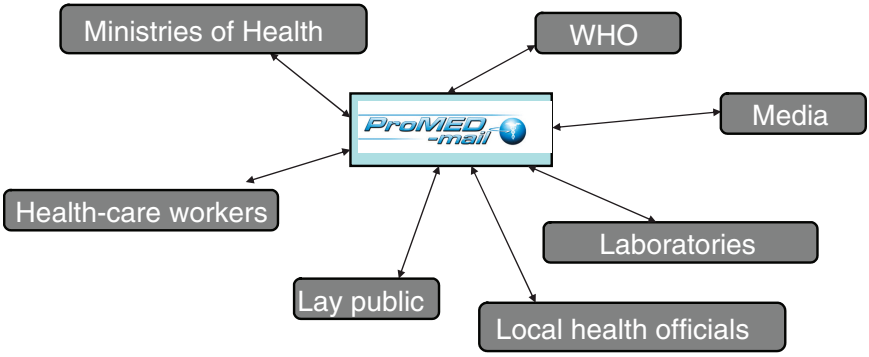

FIGURE SA-3 The power of the ProMED surveillance network.
SOURCE: Figure courtesy of Dr. Larry Madoff.

Global Outbreak Alert and Response Network

To connect the growing number of surveillance networks that followed PMM in terms of capacity for infectious disease diagnosis and response, WHO established the Global Outbreak Alert and Response Network (GOARN) in 2000.[6] Conceived as a "network of networks," GOARN pools human and technical resources from more than 100 institutions around the world (WHO, 2005) in order to rapidly identify, confirm, and respond to outbreaks of international importance. In 2002, after receiving worrisome reports from the Global Public Health Intelligence Network (GPHIN; see below) and the U.S. Global Emerging Infection Surveillance and Response System (GEIS), GOARN initiated the global response to an outbreak of a disease that would be named SARS (IOM, 2004; Heymann and Rodier, 2004).

The Global Public Health Intelligence Network (GPHIN)

Harnessing the power of automated Internet searching for disease surveillance, GPHIN scans thousands of websites in eight languages—including those identified by two "news aggregators," who monitor thousands of news sources in dozens of languages—for early signs of infectious disease outbreaks in humans, animals, and plants, as well as for chemical incidents and disease threats associated with natural disasters (Mykhalovskiy and Weir, 2006). Abla Mawudeku, manager of GPHIN within the Public Health Agency of Canada, described the network's creation by that agency in partnership with WHO in 1998, its operation and ongoing development, and its possible future as part of a planned open-access

[6]See http://www.who.int/csr/outbreaknetwork/en/.

surveillance program under the auspices of a yet-to-be-named nongovernmental organization (see Mawudeku et al. in Chapter 2).

After a scoring system sorts some 2,000 articles retrieved by GPHIN daily, a team of multilingual, multidisciplinary, and multicultural analysts review those articles deemed most relevant, Mawudeku explained. Several analysts work in staggered shifts to provide round-the-clock coverage. Upon receiving a report of concern, they follow a decision tree, based on IHR criteria (which may lead analysts to corroborate reports with other surveillance networks, such as ProMED-mail), to determine whether to post an alert. GPHIN does not systematically validate the information it posts, but relies on WHO to verify outbreak alerts through its country contacts (Mykhalovskiy and Weir, 2006). Figure SA-4 shows the source of initial reporting of events of potential public health concern by WHO in 2001–2002.

Subscribers to GPHIN receive alerts by e-mail or when they log on to the system's website. In addition to WHO and Canadian governmental agencies (e.g., food inspection, defense, police), GPHIN's audience includes ministries of health and departments of agriculture from several nations, as well as FAO, the World Organization for Animal Health (OIE),[7] and the North Atlantic Treaty Organization (NATO). Depending on the services provided, GPHIN subscriptions (which in part reflect the expense of subscribing to news aggregators) cost 30,000 to 200,000 Canadian dollars per year, according to Mawudeku (Public Health Agency of Canada, 2007).

To continue to improve its service, GPHIN has begun to evaluate its own effectiveness. Criteria are based on the number of users; the timeliness, sensitivity, and specificity of alerts; the stability of the system in terms of limited downtime; and the flexibility of the system in terms of accommodating new technologies and in modifying search criteria to gather information on a situation of interest, Mawudeku said. The cost of operating and upgrading the system is a continual challenge, she observed, as well as a barrier to use by low-resource countries and agencies. However, recent events may portend a change in this situation. Having received the Technology, Entertainment and Design (TED) prize in 2006, epidemiologist Larry Brilliant (who played a key role in WHO's campaign to eliminate smallpox, and who currently serves as Google's chief of philanthropy) is currently marshalling an effort by the influential TED community to expand and enhance the GPHIN model (Zetter, 2006; Google, 2006; Hempel, 2006). With GPHIN as a starting point, Brilliant hopes to create a freely available, internationally independent system for the early detection of infectious disease outbreaks.

Due to potential conflicts of interest with the Canadian government, GPHIN's staff cannot participate in the negotiations to make this service independent, Mawudeku explained. "I can't tell you what will happen to the GPHIN system, whether we will continue to be within the [Public Health Agency of Canada] or not," she said, adding that Google's attention to GPHIN had at least prompted

[7]Office International des Epizooties.

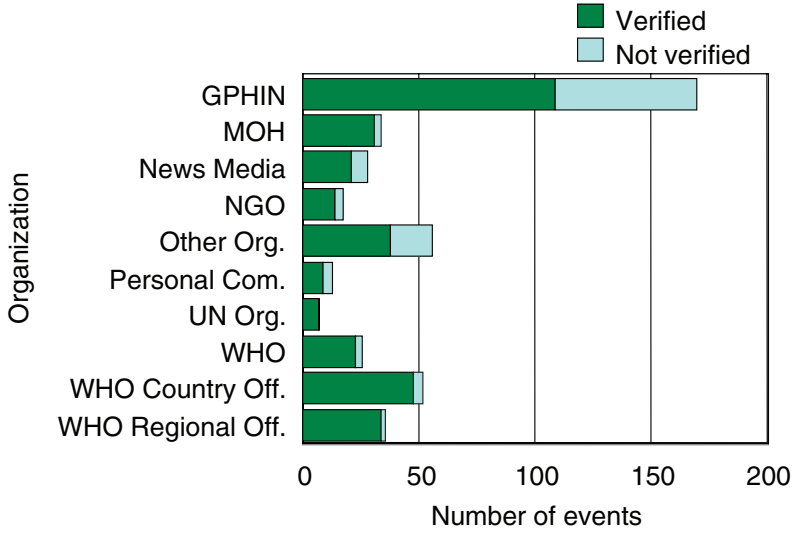

FIGURE SA-4 Source of initial reporting of potential events of public health concern by WHO between January 1, 2001, and December 31, 2002. Legend: Global Public Health Intelligence Network (GPHIN); Ministry of Health (MOH); Nongovernmental Organization (NGO); United Nations (UN); World Health Organization (WHO).
SOURCE: Mawudeku et al. (2002).

recognition that the network would benefit from greater financial support than the Canadian government currently provides. It would also satisfy the concerns of Forum member Gerald Keusch, who observed that government-operated sources of surveillance information raise "serious issues of credibility."

HealthMap

HealthMap,[8] a freely available, web-based surveillance network operating since September 2006, provides a global view of infectious disease outbreaks as reported by the WHO,[9] PMM, Google News,[10] and *Eurosurveillance*.[11] John Brownstein, of the Children's Hospital Informatics Program, Harvard–

[8]See http://www.HealthMap.org.

[9]See http://www.who.int/csr/don/en/.

[10]See http://news.google.com/news?hl=en&ned=us&ie=UTF-8&scoring=d&q=intitle:outbreak +-satire+-%22press+release%22+-%22Communiqués+de+presse%22.

[11]*Eurosurveillance*, a free and open-access multiformat journal, publishes peer-reviewed information on communicable diseases from a European perspective. In March 2007, *Eurosurveillance* became the independent scientific in-house journal of the European Centre for Disease Control and Prevention (ECDC) in Stockholm, Sweden. For more information, see http://www.eurosurveillance.org.

Massachusetts Institute of Technology (MIT) Division of Health Sciences and Technology, and the Harvard Medical School Center for Medical Bioinformatics, described the design of the system and efforts to evaluate its data sources (see Brownstein et al. in Chapter 2).

There is an abundance of open-source electronic surveillance networks for infectious disease, Brownstein said, but none provide a truly global perspective due to gaps in geographic or population coverage and expertise. HealthMap attempts to bridge these gaps by aggregating and integrating information from several surveillance networks to produce a graphic, continually updated model of global disease outbreaks over space and time. Alerts are displayed on a global map that can be viewed at a wide range of resolutions and they are linked to source sites that provide news of the outbreak and information on the disease.

Recognizing the tradeoffs between alert sensitivity and specificity, HealthMap's creators are conducting an ongoing evaluation of their data sources with respect to these criteria (see Brownstein et al. in Chapter 2). Brownstein reported that, based on their first two months' of data, PMM provided slightly greater timeliness and better coverage of rare infections as compared with Google News. On the other hand, he noted, news feeds provide a larger volume of data, making them more useful for describing the temporal and spatial distribution of large-scale seasonal infections (Figure SA-5). Brownstein believes "there is a real value in integrating these data sources . . . to get a much better picture of a global state of infectious diseases."

HealthMap's creators plan to expand their data sources to include CDC, the private sector, laboratories, the military, and blog searches. They also plan to incorporate information on animal infections and biotic and abiotic factors that influence disease emergence and transmission, Brownstein said. In addition to addressing reporting biases in current datasets, he noted that these additional sources should support the assessment of population risk, disease severity, and pathogen transmission within the HealthMap model. Data verification remains a challenge, he added; with only two employees, HealthMap must rely on data that have been validated by others—such as ProMED-mail reports.

Several participants recognized potential synergies between HealthMap and GPHIN, with each network offering important elements (HealthMap's openness; GPHIN's reach and verification capacity) of a long desired and sought-after "system of systems" approach to infectious disease surveillance. GPHIN's current status within Health Canada and its reliance on commercial news aggregation services would likely prohibit the network from supplying data to HealthMap, Mawudeku explained; however, such collaboration could be possible if GPHIN evolves into an open, nongovernmental network as envisioned by Brilliant.

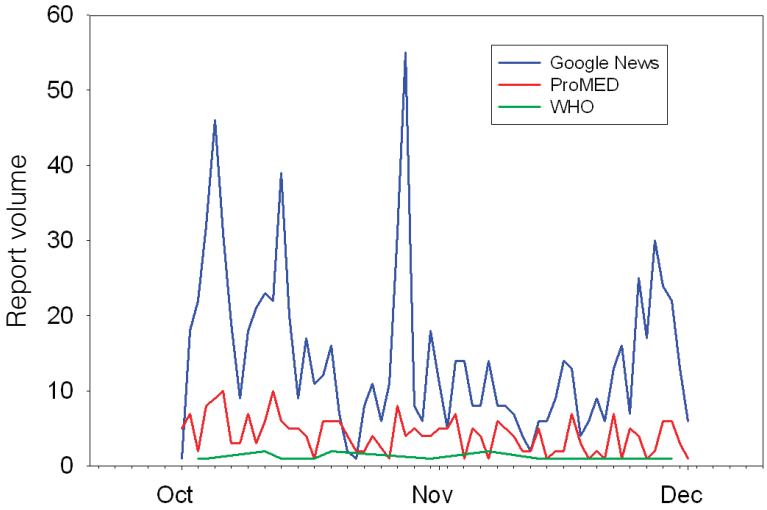

FIGURE SA-5 HealthMap alert volume by source. Google News: 899 (14.2 per day; 95 percent CI 11.8-17.2); ProMED: 257 (4.2 per day; 95 percent CI 3.5–4.7); World Health Organization: 15.
SOURCE: Brownstein (2006).

The Voxiva Model for Resource-Constrained Environments

As several workshop participants observed, a global infectious disease surveillance system capable of early detection and response must identify outbreaks where they most often arise: in the world's most impoverished communities. Many developing countries, however, lack adequate disease surveillance systems capable of finding, diagnosing, and responding to diseases of global concern. These countries must also detect and control outbreaks of common diseases, such as measles, within their own borders. This is the void Voxiva[12] attempts to fill, according to speaker Pamela Johnson, the company's cofounder (see Johnson and Blazes in Chapter 2). Although projects have been launched to enable disease reporting in low-resource settings via the Internet, personal digital assistants (PDAs), and satellite dishes, she noted that none of these technologies directly reached the inhabitants of remote communities at risk for infectious disease outbreaks. By contrast, she reported that cellular phones have begun to connect even the most isolated villages as their usage rate grows far faster than that of the

[12]Founded in 2001, Voxiva aims to find practical ways of using information technology for health and development in low-resource environments by creating innovative software that allows health professionals to enter and access data using the Internet, a cell phone, and other devices. This new capability makes early identification, treatment, and response possible for public health concerns.

Internet. Figure SA-6 illustrates the rapid growth of cell phone usage in Africa between 1994 and 2004.

Like other electronic surveillance networks, Voxiva is ultimately web-based, Johnson said. The network receives input from a variety of sources, including cellular and fixed-line telephones, personal computers, PDAs, and paper-based communications to "optimize the use of existing infrastructure to create multiple-channel, redundant systems" for data collection, she explained. Information is captured in a database that can then be shared with those who contribute reports, along with tools for data analysis and visualization. Gaining access to surveillance information and tools—in addition to acknowledgment for their participation—gives inhabitants of outbreak communities a powerful incentive for reporting, Johnson said.

Voxiva conducts both syndromic and traditional surveillance for human disease in a variety of settings in Asia, Africa, South America, and the United States, as well as systems to monitor animal health and adverse events. In Peru, Voxiva created a system to replace the paper-based monitoring of illness among members of its navy, a project described by David Blazes of the U.S. Naval Medical Research Center in Lima (see Johnson and Blazes in Chapter 2). When naval personnel or their family members present with disease symptoms at remote clinics in the Amazon jungle, for example, nurses or physicians enter data via cellular or toll-free public phones, or if necessary, relay it via radio to another site with telephone access. The data are captured, displayed in real time on a private web-based platform, and used to generate messages and alerts that feed back to

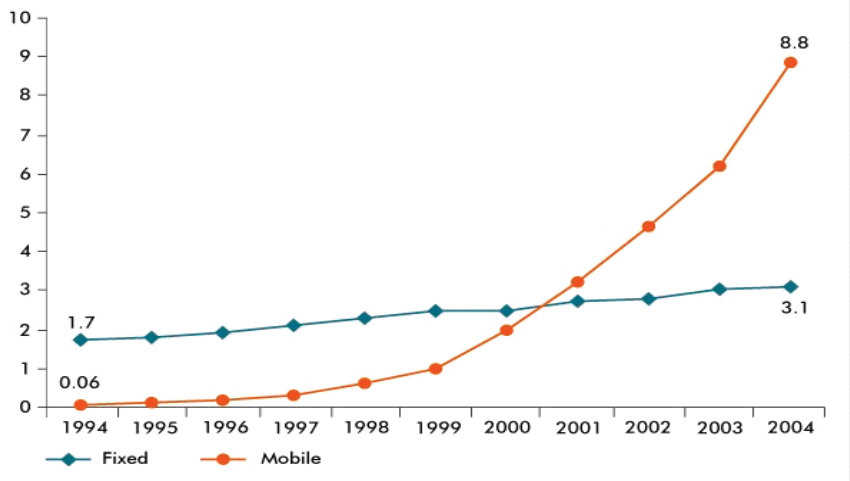

FIGURE SA-6 Telephone subscribers per 100 inhabitants, Africa 1995–2004.
SOURCE: Reproduced with the kind permission of the International Telecommunication Union (2006).

the reporting clinics. "The Peruvian Navy had no idea how many cases of any disease were occurring over a period of time," Blazes observed. "Just setting baseline trends was very important."

Like GPHIN, Blazes said that Voxiva has begun to evaluate its surveillance systems, based on criteria such as simplicity, flexibility, stability, and sustainability, as defined by CDC (CDC, 2001). But Voxiva's involvement in public health extends well beyond surveillance, he noted: Their systems are linked to diagnosis and response teams that can provide guidance or assistance in the event of an outbreak. In addition, Voxiva provides basic training in epidemiology and outbreak management to its clients, using freely available, web-based curricula.[13] All these functions contribute to Voxiva's overarching purpose, as defined by Johnson, to use informatics to build and support networks of astute clinicians.

Considerations for Surveillance Networks

In response to these presentations, workshop participants raised a series of general issues regarding the structure, function, and future of public health surveillance networks. Although the open-access PMM and HealthMap networks are well established and poised to expand, some Forum members noted that none of these networks features the sort of open editing made popular by the free online encyclopedia Wikipedia.[14] Brownstein said that HealthMap may add a user editing function, but input would be limited to a group of experts. Keusch pointed out that a similar "portal" model has been used to collect other types of information; for example, to construct the Encyclopedia of Earth, a free, searchable collection of articles on earth science and ecology written by a diverse team of experts who collaborate and review each other's work.[15] By contrast, Forum member Gary Roselle expressed concern that HealthMap's "beautiful maps of data" derive from potentially erroneous newspapers and websites, and worse, could be influenced to manipulate markets. In subsequent remarks, speaker Will Hueston (see next section and Chapter 4) asserted that the maps would "set back international development because it supports the idea that a country either has the disease or doesn't have the disease and the country either is at zero risk or is at risk." Furthermore, he predicted that the vast economic consequences (e.g., trade embargoes; decreased tourism and investment) of such labels would inhibit disease reporting.

Regarding limitations in network access, one Forum member wondered how public response to the SARS pandemic might have changed had GPHIN been

[13]To date Voxiva has trained more than 1,300 epidemiologists on the basics of outbreak management. Their objectives and curricula are in Spanish and English and are freely available on the Web. For more information about the training provided by Voxiva, see http://www.nmrcd.med.navy.mil/outbreak/.

[14]See http://www.wikipedia.org.

[15]See http://www.digitaluniverse.net/portal/earth/.

freely accessible. Mawudeku speculated that the release of unverified information might have created unnecessary panic, and she advised that such information be accompanied by qualifying commentary if it were provided in an open version of GPHIN. Another barrier to network openness exists at the level of data acquisition. Countries do not share surveillance data without government approval, participants observed, and the IHRs do not presently impose sufficient consequences to overcome economic barriers to reporting disease. This necessarily limits information available to surveillance networks, except perhaps Voxiva, whose clients own their data and use the network's information as they see fit. On the other hand, Johnson pointed out, clients sufficiently interested in collecting such data tend to have the greatest capacity to respond to an apparent outbreak.

Looking to the future, Forum member George Korch asked how surveillance data accumulated by networks might be analyzed further to tease out underlying factors and relationships, such as previously unknown societal or environmental influences on disease transmission. To the extent that they occur at all, such analyses are currently conducted on an ad hoc basis; however, both Brownstein and Mawudeku said their networks are discussing possibilities for deeper and more detailed surveillance studies, which are likely to proceed as collaborations with academia and research institutions. Brownstein also predicted that basic research in Internet-based surveillance would benefit from the recent "explosion of work" on syndromic surveillance systems; for example, by using previously developed methods to characterize datasets and reveal their hidden biases.

Finally, participants observed that surveillance networks, like other advanced technologies that have been integrated into the practice of public health, tend to be driven by innovation rather than designed to solve important problems. They urged greater involvement by the public health community in creating tools in response to pressing public health challenges, and noted that the development of a common lexicon by technologists and public health practitioners is crucial to advancing their collaboration.

Detection and Diagnostics

Current microbial detection and identification methods include microbiological culture, nucleic acid-based techniques such as gene amplification via PCR, and immunological (antibody-based) assays (Peruski and Peruski, 2003; Fredricks and Relman, 1999; Tang et al., 1997). Each of these platforms offers complementary advantages and disadvantages for infectious disease diagnosis:

- **Microbiological culture,** with staining and microscopy, is the most widely used method for identifying pathogens, particularly in developing countries. Despite being slow and limited in sensitivity for some clinically relevant microbes, culture often provides the best means to assess complex microbial phenotypes, such as drug resistance.

• **PCR** is a sensitive, specific, and rapid approach for identifying microbes, including those that are nonviable or inactivated (Peruski and Peruski, 2003; Gilbert, 2002). Hundreds of different microbe-specific nucleic acid amplification tests have been described, but only a few such tests are routinely used in a clinical setting to detect pathogens that include *N. gonorrheae*, *C. trachomatis*, herpes simplex virus, and HIV (Fredricks and Relman, 1999; Tang et al., 1997). PCR methods may also be used to detect drug resistance in pathogens (Fluit et al., 2001), but the diversity of genotypes and mechanisms associated with this phenotype, and the difficulty of predicting expression from simple gene detection, have hampered the universal adoption of this approach. Real-time quantitative PCR, which permits sample processing in minutes, powers environmental detection systems for infectious diseases and biological warfare agents, as well as innovative point-of-care diagnostic tests (Ivnitski et al., 2003; Peruski and Peruski, 2003; Raja et al., 2005).

• **Immunoassays** are usually less sensitive and specific than culture and PCR (Peruski and Peruski, 2003). Solid-phase, "hand-held" immunoassays for specific pathogens are rapid, rugged, and easy to use. However, their application is generally limited to screening or confirming diagnoses.

Newer diagnostic platforms, still largely in development, include nucleic acid microarrays ("labs on chips" containing hundreds to thousands of oligonucleotide probes for signature sequences) and mass spectrometry techniques for sequence analysis (Briese et al., 2005; Palacios et al., 2006; Palacios et al., 2007; Anthony et al., 2001). These technologies permit detection of a wide range of known disease-causing organisms (not limited to microbes) and can often distinguish new pathogen species, strains, and genotypes. Additional innovations include methods for the simultaneous identification of complex mixtures of organisms (Ecker et al., 2005; Hofstadler et al., 2005). Potential applications of such multiplexed detection technologies include the characterization of polymicrobial infections common in epidemics of respiratory disease, and the creation of "universal biosensors" to permit the simultaneous identification of a broad range of infectious agents in an environmental or clinical sample.

The Diagnostic Landscape

Workshop presentations on infectious disease detection and diagnostics followed a metaphorical road as they surveyed the immediate landscape of capacity, needs, and challenges; anticipated developments around the next turn; and imagined a far horizon of disease diagnosis prior to the appearance of symptoms. In the course of this journey, participants examined a variety of approaches to infectious disease detection and diagnosis and raised significant considerations for continued development of this field.

Developing Countries

While threats posed by emerging diseases, pandemic influenza, and bioterrorism underscored workshop discussion, Mark Perkins of the Foundation for Innovative New Diagnostics (FIND) reminded participants of the severe burden presently imposed on the developing world by infectious diseases such as tuberculosis (TB) and malaria (see Perkins and Small in Chapter 3). Culture and microscopy are often the only diagnostic technologies available in developing countries, typically through a small number of facilities that cannot begin to meet national needs. This not only hinders treatment for infectious disease in developing countries, he noted, but surveillance as well. Perkins reported that half of the 22 countries with the highest burden of disease from TB have three or fewer laboratories that can perform drug-susceptibility testing, a key component of TB treatment and control; similar barriers also deter the detection and treatment of trypanosomaisis and malaria.

Developing countries' needs for rapid, accurate, inexpensive, and robust diagnostics could be met by recent advances in genomics, proteomics, and materials science, but for the lack of a profitable market for such developments, Perkins observed. FIND therefore guides the development and adoption of novel diagnostic products for diseases of the developing world in much the same way as public–private partnerships have been established to produce drugs and vaccines for low-resource settings (Perkins and Small, 2006). With FIND's support, companies that produce low-cost diagnostics for use in developing countries realize sufficient cost savings (in manufacturing, approval procedures, and marketing) to sustain profits. "So far it has been a very successful model," Perkins reported. "We have about 18 different technologies in the pipeline."

Diagnostics for TB figure prominently among the Foundation's current projects. Perkins described a liquid culture system for TB that reduces detection time by several weeks; a phage replication assay and an automated detection system, both capable of detecting rifampicin-resistant TB in sputum (signaling a patient that will fail standard therapy); and an easy-to-use PCR diagnostic system that can be performed in clinics without laboratory support. He cautioned that many substandard rapid tests for TB (as well as other diseases, including malaria) have already appeared on the market. "Small companies, the kinds of companies that are making these tests, are not going to invest in going back to the genome and figuring out what the right targets are," he observed. Nevertheless, Perkins concluded, "Our belief at FIND is that if you make the right technology, people will use it."

On the Battlefield

Much like public health workers in developing countries, soldiers at risk of contracting infectious diseases, either from the natural environment or from

bioweapons, need diagnostics that are rugged, rapid, and easy to use. According to speaker Mark Wolcott of the Diagnostic Systems Division at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), diagnostic assays must satisfy additional criteria for use in battle. Accuracy is paramount, and tests must recognize a broad range of potential pathogens, he explained. "Negatives are problems," he said, "and false negatives [which may result from a bioengineered pathogen] are of greater concern than false positives." The military currently relies on a combination of PCR tests, immunoassays, and traditional microbiology to diagnose infectious diseases in the field, while pursuing a strategy to develop comprehensive diagnostic tools.

Animal Diseases

Recognizing the advantages of DNA-based diagnostic tools, Alex Ardans and colleagues have developed PCR-based assays to screen for pathogens associated with exotic Newcastle disease (END) in poultry and foot-and-mouth disease (FMD) in cattle (Crossley et al., 2005; Heller, 2006; Thurmond and Perez, 2006). Ardans, who directs the California Animal Health and Food Safety Laboratory System, also described how the discovery of TB among cattle in several of the state's large dairies led to the development of a highly efficient testing program.

Although the state laboratory system spearheads surveillance for several important animal diseases (including zoonoses such as avian influenza, bovine spongiform encephalopathy, and West Nile encephalitis), Ardans suggested that its most crucial role is in recognizing unusual disease events. He noted, for example, that while END was "no stranger" to rural California, a recent outbreak in an urban setting—among fighting cocks, whose handlers worked in and spread the disease to commercial operations—took the state by surprise. The laboratory responded by optimizing an existing real-time PCR assay for END that was used to perform more than 85,000 tests (Crossley et al., 2005). "These emergency efforts are a real opportunity to develop some new knowledge," Ardans said. "They are unique in what they will give us, and it's a rare opportunity to improve the diagnostics. [How else] would you get a chance to validate an assay using 85,000 samples?"

Such situations, Ardans observed, also highlight the importance of meeting diagnostic needs with appropriate technologies. In pursuing the source of *E. coli* O157:H7 in a recent outbreak in spinach, laboratory researchers discovered that the use of a gauze swab to sample irrigation waters for contaminants performed better than newer concentration technologies. (As previously noted, surveillance for infectious plant diseases depends largely on available methods of disease detection and diagnosis; see also Chapter 1.)

The Road Ahead: Diagnostics in Development

Inspired in part by the image of the original Star Trek's character "Bones"® diagnosing a patient with a wave of his medical tricorder (Figure SA-7), Wolcott and fellow DoD researchers are attempting to construct an "integrated diagnostic system" for field use that can detect viruses, bacteria, toxins, "and anything else that could possibly be thrown at us in the biological detection arena," he said. The current prototype relies on automated real-time PCR, but DoD researchers are testing a wide range of diagnostic technologies (e.g., microarrays, handheld immunoassays, electrochemiluminescence) and targets (e.g., microbial toxins, as well as nucleic acids), according to Wolcott. "We have to have multiple platforms to give us the assurance that what we are reporting up the chain of command is actually there," he said. The ultimate goal is to combine multiple platforms into a single, universal system for field diagnosis. While the time constraints and primitive conditions of battle present significant barriers to the use of microarrays, Wolcott speculated that chip technology eventually would be adapted to provide point-of-care diagnosis for soldiers in action.

FIGURE SA-7 Star Trek medical tricorder.[16]
SOURCE: Printed with permission from CBS Paramount.

[16]The medical tricorder was a palm-sized, handheld, device used by doctors in the Star Trek universe of the 23rd and 24th centuries to help diagnose diseases and collect bodily information about a patient. The device scanned a living patient, interpreted and displayed the data obtained from the scan to the user, and recorded the data to isolinear chips (Wikipedia contributors, 2007).

Following a similar technological progression from PCR to microarrays, the Pandora's Box Project, based at Columbia University's Greene Infectious Disease Laboratory, employs a staged strategy for molecular pathogen surveillance and discovery (see Lipkin and Briese in Chapter 3) (Palacios et al., 2007). As described by speaker and Greene Laboratory director W. Ian Lipkin, the first stage consists of MassTag PCR, a technique that attaches reporter "tags" of distinct masses to the amplified sequences, permitting the simultaneous, highly sensitive detection of more than 20 different pathogens. This platform, which is both inexpensive (at approximately $10 per 20-plex assay) and rapid, has been used to distinguish among various viral hemorrhagic fevers, Lipkin said; it is currently being adapted for the diagnosis of gastroenteritis. MassTag PCR has also enabled the recent discovery of a virus responsible for a significant proportion of flu-like respiratory disease (Lamson et al., 2006).

A second stage of diagnosis becomes necessary when the first stage fails, or when a larger number of sequences must be screened, Lipkin continued. For this purpose, the researchers first designed a pair of extensive microarrays, called GreeneChips, for viruses and other respiratory pathogens, and then a panmicrobial array that incorporates more than 29,000 60-mer probes from filamentous fungi and yeasts, and parasites, as well as from viruses and bacteria that infect vertebrates (Palacios et al., 2007). Together, these arrays comprise a system for assaying nucleic acids extracted from clinical samples (e.g., nasopharyngeal aspirates, blood, urine) or cell culture. If the less expensive ($100 per assay) respiratory or viral arrays fail to detect a pathogen, he explained, "then we go to progressively more comprehensive chips that top out at approximately $350."

"These are surveillance tools," Lipkin said of both MassTag PCR and GreeneChips. "All they do is give you a plus/minus, presence-or-absence, sort of an answer, if they give you an answer at all. You ultimately have to come back to surveillance assays [such as] quantitation, with real-time PCR, [and] you have to do serology." More importantly, he observed, because diagnosis requires the integration of various test results with other information, such as epidemiological data, the GreeneChip "is never really going to replace a seasoned, thoughtful clinician."

Lipkin also noted that, despite the obvious advantages of multiplexed detection (and in anticipation of less expensive versions of microarrays), the widespread adoption of microarrays for disease detection would require a revision in regulatory standards based on the more sensitive single-agent model. "The gold standard, invariably, is single-agent [detection] with an identical match between template and probe as opposed to multiplex systems, which tolerate sequence divergence," he explained. The need to obtain intellectual property licenses for each of potentially thousands of sequences restricts the development of array-based diagnostics, Lipkin added. However, both regulatory and intellectual property barriers could be minimized by constructing multiplex assays of 20 or so carefully chosen sequences, according to Forum member Patrick Fitch,

of Battelle Memorial Institute. "Defining the problem space goes a long way to getting optimization of the assay you want," he concluded.

GreeneChips are tools for discovery, as well as for diagnosis. Because as many as 100 different regions of a genome may be represented on the chip, assays reveal enough sequence information to enable the rapid sequencing of novel pathogens, several of which have been characterized. Analyses of GreenChip data have led to the identification of a novel target for antiviral drugs, which Lipkin described as an "on/off switch in the human immune system." He predicted that broad, unbiased pathogen-detection methods will continue to provoke unanticipated discoveries and enable researchers to explore the apparent link between infectious and chronic diseases.

The Far Horizon: Presymptomatic Diagnosis

Imagining a future in which bioterrorism agents are continually reengineered to evade standard detection and diagnostic methods, as well as therapeutics, speaker and Forum member Stephen Johnston proposed a model of diagnosis for exposure to a pathogen prior to the appearance of symptoms (see Johnston in Chapter 3). In this situation, he argued, specific defenses against threat agents (e.g., vaccines) will be useless. Instead, he envisions the creation of platforms for defense against the full range of potential bioweapons, such as the means to recognize and respond to the earliest possible signs of infectious disease in individual patients. Host-based, presymptomatic diagnosis could be accomplished by monitoring a person's blood serum chemistry for changes suggestive of compromised health status, Johnston explained; he is currently involved in developing a device to perform such analyses. He noted that the noninvasive sampling of breath and saliva is attractive in theory, but that neither of these sources offered the diversity or concentration of metabolic components found in blood.

Monitoring the biological signatures of infectious disease will require making thousands to millions of simultaneous measurements and comparing them to well-established baselines, Johnston said. Ideally, this would occur through a continuous process. Therefore the monitoring device would need to be easily accessible (e.g., in the home), robust, inexpensive, and capable of quickly measuring thousands of variables—specifications that also apply to point-of-care devices for low-resource settings. Because the symptoms of respiratory viruses appear in as little as one day, Johnston hypothesized that presymptomatic detection would need to register changes in the nanomolar-to-picomolar range and would require clear baselines and the integration of multiple measurements to avoid an unacceptable level of false positives. In response, Forum member David Relman of Stanford University referred to an article by Kohane and colleagues (2006), who describe substantive risks inherent in the practice of personalized, genomic medicine, among them the imprudence of using "testing panels comprising a sizeable fraction of the genome for clinical care or screening" (Kohane et

al., 2006). Johnston acknowledged that scant evidence—most of it derived from early postinfection transcription patterns—suggests such measurements could actually anticipate the development of respiratory symptoms. He attributed this dearth of supporting data to the lack of funding for research in this area and to the yet-unsolved problem of what, exactly, to measure, and how. Johnston and coworkers are currently attempting to develop synthetic antibody techniques for monitoring infection-related changes in protein levels.

In addition to offering the best chance of treatment for known, emerging, or bioengineered pathogens, detecting infectious disease at the earliest possible moment would permit diagnosis-based triage and increase the effectiveness of quarantine or other social distancing measures, Johnston predicted. He anticipated that presymptomatic diagnosis will have an even greater impact on everyday medical care. "We have a healthcare system that can't be sustained in terms of physical economy," he said, adding that care for ill patients accounts for nearly 90 percent of health-care spending. "Why does it cost so much? Because we are diagnosing sick people, taking care of sick people; we even develop our drugs for sick people." Therefore, he insisted, our society has no choice but to move from postsymptomatic to presymptomatic diagnosis.

Considerations for Detection and Diagnosis

Given the considerable interdependence of surveillance, detection, and diagnostic activities as they relate to infectious disease, it is not surprising that key challenges identified by workshop participants in their discussions of surveillance strategies would resurface as they explored current and future prospects for disease detection and diagnosis. Once again, participants stressed the importance of selecting and acquiring clinically relevant samples or specimens, the establishment of said relevance against a background of natural variation, and the need for standards to guide system design and evaluation.

Workshop participants also considered the status of infectious disease diagnostics, which they characterized as a largely unsupported area within the crowded field of medical diagnostics. Fitch observed that pharmaceutical companies tend to develop relatively low-margin diagnostic tests only when they can be linked to highly profitable therapeutics (e.g., for cardiac disease and cancer). Nevertheless, participants urged that the vast experience of commercial producers of medical diagnostics be brought to bear on public efforts to develop applications for infectious diseases. For example, Relman suggested that industry could participate in efforts to identify and evaluate common principles and platforms for sample processing, signal generation and detection, and data analysis. However, he added, these considerations are contingent on a more fundamental set of yet-to-be-determined specifications for any surveillance or detection program: the exact set of questions to be answered and the appropriate setting in which to ask them.

The Challenge of Coordination

Workshop participants, having considered a broad range of tools and strategies for infectious disease surveillance, detection, and diagnosis, turned to the difficult issue of effectively combining them. Hueston, director of the University of Minnesota's Center for Animal Health and Food Safety, launched this discussion with his presentation on the coordination of disease surveillance, detection, diagnostics, and reporting. This topic is a frequent focus of Hueston's work, which emphasizes risk communication and the facilitation of public–private partnerships (see Chapter 4).

Shifting the Public Health Paradigm

Certain powerful concepts and conditions that influence the practice of public health inhibit the coordination of infectious disease surveillance, detection, and diagnosis, according to Hueston. Table SA-2 summarizes these elements of the current public health paradigm, as defined by Hueston, and pairs them with his proposed alternatives.

Hueston identified several factors driving the current paradigm that specifically undermine public health coordination. Chief among them is high health

TABLE SA-2 Current Public Health Paradigm and Alternative World View

Current Paradigm	Alternative World View
Health focus is individual; benefits accrue primarily to the developed world	Health focus is global society; benefits accrue to all
Health is absence of disease	Health is well-being (in mind, body, spirit)
Infectious disease is all about the agent	Infectious disease emerges at the convergence of agent, host, environment
Zero risk is achievable	Zero risk is unachievable; risk management is the goal
Success is eradication/cure	Success is homeostasis with microbes that are ubiquitous, constantly evolving, and adapting
Public health function is to react	Public health function is health promotion
Reaction requires agent detection	Risk management can be successful whether or not microbe is identified
Urgency dictates priority	Surveillance informs policy and guides action on basis of importance
Answers lie solely in technology	Answers involve people, politics, partners

SOURCE: Hueston (2006).

status in the United States, which reinforces the tendency of public health to focus on the urgent (i.e., the disease or agent du jour) rather than the important (i.e., emergency preparedness); this situation is exacerbated by a budget process that takes money from "important" programs to fund "urgent" ones. Parochialism influences our sense of urgency, he observed, causing us "to focus on those things about which we are most interested in the United States as opposed to looking at the true [global] public health priorities." Hueston added that assigning blame for public health threats—and especially the tendency to "shoot the messengers" who identify them—suppresses essential collaboration in surveillance. For example, before the United States adopted a policy of "zero tolerance" for food contamination, companies monitored for more pathogens and kept records of their findings, a practice that supported scientific evaluation of the impact of new intervention strategies. Now, he said, "if they monitor and get positive reports, they are culpable and have self-incriminated, so they stopped monitoring."

Coordinating the spectrum of public health activities associated with disease surveillance and detection is an inherently political task, and therefore strongly influenced by societal and organizational culture, Hueston asserted. "To be effective in politics over the long term and to build coordination and collaboration requires people skills," he observed, and yet increasingly in educational fields relevant to public health, considerations of interpersonal and executive skills are largely ignored under the misguided assumption that science and technology can replace them. Rather, as Korch noted in the ensuing discussion, in a risk management model of public health, understanding and responding to specific social contexts is crucial to effective risk reduction and communication.

There is no "magic bullet to change paradigms," Hueston stated, stressing that steady progress can be made through small successes. This progress, albeit slow, needs to be properly recognized and celebrated. Because the most effective engine for change is educating the next generation of leaders early in their careers, he urged educators to encourage greater global and transdisciplinary awareness in future public health professionals.

Optimal Surveillance for Risk Management

Clearing the way for true coordination and collaboration would enable optimal surveillance, as Hueston defined it: an integrated and dynamic system with ongoing data collection and real-time analysis to inform risk management, and thereby drive policy and action, with a feedback process to facilitate continuous evolution and adaptation. Information would be drawn from a broad range of disciplines relevant to physical and mental health, as well as domestic and wild animal health and plant health, through the complementary processes of agent surveillance and host and environmental monitoring.

In the discussion that followed his presentation, Hueston noted the potential economic benefits of surveillance systems for both developing and industrial-

ized countries, but also warned that too much openness could undermine such systems. "If our goal is to promote public health, and surveillance precipitates action to control the disease, do we always have to make the information public?" he wondered aloud. Forum member Johnston responded emphatically that such secrecy "has only gotten us in trouble, that it is elitist and that it is only going to come back and bite us in the long run. If we want to foster a further schism between the public and the scientific community, the best thing we can do for that is to withhold information." Hueston responded that he agreed with Johnston's position in principle, but insisted that under some circumstances, the unintended consequences of publicizing information outweighs the potential benefits, such as sharing of animal disease surveillance data in wildlife that precipitates unwarranted trade restrictions on commercially produced products. He concluded that the release of surveillance information should be evaluated on a case-by-case basis. Forum member Margaret Hamburg noted that timing is crucial to such communication and observed that public health officials "get into trouble if we provide information before we fully understand it and before we understand how we are going to respond."

Because the definition of risk is individual and fueled by emotion, public health professionals must address the *perception* of risk, Hueston explained. Trust is not built merely by sharing data, but by helping people understand information by providing it in context, he said. But, he continued, this is only the first stage. The public must then be actively engaged to discuss their perception of risk and identify priorities for action.

Needs and Opportunities

This section recounts needs and opportunities for both research and policy derived from workshop discussions on infectious disease surveillance, detection, and diagnosis. Participants, including members of a concluding discussion panel (see Chapter 4 overview), identified a series of issues critical to the development and implementation of effective methods and strategies for the detection of infectious disease and described key challenges in responding to increasingly early disease alerts.

Critical Issues in Infectious Disease Surveillance and Detection

The following areas were the subject of extended discussion with reference to both surveillance and detection.

System Design and Development

Hueston captured a recurring theme in this workshop's discussion when he quoted management guru Stephen Covey's advice to "begin with the end in

mind" (Covey, 1989). As previously noted, many decried the evolution of surveillance and detection systems based on available technologies and databases, rather than in response to well-defined public health needs. Participants suggested the following actions to improve the design and development of surveillance and detection systems:

- Develop a common design lexicon to improve communication and collaboration between public health practitioners and information technologists.
- Devise methods to analyze surveillance data through time in order to understand factors and mechanisms that underlie apparent trends.
- Create syndromic surveillance systems that can adapt to signals as they are received so that an increase in symptom prevalence prompts intensified testing.
- Broaden the purview of surveillance to encompass social circumstances that affect public health.
- Incorporate mechanisms to filter surveillance data to reduce false-positive (and panic-inducing) alarms.
- Recognize and incorporate promising surveillance concepts from noninfectious disease applications.
- Support basic research in disease surveillance, especially among plant and animal populations.
- Develop incentives to promote the development of infectious disease diagnostics and to integrate academic and commercial efforts toward this goal.
- Consider models of infectious disease beyond the replication of viruses or bacteria within organ systems. These would include toxin-producing microbes (e.g., *Clostridium botulinum*) and pathogens that affect the immune system or immune responses (including delayed or chronic effects, such as those associated with hepatitis C and human immunodeficiency virus [HIV]).
- Do not overlook longstanding and effective elements of disease detection: pathology, microbiology, and of course, the astute clinician.

System Evaluation

Workshop participants encouraged critical analysis, comparison, and evaluation of the performance of existing surveillance and detection systems, and in particular, of the U.S. BioSense (syndromic surveillance) and BioWatch (specific threat detection) programs. Their suggestions include the following:

- Identify the essential components of a global infectious disease surveillance system in order to prioritize funding.
- Support operational research to evaluate and optimize informatic systems for processing epidemiological data, particularly when used in syndromic surveillance.

- Develop methods to analyze and compare cost-effectiveness of surveillance and detection systems.
- Design mechanisms for continuous feedback and improvement into surveillance and detection systems.
- Reconsider the role of syndromic surveillance in disease control, given the lack of evidence for its effectiveness in early detection of biological attacks and its promise for tracking large-scale, natural disease outbreaks such as H5N1 avian influenza.

Integration of Information

Workshop participants also stressed the importance of integrating information on infectious diseases from diverse sources and methods to obtain a comprehensive view of disease risk and severity. In particular, they encouraged the development of mechanisms to connect local sources of surveillance data (including information on animal infections, insect vector distributions, climate, and vegetation) with global surveillance networks.

Information Transparency, Control, and Access

As noted in the previous section, workshop participants expressed divergent opinions concerning the risks and benefits associated with the public disclosure of surveillance findings. Most participants acknowledged a need to balance transparency—a foundation of both public and international trust—against the potential consequences associated with public misinterpretation and overreaction. Several participants urged consideration of political and economic factors, as well as timing (i.e., releasing surveillance information by public health authorities only after it is fully understood and a response is planned or underway), in making such decisions.

Reporting

Recognizing that the reporting of unusual findings by health practitioners (and subsequently by governments) is essential to infectious disease surveillance and detection, workshop participants considered a range of incentives to promote the affirmative reporting of human, animal, and plant health status at all levels, including the following:

- Develop and broadly implement standards for infectious disease reporting and sample submission to public health laboratories.
- Pay clinicians, especially those in developing countries, to report findings to national public health authorities.

- Ensure the confidentiality of health practitioners who report infectious disease, while recognizing their contribution to public health. In the case of agricultural diseases, provide financial support for farmers who report disease and guard intellectual property rights of seed companies who assist in identifying vulnerable germplasm.

Participants also suggested a variety of mechanisms and tools to improve the collection and use of reported information, as follows:

- Fund the procurement, storage, submission, and diagnostic testing of clinical and animal specimens from a broad spectrum of private and public sources.
- Encourage data collection to support the characterization of natural variation and define baseline health status; reward the reporting of negative data. WHO's Health Metrics Network, a global partnership to build capacity and expertise to provide better health information to decision makers at all levels, represents a potential source of baseline data.[17]
- Support the development of global surveillance and laboratory capacity as mandated by recent revisions to the IHRs. Some suggested that this could be accomplished through increased funding to WHO; others argued that WHO must first be reformed and strengthened; others questioned whether a new intergovernmental entity would need to be invented to achieve the goals set by the IHRs.
- Support parallel efforts by OIE, NATO, USDA, and the European Union to develop global surveillance capacity for animal and plant diseases.

From Alarm to Action

In the spirit of beginning with the end in mind, workshop participants also considered the fate of information derived from infectious disease surveillance and detection systems. Several participants observed that U.S. government investment in the detection of biological threats far outstrips its ability to respond to such crises. Some decried the shortsightedness of creating global surveillance networks for infectious disease without also providing for disease control and containment, as well as for public preparedness and risk communication. As Kelley acknowledged, far more than science will be required to help affected communities accept the uncertainty that characterizes the course of an infectious disease emergency and the ensuing public health response.

[17]See http://www.who.int/healthmetrics/about/whatishmn/en/print.html.

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1

Surveillance Strategies

OVERVIEW

This chapter includes workshop presentations that illustrate a variety of goals, approaches, and methodologies for disease surveillance in humans, animals, and plants. As noted in the chapter's first paper by keynote speaker Patrick Kelley, director of the Institute of Medicine's Board on Global Health, current concepts of public health surveillance, inspired by approaches to military intelligence data gathering, originated in the 1950s. Today, traditional surveillance practices of disease reporting (by physicians, veterinarians, infection control practitioners, laboratorians, and medical examiners), followed by epidemiological and laboratory investigation, constitute the mainstay of local infectious disease surveillance where such expensive methods are feasible (mainly in developed countries). However, a range of nontraditional strategies including syndromic surveillance (the topic of Kelley's paper, and another in this chapter by Michael Stoto) and electronic surveillance (the subject of Chapter 2), may prove well suited to settings where clinicians, laboratories, and hospitals are in short supply.

Local Surveillance: New York City

Although New York City's size, diversity, and significance to international transportation create considerable opportunities for infectious outbreaks, local approaches to surveillance resemble those of many communities around the world, according to presenter Marci Layton of the New York City Department of Health and Mental Hygiene (DOHMH). New York health codes mandate disease reporting for more than 70 infectious diseases, ranging from common

pathogens such as *Salmonella* to the potentially disastrous, such as smallpox and anthrax. The health department receives reports by traditional phone, mail, and fax and—following a significant recent investment—by electronic and web-based methods as well. Participation in an electronic clinical laboratory reporting system, a secure network that allows DOHMH to receive laboratory-confirmed diagnoses in a timely manner, is mandated for all laboratories that diagnose New York City residents. This system enables DOHMH to spot citywide and neighborhood disease trends in routinely reported data that an individual physician would not be able to recognize, Layton said.

Upon receiving a report, DOHMH initiates an investigation to examine risk factors for infection in order to determine disease transmission routes, and, if appropriate, to arrange prophylaxis. "The most important thing we try to do is to make sure that every health care provider knows who and how to call to make a report," Layton said.

In the event of an apparent or actual public health emergency, New York City's health alert system quickly disseminates information to providers on the nature of the emergency and instructions on preparing and delivering diagnostic specimens. Because New York City is at high risk for receiving imported disease, DOHMH stays attuned to global infectious disease issues via surveillance networks such as ProMED-mail (see Morse in Chapter 2) and responds to reports of significant disease activity abroad by ramping up surveillance and alerting health-care providers in New York City to look for signs of an outbreak. After an outbreak of West Nile virus in 1999, and in light of increasing concern regarding the potential use of zoonotic diseases as bioterrorism agents, animal diseases were made reportable in New York City in 2000.

DOHMH has invested considerable hospital-preparedness funding to improve the ability of triage systems to recognize patients with significant risk factors for infectious disease, particularly patients with fever and respiratory illness who have traveled recently. This is crucial because, in Layton's words, "New York City could be the next Toronto, with an unrecognized imported outbreak of severe acute respiratory syndrome (SARS)—or of bioterrorism, *E. coli*, or most worrisome of all, avian influenza."

The realization that many unreported, hospitalized cases of viral encephalitis (a reportable disease) manifested during the West Nile virus outbreak caused DOHMH to adopt procedures to monitor similar nonspecific clinical syndromes. In 1998, the city began syndromic surveillance based on ambulance dispatch data; the system was expanded to monitor the entire emergency department in the wake of the 2001 World Trade Center attack, then further to monitor pharmacy sales, employee health, school absenteeism, and primary care visits. One of the most challenging aspects of responding to a syndromic signal is getting specimens to a lab for diagnostic testing, Layton observed, particularly specimens from the acutely ill patients typically seen in emergency departments. Rapid diagnostic testing is performed for a variety of pathogens at a single New

York City hospital, but only limited information is obtained from this proof-of-concept project.

To better balance time spent investigating syndromic surveillance signals versus outbreaks detected through traditional means, DOHMH is developing a protocol to reduce time wasted on false positives while ensuring the prompt investigation of real outbreaks. Syndromic surveillance systems have proven to be most useful for monitoring citywide seasonal outbreaks of infectious diseases (e.g., norovirus, influenza, respiratory syncytial virus [RSV]), Layton said, and less useful for detecting localized outbreaks.

"In my view, syndromic surveillance will never replace traditional surveillance, which is where most surveillance resources should continue to be invested," she concluded. "The real public health challenge lies in creating the necessary infrastructure to analyze surveillance data, set priorities, and conduct investigations. I am concerned that increased investment in syndromic surveillance may occur at the expense of state and local public health infrastructure. More generally, if current funding patterns continue, whereby national programs addressing emerging infections and bioterrorism receive more and public health at the state and local levels receive less, our ability to make use of surveillance information will suffer."

Toward Earlier Warning

Through the use of prediagnostic data, syndromic surveillance aims to provide timelier identification of disease outbreaks than can be attained through traditional surveillance methods, Kelley writes. After reviewing the theoretical underpinnings and historical development of syndromic surveillance, he discusses its potential applications in developing countries and its promise as a vehicle for achieving global disease surveillance as mandated in recent revisions of the International Health Regulations (IHRs). Unfortunately, "hasty, opportunistic implementations of syndromic surveillance," including some U.S. projects, "have not allowed the theoretical power of the method a fair test," he observes. In their stead, Kelley advocates the creation of surveillance systems, including syndromic components, designed to answer clear and specific questions. He also considers how syndromic surveillance could be applied to detect serious but low-frequency threats such as bioterror attacks, SARS, or avian influenza in time to contain their further spread.

Following Kelley's paper, with its focus on the design of syndromic surveillance systems, Stoto's essay considers their evaluation. He defines and applies a framework for gauging the usefulness of syndromic surveillance in public health practice, then uses it to identify a number of statistical and practical challenges to using such surveillance for detecting bioterrorist events. By contrast, he finds promise in using syndromic surveillance to detect natural disease outbreaks (including seasonal and pandemic influenza), and in monitoring public health

response to disease outbreaks. Realizing this potential will require designing systems that focus on these uses rather than being optimized for timely detection of large-scale bioterrorist attacks, Stoto concludes.

The next paper, by Joseph Lombardo of the Johns Hopkins Applied Physics Laboratory, addresses another aspect of timeliness in surveillance: the implications of "real-time" versus "batch reporting" of surveillance information. Noting that confusion has arisen around the use of these terms, Lombardo carefully defines them and provides illustrative examples. He concludes by describing the possible combination of both modes in surveillance systems that use efficient "batched" surveillance processes for the routine monitoring of public health, and more resource-intensive "real-time" processes to examine specific threats as they arise.

Surveillance of Animal and Plant Diseases

Recognizing that "the health of people, animals, plants, and the environment in which we all live are inextricably linked," in the words of workshop presenter William Karesh, surveillance must encompass far more than human diseases. Karesh's contribution to this chapter describes initial efforts toward this goal, focusing on projects undertaken by his own organization, the Wildlife Conservation Society (WCS). He describes the threat spectrum, origins, risk factors, and consequences of infectious disease in wild animals, and he observes that "the immediate effects of the diseases themselves are often the least of the worries. Infectious diseases of people and animals are drivers of poverty and associated civil unrest, disrupt 'free' ecosystem services such as drinking water and plant pollination, and can ruin otherwise well-planned and sustainable economic development efforts."

In two papers that conclude the chapter, plant pathologists Jacqueline Fletcher of Oklahoma State University and James Stack of Kansas State University define threats (both natural and intentional) to U.S. crops and provide examples of high-consequence plant diseases. The first paper outlines components of a strong plant biosecurity strategy, discusses progress toward its achievement, and notes opportunities for further improvement. In the second paper, the authors evaluate each component of the biosecurity strategy (prevention, surveillance, detection, diagnosis, response, and recovery) and suggest specific actions the United States could take to support each area.

SYNDROMIC SURVEILLANCE: MOVING FROM THEORY TO PRACTICE

Patrick W. Kelley, M.D., Dr.P.H.[1]
The National Academies

Assessing the health of a community has similarities to assessing the health of a person. A variety of detectors of ill health can be brought to bear in ways that range from passive monitoring that depends on those affected to raise a concern to active and aggressive monitoring of those apparently without complaint to identify the earliest manifestations of a problem. The desire for earlier detection of acute health problems at either the individual or community level has in recent years stimulated the search for better "detector" mechanisms. Syndromic surveillance is one of these now in vogue as a solution to the growing challenge of early disease detection in communities and management of consequent public health interventions.

Though infectious disease reporting started in Europe and the United States in the late 1800s, it was not until 1925 that all U.S. states participated in national morbidity reporting. Only after Alex Langmuir went to the Centers for Disease Control and Prevention (CDC) in 1950 did the term "surveillance" become conceptualized beyond the monitoring contacts of persons with contagious diseases. At CDC Langmuir developed a concept of surveillance inspired by military intelligence data gathering and incorporated the approach into daily public health practice. Soon CDC had national systems for malaria, polio, and influenza. In more recent times, advances in laboratory and mathematical methods and technologies have pushed horizons farther and stretched academic definitions. These cutting-edge approaches to disease detection at the community level encompass networks for surveillance using molecular fingerprinting and exciting, web-based methods of information capture and assessment such as the Program for Monitoring Emerging Diseases (ProMED) and the Canadian-World Health Organization (WHO) Global Public Health Intelligence Network (GPHIN). In this more demanding context, we now have the evolution of automated syndromic surveillance.

The elaboration of more sophisticated approaches to surveillance has been stimulated by the recognition over the past 30 years of at least 30 "new" emerging infectious diseases. These encompass infections of plants, animals, and human beings. Of course, an acute concern is the threat of bioterrorism but many naturally occurring emerging disease outbreaks have highlighted the need for rapid detection and characterization. Perhaps the greatest concern now is the need to promptly recognize the syndromic pattern of an H5N1 influenza outbreak, here

[1]Director, Board on Global Health and Director, Board on African Science Academy Development, Institute of Medicine.

or in remote parts of Asia or Africa, so that aggressive attempts to eliminate it can be instituted before it becomes uncontainable. Similar urgency arose during the 2003 severe acute respiratory syndrome (SARS) epidemic. For some of these emerging infections, it was months before an agent was isolated, and thus timely and sensitive public health surveillance and response was syndromic to a great degree. The tragedies of HIV in Africa and the slow recognition of SARS in China are reminders of the consequences of slow responses and motivate the question of what surveillance system designs could have made a difference. With bioterrorism a rapid assessment and response is even more critical.

"Syndromic surveillance" is defined by CDC as the collection and analysis of "health-related data that precede diagnosis and signal with sufficient probability of a case or an outbreak to warrant further public health response" (CDC, 2006a). This differs from more traditional surveillance in several ways but primarily the objective is that by using prediagnostic data, syndromic surveillance aims to be *timelier* in identifying emerging problems. The phenomena of emerging infections and all the associated aspects of globalization that accompany them, as well as the specter of bioterrorism, drive the need to be more cognizant of public health events and to act despite limited information. Timeliness is not the only advantage of the method, though. An additional goal is that syndromic surveillance should be more sensitive at detecting aberrations in normal patterns because it does not depend on confirmed diagnoses, something that can be an expensive proposition, especially in developing countries.

Some advocates have great enthusiasm for transitioning syndromic surveillance from the epidemiologic laboratory into routine practice, but others are skeptical, preferring to put their confidence in traditional approaches and the "astute clinicians" who have risen to the occasion so often in this country. Unfortunately, while developed countries have a fair number of clinicians who are astute at least much of the time, the developing world, where so many disease problems emerge, is a different case. A system of complementary systems—including clinicians, traditional methods, and well-designed syndromic surveillance tailored to the setting of a particular community—may ultimately yield the wide range of perspectives needed to meet the demanding public health challenges of emerging infections and globalization. The best mix of surveillance interventions will vary from community to community. A challenge now is to do the operations research to adapt academic surveillance concepts to unique community circumstances. This is important not only in communities with strong health systems, but also in developing countries, where nontraditional approaches may be more essential and affordable than in places with a relative abundance of astute clinicians, laboratories, and hospitals, such as the United States.

Some observers seem frustrated by syndromic surveillance because it has detected few outbreaks, as implemented in the United States over the past few years. Many doubt that it will perform better than alternative mechanisms to alert the public health community to a problem. Perhaps though hasty, opportunistic

implementations of syndromic surveillance have not allowed the theoretical power of the method a fair test. Also, the purposes of syndromic surveillance go beyond earlier detection and provide situational awareness across a community, something that individual clinicians can rarely provide. Though other mechanisms, to include astute clinicians, may help recognize a problem, an effective surveillance system, syndromic or otherwise, should also rapidly characterize a problem epidemiologically because this is essential to efficiently target what are invariably limited response assets. A system should enable civic leaders to establish the boundaries of the problem and allay some unjustified fears through more credible risk communication.

In tabletop exercises of public health crises, the value of information for management has been highlighted both as being in short supply and as being something that a properly constructed syndromic surveillance system should help develop. In one important biodefense tabletop simulation exercise, "Dark Winter," Frank Keating, former governor of Oklahoma, said:

> You can't respond and make decisions unless you have the crispest, most current, and best information. And that's what strikes me as a civil leader . . . that is . . . clearly missing (O'Toole et al., 2002).

Central to effective surveillance is beginning with a clear appreciation for the capabilities sought. Precisely what phenomena need detection, in precisely what populations is the detection needed, and what data would be most effective for that purpose? Much work has been accomplished in developing syndromic definitions and analytic algorithms but before syndromic surveillance is seen as the solution, the full range of scenarios that need to be detected must be considered as well as how best to build epidemiologic "detectors" for demographically different communities in both rich and poor countries.

Although in the United States there is a tendency to associate syndromic surveillance with the specter of bioterrorism, WHO has come to recognize that the protection of global health against emerging infections was poorly served by the last version of the International Health Regulations (IHRs), which mandated reporting to WHO *only* three specific diseases: yellow fever, plague, and cholera. Realizing that some of the most critical recent global public health threats—such as AIDS, SARS, Ebola, pandemic influenza, and Nipah virus—initially were ill-defined syndromes, a new version of the IHRs has been adopted by member states and is set to go into effect in 2007. This document calls on countries to maintain, at the local level, capabilities to detect and assess *not only* well-defined diseases and established causes of death, but also to report *any* significant levels of morbidity of potential international public health importance. So, the mandate for general global public health surveillance is moving beyond defined diseases to encompassing a global responsibility to detect and report, in a timely manner, internationally important disease events whether they are well or ill defined and

whether they are individual cases or clusters. A capability for syndromic detection seems central to the new paradigm, especially in countries that lack the resources for extensive use of more specific approaches.

Although the term "syndromic surveillance" has only been in vogue for about a decade and is thought to represent somewhat of a frontier in surveillance, the potential contributions of "prediagnostic surveillance" have been long established. In tracking down the last cases of smallpox and polio in developing countries, syndromic monitoring has been central. For decades, the military has also used syndromic approaches to monitor unit health on deployments and in training because it was the most cost-effective, rapid, and reliable way to monitor the health of the force, especially in austere conditions. The military often operates in settings with limited laboratory support, but with a critical need to detect health threats in a timely manner. For example, Figure 1-1 illustrates the tracking of diarrheal syndromes in a U.S. Marine force during the first Gulf War of 1990–1991. With regular syndromic tracking of morbidity seen in sick call, outbreaks were routinely recognized quickly by competent epidemiologists against normal background rates. Investigations were launched rapidly to contain problems that could debilitate unit combat effectiveness.

In U.S. military basic training camps, where respiratory syndromes are particularly devastating, for decades there has been well-developed, centrally monitored syndromic surveillance for acute respiratory syndromes (Gray, 2005; Gunzenhauser, 2003). Syndromic surveillance in the basic training setting has been used routinely to guide the use of mass antibiotic prophylaxis to prevent outbreaks of rheumatic fever when syndromically associated thresholds are crossed.

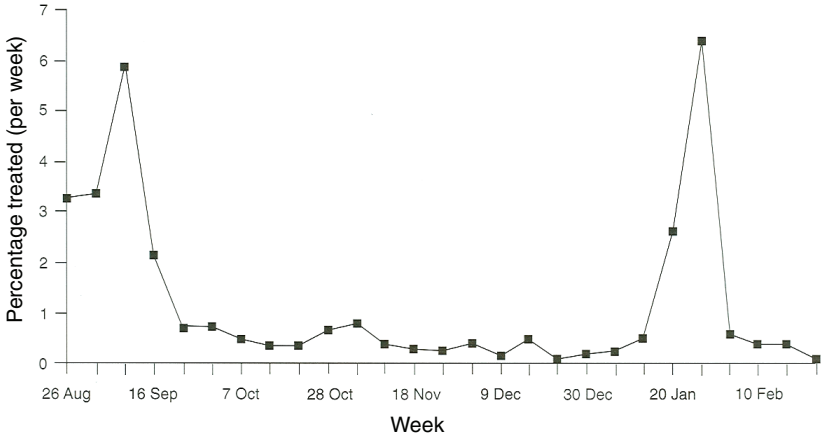

FIGURE 1-1 Syndromic surveillance of U.S. marines for treated diarrheal syndromes during the lead-up to the Persian Gulf War, 1990–1991.
SOURCE: Hanson (2005).

All of these practical implementations of syndromic surveillance reflect movement from theory and simple systems to complex systems. Moving from theory to practice involves a larger context where pieces must be made to work together and adapted to the locality.

Reflecting all the elements to be integrated, one might define a surveillance *system*, as distinct from surveillance, as follows:

> A system for public health surveillance is a group of integrated and quality-assured, cost-effective, and legally and professionally acceptable processes, designed for the purpose of identifying in an ongoing, flexible, standardized, timely, simple, sensitive, and predictive manner the emergence of meaningful epidemiologic phenomena and their specific associations. These processes include human, laboratory, and informatics activities to skillfully manage information derived from an entire defined community (or a subgroup thereof that is sufficiently representative and large) and to disseminate that information in a timely and useful manner to those able to implement appropriate public health interventions.

As shown in Figure 1-2, a surveillance system needs to be seen in the context in which it works and as reflecting a hierarchy of elements that depend on each other. One needs a clear and specific idea of what questions the system should address. Who should be under surveillance and for what are most critical. Developers of syndromic surveillance systems often start to conceptualize

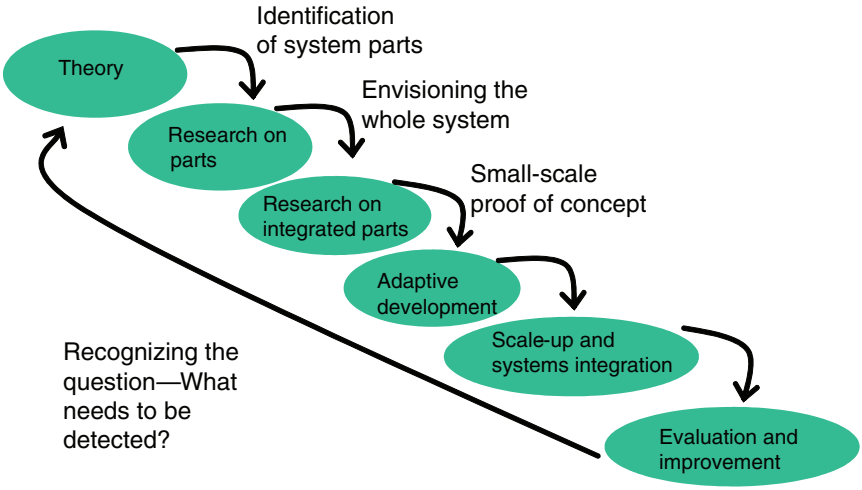

FIGURE 1-2 Conceptual steps in development and implementation of a syndromic surveillance system in a community.
SOURCE: Kelley (2006).

a system with opportunistically available data rather than a clear definition of the range of scenarios that their surveillance system must be able to recognize as priorities. Typical "opportunistic" data might be routinely collected for other purposes during an emergency room consultation or from "convenient" sources such as government clinics regardless of how well they sample the community of interest. Opportunistic datasets are rarely the strongest cornerstone on which to build and can handicap an otherwise rigorous implementation.

Different epidemiologic scenarios will affect populations in different ways. Key though is that if one wants to detect any epidemiologic scenario, the population under surveillance should include the one likely affected. If space and time separate these populations, as may be the case with the most easily available "opportunistic" datasets, little signal will be generated. If demographic misclassification affects the description with respect to person, place, and time, associations may be missed. If one lets the surveillance question drive the development of the database used, there is a better chance that the population under surveillance will generate a strong signal because it will include a substantial fraction of those exposed. Resources should be invested into negotiating for and developing data with the richest "veins of ore" rather than focusing it proportionately on the mining of poorly conceived data sources with ever more complex analytic methods. An example of this became obvious in looking at convenient outpatient data in the Department of Defense (DoD) Electronic Surveillance System for the Early Notification of Community-based Epidemics (ESSENCE), developed in the late 1990s for use for surveillance in the National Capital Region.

Like syndromic surveillance systems, the datasets initially available to ESSENCE routinely classified patients experiencing morbidity by the ZIP code of residence. The problem is that one could reasonably assume that most exposures, natural or manmade, would occur away from home in places such as the Pentagon, the Capitol, a sports venue, or the subway. As became evident in a geographic analysis, the bulk of military health-care beneficiaries tracked through ESSENCE did not live where many exposures would most likely occur, in the District of Columbia, but rather had homes scattered over a hundred ZIP codes throughout the region. This residence-based misclassification, stemming from the use of "opportunistic data" easily at hand, would have greatly diluted syndromic signals arising from exposures at the workplace. This misclassification produces what might be termed the "donut-hole effect" (Figure 1-3).

As exposed persons migrate from a center city worksite of exposure, where they might be classified most effectively as an "exposed" population, they disperse into the suburbs, where they blend with unexposed populations so completely that any signal is greatly damped out. Overcoming this depends on not settling for datasets of convenience. Populations in which those under medical surveillance have limited geographic mobility can help correct for the donut-hole effect. Students at universities might be one example. Residents of nursing homes and prisons may be other populations where there is less risk that place of

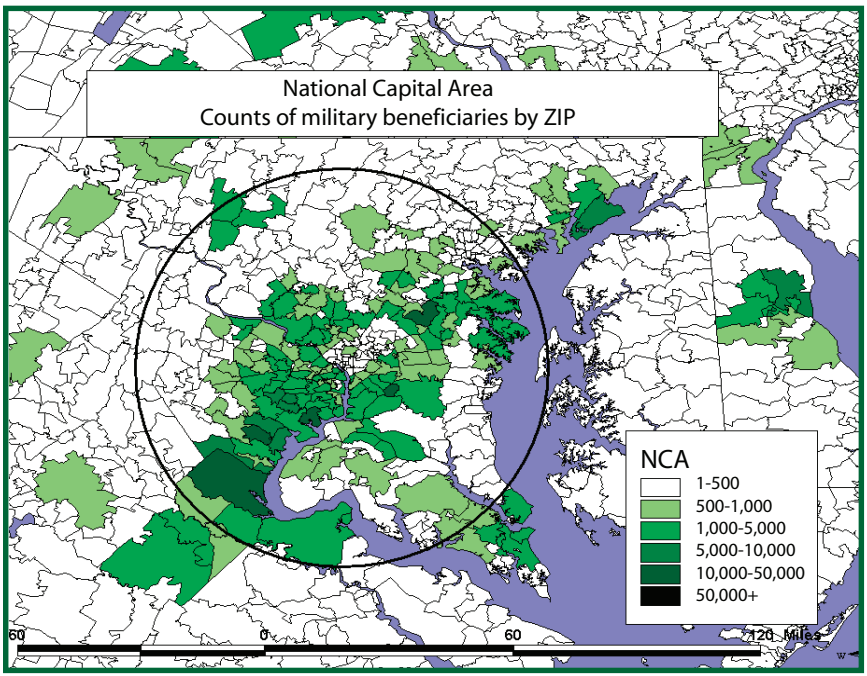

FIGURE 1-3 The donut-hole effect.
SOURCE: Kelley (2006).

exposure and place of residence differ. Another setting is military basic training. However, a limitation of many of these populations is that they may not be near the locations where surveillance is most critically needed, making their ability to serve as sentinels less than ideal.

With the DoD ESSENCE, some of the most impressive syndromic signals have come from basic training outbreaks, where the exposed population lived and worked in the same location. This meant there was no problem with the migration phenomena causing people exposed in one place to be classified geographically in another. The strength of the signal and its rapid detection was also greatly facilitated by the ability to attribute morbidity to a well-defined denominator population that included most cases. For populations on the move, if they work in high-value targets such as centers of government, it may be a high-yield investment to develop a way to ensure that they can be classified by both their primary residence and primary workplace.

In moving from syndromic surveillance theory to practice, the first step is appreciating not what data are at hand, but what are the "who, what, and when" questions that need to be answered. The most effective surveillance systems will likely be systems of systems because the questions to be answered will reflect

multiple scenarios, each of which presents a different challenge. The classic incident is an exposure to a whole community. In the bioterrorism scenario, this might be a regionwide aerosol plume, but many other scenarios may be even more likely and successful. Potential exposure scenarios include the following:

- Regionwide aerosol plume
- Seeding of a focal or traveling population with contagious (suicidal) persons (e.g., smallpox)
- Contaminated food distribution (e.g., S*almonella spp.*, hepatitis, *E. coli*, or bovine spongiform encephalopathy)
- Contaminated water supply (focal or general)
- Focused attack against high-value worksite or event (e.g., letters to Congress)
- Generalized aerosol plume against high-value site
- Focused aerosol attack against general population (e.g., mass transit)

The classic image is of a region-wide aerosol plume that distributes kilograms of an agent upwind from a population center with the idea of causing tens of thousands of deaths and incapacitations. This is perhaps the worst case, but likely the easiest to detect because it could affect large numbers of people across a wide geographic swath. Perhaps a more likely challenge for public health would be the seeding of a focal or traveling population with an infectious agent, such as SARS or pandemic influenza. Debate is needed on the question of how best to apply syndromic surveillance methods to detect serious, but lower frequency, events in time to contain their further spread. Beyond the astute clinician, who may be an uncommon commodity especially in some developing countries, what is the most sensitive mechanism to detect aberrancy at the population level when only a handful of nondescript cases are initially involved, as might be the case with an early human pandemic influenza scenario? Could the initial hands full of cases of SARS in Viet Nam or China have been better contained if alerts had been raised earlier and if communications to those who could have acted had been more rapid? How could syndromic surveillance have been adapted to supplement the astute clinician in the scenarios in Hanoi, Hong Kong, Singapore, or Toronto? Does syndromic surveillance have a role in scenarios such as these or in identifying clusters of avian flu in Indonesia or Cambodia?

In considering rare but important low-frequency emergences of a new infectious disease, the example of West Nile further illustrates the fact that the questions asked of a surveillance system differ based on the agent and the scenario to be detected. For West Nile encephalitis, tracking infrequent and not highly unique human syndromes across a large general human population may not be the most effective way to achieve the rapid recognition envisioned in the new IHRs. Figure 1-4 shows the estimated sensitivity for West Nile virus by different surveillance methods. A system of systems that includes animals that

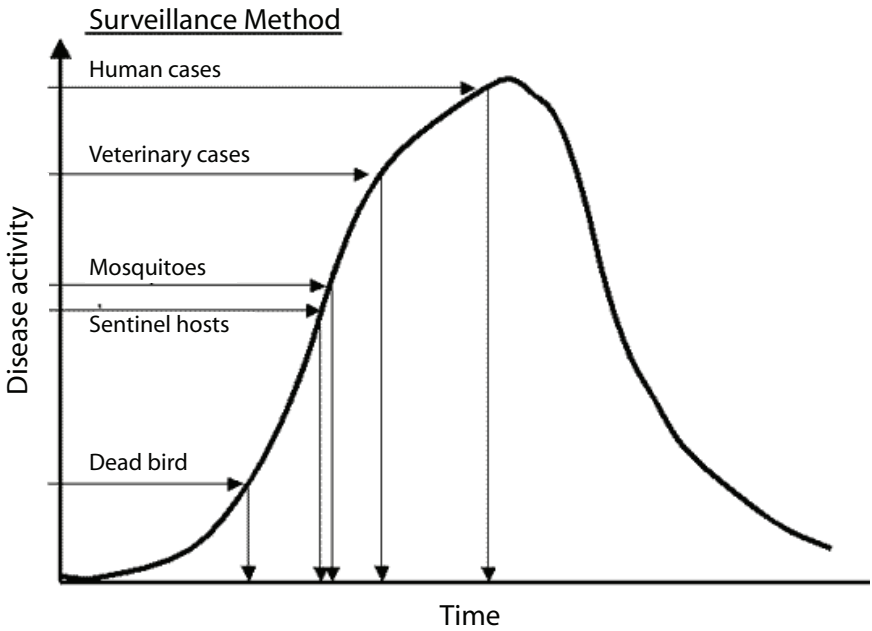

FIGURE 1-4 Estimated sensitivity for West Nile virus by different surveillance methods.
SOURCE: CDC (2003).

manifest aberrations earlier in time would be preferable to waiting until larger numbers of people develop encephalitis and are admitted to intensive care units.

One of the more recent national public health concerns in the United States has been the outbreak of *E. coli* O157:H7 associated with consumption of raw spinach. Could a configuration of syndromic surveillance detect a focal or a dispersed outbreak from contaminated food? The *E. coli* outbreak involved a few hundred cases across the country (Figure 1-5) (FDA, 2006). Would a focus on unexplained hemolytic uremic syndrome be a way to complement the impressive but slow molecular fingerprinting approaches that ultimately carried the day? The molecular approaches to DNA fingerprinting for outbreak identification were certainly valuable, but more than 10 days could easily pass between when a patient develops symptoms and when a case is confirmed and linked with other cases with the same fingerprint (Figure 1-6). Syndromic surveillance seeks to narrow the gap.

Another important outbreak scenario to detect is the contaminated water supply. The infamous Milwaukee cryptosporidiosis outbreak caused hundreds of thousands of cases of diarrhea, but its nature was such that recognition of

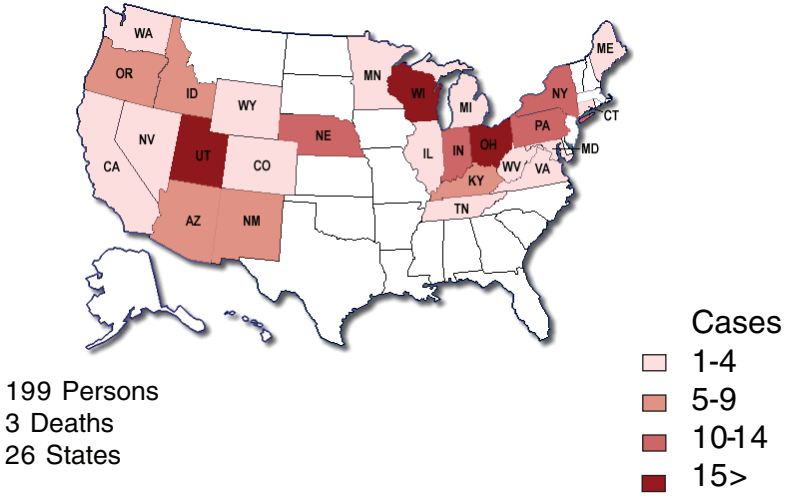

FIGURE 1-5 *E. coli* O157:H7 spinach-associated outbreak, 2006.
SOURCES: CDC (2006b) and Kelley (2006).

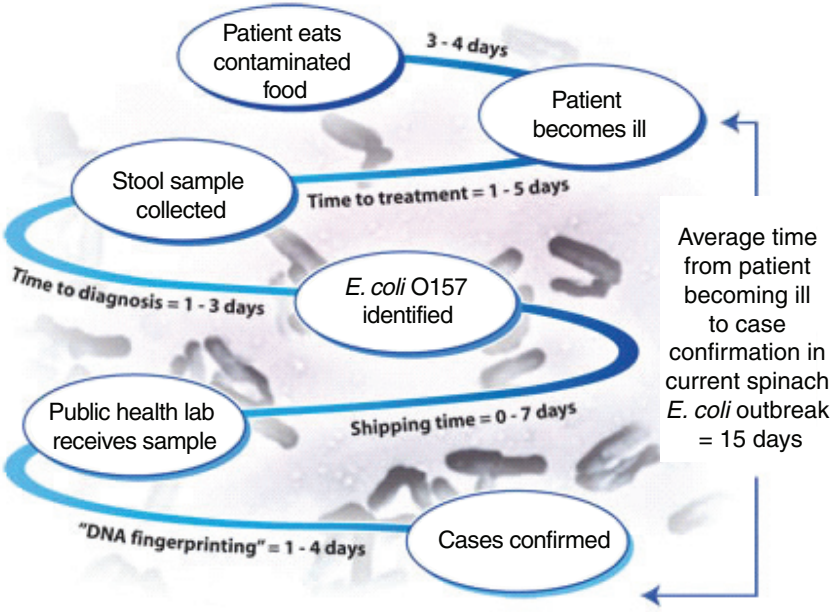

FIGURE 1-6 Time associated with confirming spinach-related illness.
SOURCE: CDC (2006c).

cryptosporidiosis as the specific cause was quite delayed (MacKenzie et al., 1994). Most sick people did not seek care. Labs were not testing for the agent routinely, and many cases were just diagnosed as viral gastroenteritis. Could a thoughtfully designed syndromic system of systems have led to more prompt recognition and mitigation of the outbreak? The epidemiology of this significant public health event should make operators of syndromic surveillance systems consider how well their systems and the datasets used would pick up a problem with a municipal water system. For example, this outbreak pointed out how small a fraction of those affected may actually seek medical care (6.5 percent here), much less go to an emergency room. How can the morbidity represented by these individuals not be lost for surveillance purposes? Furthermore, as noted earlier, many syndromic systems analyze data routinely by residential ZIP code, but how many routinely group residences based on an appreciation for how water flows through the municipal water distribution system in their city? In Milwaukee it was clear that the map of the distribution system would have correlated powerfully with a pattern of attack. The sparing of special populations such as nursing home residents was reminiscent of John Snow's observations on the sparing of the Whatney's Brewery workers from the cholera outbreak in London in the late 19th century.

Another important scenario to think about is the focused attack against a high-value site such as the 2001 anthrax letter attacks. Tragically in this attack a number of people died, but some lives were probably saved by the action of the hoped for astute clinician. Beyond the astute clinicians, however, what system configuration would pick up those low-frequency cases that may reflect serious morbidity as a harbinger of a more widespread exposure? Individual cases were identified in emergency rooms in this attack. Some were not so quickly recognized and may have taken on a different characterization if appreciated in a larger epidemiologic context rather than counting on an individual astute clinician to sense a "big picture" beyond his field of vision. Perhaps rigorous surveillance of intensive care units (ICUs) for epidemiologically unexpected admissions may be a critical underdeveloped element of syndromic surveillance for problems such as this anthrax episode and outbreaks of problems such as West Nile or SARS. ICU surveillance may permit the time for more detailed epidemiologic characterization of epidemiologically suspect cases, that is, cases that are admitted with no obvious predisposing reason. Pooling across a municipal region may allow appreciation of patterns that no single astute clinician could be counted on to detect, much the same way that unexplained death surveillance may be helpful, if not too late.

Perhaps the most important scenario to detect is the "failed scenario." We know that the worst case scenario of a biological attack would not be easy for most perpetrators, but that does not necessarily discourage them from trying. Being able to detect a modest trial run outcome would be a much more useful capability than designing a system for a more obvious worst case scenario.

The first generation of an avian influenza cluster would also be the best time to appreciate a problem. A goal of surveillance systems should be to not only detect the classic worst case attack early or the widespread deaths of chickens, but also to detect what may more often be a botched attempt that falls far short of the perpetrators' hopes or the earliest generation avian flu outbreaks. The unsuccessful 1993 attempts by Aum Shinrikyo to spray anthrax over the city of Tokyo illustrate this point (Takahashi et al., 1994). Fortunately this incompetent attempt did not cause a single case, but if it had, even one case could have been valuable to recognize as a harbinger of future threats. Perhaps the complete failure of this anthrax attempt caused Aum Shinrikyo to move on and use sarin in the Tokyo subway. A lesson is that motivated enemies will keep trying and could get better with practice. A comprehensive surveillance system should set its sights on detecting a wide range of scenarios to include trial runs or largely botched low-yield events that may indicate that more effective efforts are in the offing.

A recent review of abstracts accepted for presentation at the October 2006 International Disease Surveillance Conference in Baltimore, Maryland, showed that *more states than not* have started to explore syndromic approaches to disease detection and management. In addition to the United States, seven foreign jurisdictions also came to the meeting to present systems for syndromic surveillance. In comparing the datasets represented in systems described at the 2003 meeting with the 2006 abstracts, implemented systems are still overwhelmingly focused on emergency rooms and hospital diagnoses—81 percent in 2006 (Figure 1-7 and Table 1-1). Although these data sources are obviously relevant for many scenarios mentioned and may be the most convenient, they are not necessarily the answer to all challenges. Other populations and venues may lend themselves to better classification with respect to person, place of exposure, and time. To get the most power out of the analytical methodologies being developed, there may be justification to put the focus on other datasets to illuminate different aspects of the clinical continuum and work so they contain the most informative fields.

Each of these varied data sources in Table 1-2 may provide a unique perspective on a particular epidemiologic scenario, especially if public health practitioners help shape the characteristics of the data rather than just settling for what data are readily available. If public health practitioners are on the alert for emerging infections, including bioterrorism, the aim should be to do more than detect only large unexplained outbreaks, but also to have the ability to detect isolated, unexpected cases with unusual age, gender, or occupational characteristics. The need to do this is driven not only by American concerns over bioterrorism, but is also reflected in visions of the new IHRs. If public health officials are to detect and contain pandemic influenza, it is doubtful that they will be very successful if they fail to recognize emerging patterns until there is a large unexplained outbreak.

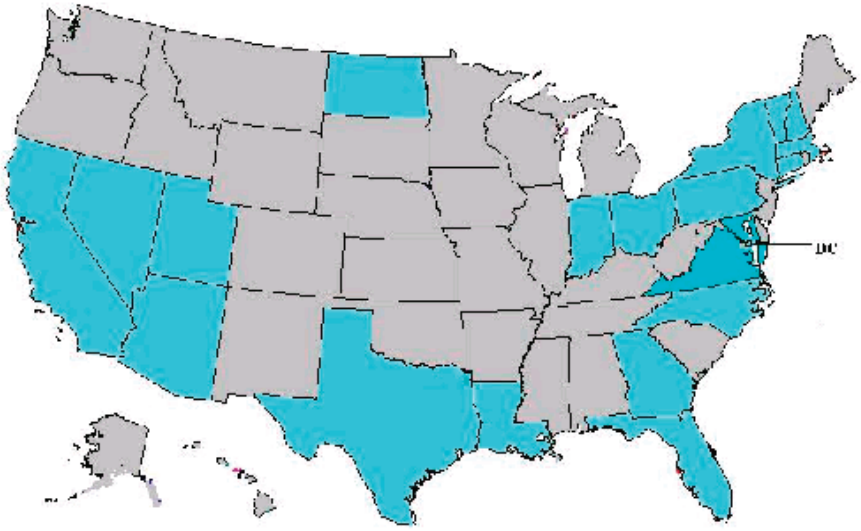

FIGURE 1-7 Locations of surveillance systems in abstracts for the 2006 International Society for Disease Surveillance (ISDS) meeting. Countries represented include United States, Canada, Netherlands, Taiwan, Hong Kong, France, Scotland, and Greece. States represented include AZ, CA, CT, DC, FL, GA, IN, LA, MA, MD, NC, ND, NH, NV, NY, OH, PA, TX, UT, VA, VT.
SOURCE: Kelley (2006).

To summarize, as demonstrated by Figure 1-8, public health surveillance begins with understanding the questions "who, what, and when" that need to be asked, and then it seeks the most effective data sources.

A system for public health surveillance, which is what needs to be built in the move from academic theory to practice, is built on that data foundation, but it also needs a set of powerful analytic tools and skillful people to use them and interpret the findings. The skill sets of local public health staff to interpret data of this type need expansion. Because this is a complex science still under development, perhaps academic partnerships need to be sought for all serious adaptations of these concepts to specific localities. Few approaches can be just "dropped in" without an appreciation for local epidemiologic and demographic peculiarities. Perhaps most in short supply are the resources to do something promptly to respond to findings. Budgets for surveillance systems should be accompanied by budgets for a serious response capability. Finally, the underlying population demographic structures and exposure likelihoods of some localities may make syndromic surveillance a low-yield, cost-inefficient activity. This may not be the destination for every community. Guidelines for where performance is expected to be lower are needed as well as insights into where value is likely to be added.

TABLE 1-1 Sources for Syndromic Surveillance, 2003 and 2006 Annual Meeting Abstracts

	2003		2006	
Data Sources	# of Abstracts	% of Abstracts	# of Abstracts	% of Abstracts
Emergency departments	29	48	38	56
Hospital diagnosis	7	12	17	25 ↑
Office/clinic visits	13	22	11	16 ↓
Over-the-counter drugs	5	8	7	10 ↑
911/emergency medical service runs	6	10	6	9 ↓
Laboratory results	2	3	5	7 ↑
Nurse advice lines	4	7	3	4 ↓
Laboratory orders	1	2	1	1
School nurse records	—	—	1	1
Poison control center	5	8	1	1 ↓
Veterinary diagnosis	3	5	1	1 ↓
Health-care employee absenteeism	—	—	1	1
School absenteeism	7	12	1	1 ↓
School perception of an outbreak	1	2	—	—
Medical examiners	2	3	—	—
Thermometer sales	—	—	1	1
Evacuation shelter primary reports	—	—	1	1
Local/regional news sources	—	—	1	1
Web logs	—	—	1	1
Online obituaries	1	2	—	—
Medical center parking lot volume	1	2	—	—

SOURCES: Sosin and DeThomasis (2004) and Kelley (2006).

TABLE 1-2 Potential Sources of Data for Syndromic Surveillance

- Emergency rooms
- Over-the-counter drug sales of symptomatic therapies
- School and/or work absenteeism
- Nurse advice lines
- Ambulatory clinics
- Laboratory test requests (e.g., fecal ova and parasite)
- Prescriptions
- Emergency medical systems (911)
- Hospital and intensive care unit surveillance for syndromes
- Unexplained deaths
- Wild and domesticated animal health

SOURCE: Kelley (2006).

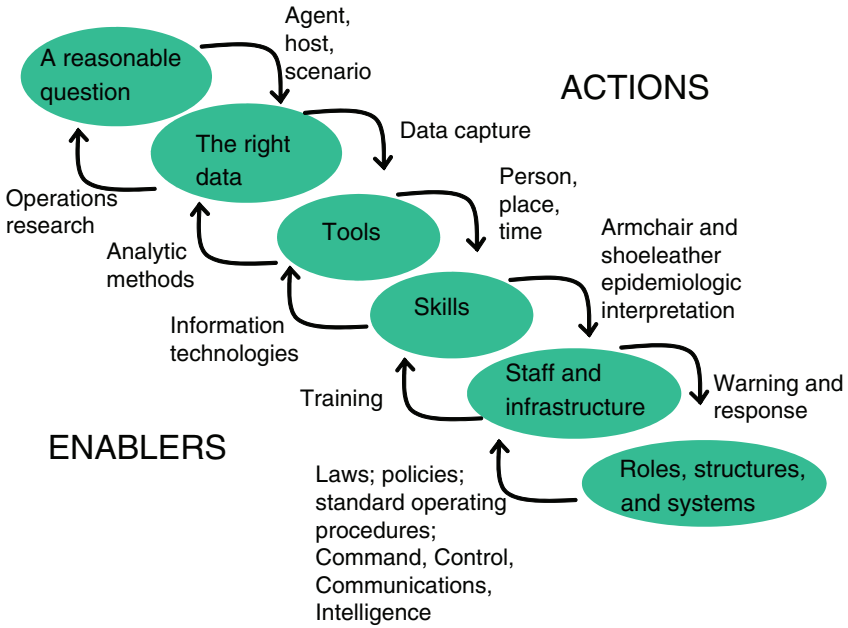

FIGURE 1-8 System requirements for public health surveillance.
SOURCE: Kelley (2006).

SYNDROMIC SURVEILLANCE IN PUBLIC HEALTH PRACTICE

Michael A. Stoto, Ph.D.[2]
Georgetown University

Heightened awareness of the risks of bioterrorism since 9/11, coupled with a growing concern about naturally emerging and reemerging diseases such as West Nile, severe acute respiratory syndrome (SARS), and pandemic influenza, have led public health policy makers to realize the need for early warning systems and, more generally, improved surveillance. The sooner health officials know about an attack or a natural disease outbreak, for example, the sooner they can treat those who have already been exposed to the pathogen to minimize the health consequences, vaccinate some or all of the population to prevent further infection, and identify and isolate cases to prevent further transmission. In addition, improved surveillance systems should allow for better "situational awareness" and thus help to manage the response to public health emergencies.

[2]School of Nursing and Health Studies.

Traditional public health surveillance approaches monitor disease using prespecified case definitions and employ manual data collection, human decision making, and manual data entry. In contrast, newly developed syndromic surveillance systems employ sophisticated information technology (IT) and statistical methods to gather, process, and analyze large amounts of data and display the information for decision makers in a timely way. For example, syndromic surveillance systems assume that during an attack or a disease outbreak, people will first develop symptoms, then stay home from work or school, attempt to self-treat with over-the-counter products, and eventually see a physician with nonspecific symptoms days before they are formally diagnosed and reported to the health department. To identify such behaviors, syndromic surveillance systems regularly monitor existing data for sudden changes or anomalies that might signal a disease outbreak. Syndromic surveillance systems have been developed to include data on school and work absenteeism, sales of over-the-counter products, calls to nurse hotlines, and counts of hospital emergency room (ER) admissions or reports from primary physicians for certain symptoms or complaints (Mandl et al., 2004).

Recognizing that the "ability to gather and analyze information quickly and accurately would improve the nation's ability to recognize natural disease outbreaks, track emerging infections, identify intentional biological attacks, and monitor disease trends," the Institute of Medicine (IOM) recently called for more research on syndromic surveillance and other "innovative systems of surveillance that capitalize on advances in information technology." However, because surveillance systems in the United States "remain fragmented and have not evolved at the same rate as . . . electronic technological advances," the IOM calls for these systems to be "carefully evaluated for their usefulness in detection of infectious disease epidemics, including their potential for detection of major biothreat agents, their ability to monitor the spread of epidemics, and their cost effectiveness" before widespread implementation (IOM, 2003).

To address the issues identified by the IOM, this paper begins by describing a framework for evaluating the usefulness of syndromic surveillance in public health practice. Application of this framework to existing systems identifies a number of statistical and practical concerns when syndromic surveillance is used to detect bioterrorist events. The analysis suggests, however, that these systems may be more useful in detecting natural disease outbreaks (including seasonal and pandemic influenza) and in the public health response to known disease outbreaks.

Evaluation of Syndromic Surveillance Systems' Usefulness

Asking whether syndromic surveillance "works" or not is not particularly helpful. Rather, just as clinicians need to know the performance characteristics of screening and diagnostic tests, public health epidemiologists need to charac-

terize the performance of syndromic surveillance detection systems in terms of the kinds of events that can be detected as a function of the responsible antigen, outbreak size, timing, and other characteristics. Thus, evaluation of syndromic surveillance systems' usefulness involves a number of dimensions.

Evaluations of data accuracy and use, for example, include studies of the accuracy of electronic records that form the basis of the systems compared with an independent source, the accuracy of use of standard codes, the accuracy of data preprocessing, and similar issues. This aspect of evaluation also includes studies of the appropriateness of methods and protocols for data analysis, data display, monitoring, and reporting, as well as how these methods are applied and how they lead to action.

Evaluations of system utility include studies of the costs and benefits of day-to-day use of syndromic surveillance, relative to existing systems, to identify communicable or reportable diseases, to increase situational awareness, or to assist in investigation and management of a disease outbreak. These studies also assess the costs and benefits to users of identifying and evaluating data anomalies using the system, as well as flexibility, acceptability, and stability. Finally, evaluation studies characterize statistical properties such as sensitivity, false-positive rates, and timeliness. As illustrated below, statistical evaluations can be based on simulation studies and comparisons of syndromic surveillance findings with known actual events.

Concerns About Syndromic Surveillance in Public Health Practice

Despite the generally recognized promise of syndromic surveillance systems, there are many practical concerns about the use of these systems in state and local public health practice. The possibility of earlier detection and more rapid response to a bioterrorist event has tremendous intuitive appeal, but its success depends on local health departments' ability to respond effectively. When a syndromic surveillance system sounds an alarm, health departments typically wait a day or two to see if the number of cases continues to remain high or if a similar signal is found in other data sources. Doing so, of course, reduces both the timeliness and sensitivity of the original system. If the health department decides that an epidemiological investigation is warranted, it may begin by identifying those who are ill and talking to their physicians. If this does not resolve the matter, additional tests must be ordered and clinical specimens gathered for laboratory analysis. Health departments might also choose to initiate active surveillance by contacting physicians to find out if they have seen similar cases.

The detection of a sudden increase in cases of influenza-like illness (ILI)—the kind of condition that syndromic surveillance can detect—can mean many things. It could mean a bioterrorist attack, but is more likely a natural occurrence, perhaps even the beginning of the annual flu season. An increase in sales of flu medication might simply mean that pharmacies are having a promotion. A surge

in absenteeism could reflect natural causes, or even a period of particularly pleasant spring weather. Similar problems can occur when changes in local hospital systems, or even in coding practices, can result in substantial changes that could raise concern if they are not understood.

Additionally, a syndromic surveillance system that says only that "there have been five excess cases of ILI at hospital X" is not of much use unless the five cases can be identified and reported to health officials. For example, if there are 65 cases rather than the 60 expected, syndromic surveillance systems cannot say which 5 are the "excess" ones, and all 65 must be investigated.

Like all alarm systems, syndromic surveillance detection algorithms have intrinsic statistical tradeoffs. The most well known is between sensitivity, the ability to detect an attack when it occurs, and the false-positive rate, the probability of sounding an alarm when in fact there is no attack. The costs of excessive false alarms are both monetary, in terms of resources needed to respond to phantom events, and operational, as too many false events desensitize responders to real events. Taking into account the different data types and multiple jurisdictions, thousands of syndromic surveillance systems soon will be running simultaneously in cities and counties throughout the United States. If 1,000 data streams are being monitored, each with a 0.1 percent false-positive rate (which is very low), there will be approximately one false alarm per day.

The timeliness of a surveillance system depends on the time it takes to generate and acquire data, analyze it, and take action (Buehler et al., 2003). Even when the cause and route of exposure are known, the available control strategies—quarantine of suspected cases, mass vaccination, and so on—are expensive and controversial, and often their efficacy is unknown. Coupled with the confusion that is likely during a terrorist attack or even a natural disease outbreak, deciding what to do could take days to weeks.

With syndromic surveillance, an additional component is the time required to accumulate enough evidence of an outbreak to trigger a detection algorithm. To illustrate this point, Stoto and colleagues used a simulation approach to analyze ILI emergency department admissions data from a typical urban hospital. A hypothetical number of extra cases spread over a number of days were added to actual baseline data to mimic the pattern of a potential bioterror attack. Figure 1-9 (A and B) indicates the size and speed that outbreaks must attain before they are detectable, according to four statistical detection algorithms. The solid bar represents an algorithm that uses only one day's data. The other three detection algorithms, shown with shared bars, average cases over several days. These results are sobering: Even with an excess of nine cases over two days (the first two days of the "fast" outbreak), three times the daily average, there was only about a 50 percent chance that the alarm would go off. When 18 cases were spread over nine days, chances were still no better than 50-50 that the alarm would sound by the ninth day (Stoto et al., 2004).

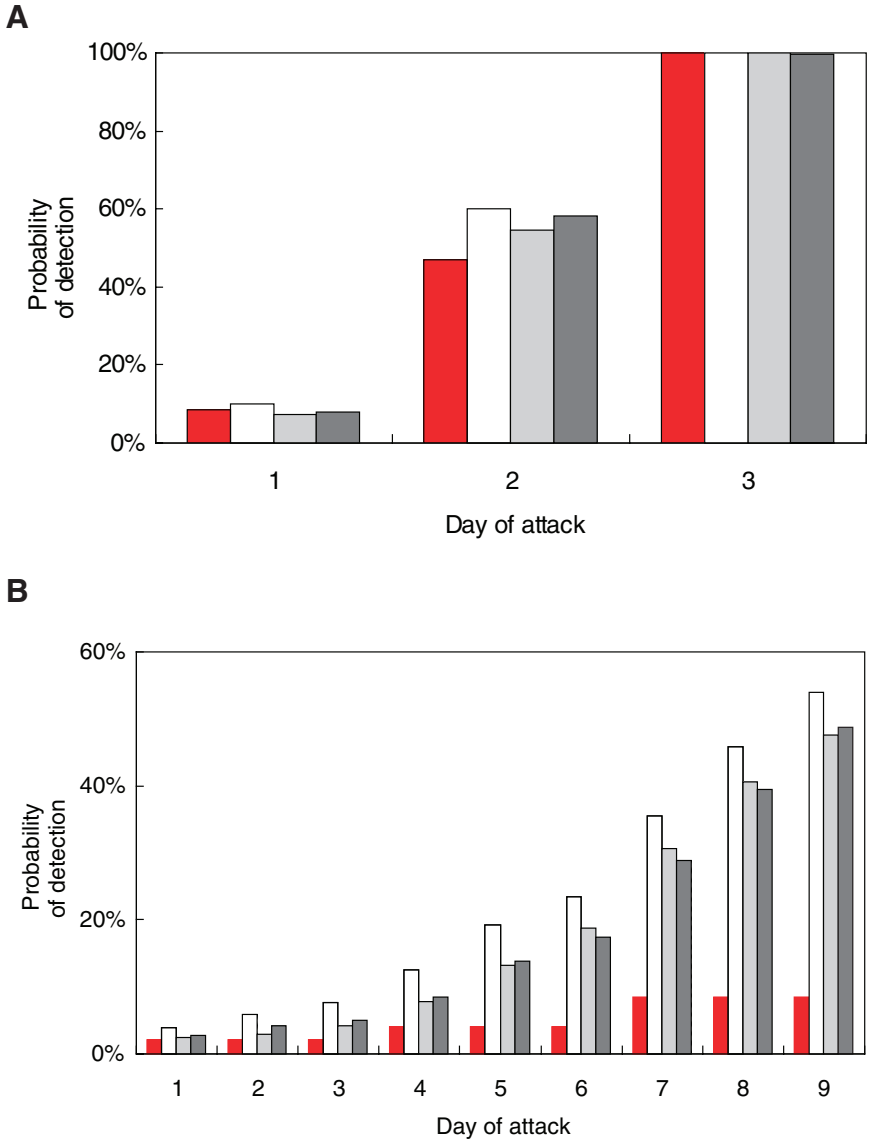

FIGURE 1-9 Sensitivity of syndromic surveillance (probability of detection by day) for influenza-like illness at a typical urban hospital emergency room using four detection algorithms, as indicated by shading pattern (see text). A) fast outbreak: 18 cases over three days, B) slow outbreak: 18 extra cases over nine days.
SOURCE: Stoto et al. (2004). Reprinted with permission from *Chance.* Copyright 2004 by the American Statistical Association. All rights reserved.

Can Performance Be Improved?

Simulation studies such as the one summarized in Figure 1-9 (A and B) has shown that unless a bioterrorism outlook is exceptionally large, syndromic surveillance detection algorithms take days to be detected (Stoto et al., 2004; Jackson et al., 2006; Buckeridge et al., 2006; Stoto et al., 2007). Results like this naturally lead one to ask whether this performance can be improved. Indeed, there are a number of approaches; however, although these approaches may lead to better performance for some outbreak types, they are less able to detect others.

Syndromes other than ILI, for example, might be more easily detected because they are less common, but this only works if a terrorist—or nature—chooses to use an agent that caused those symptoms. Systems can and typically are set up to monitor eight or more separate sets of symptoms. Doing so increases sensitivity simply because more conditions are monitored, but as discussed above, increasing the number of syndromes monitored will also increase the number of false positives.

Another possibility is to pool data over multiple data streams, perhaps from all hospitals in a metropolitan area or state. A number of cities are currently doing this. If this results in both the signal and the background increasing proportionally, it will result in a more effective system. If, however, there were 18 extra cases of ILI in a city, but they all appeared at one hospital, this signal would be lost in the noise of the entire city's cases. Moreover, such an increase would be clear without any sophisticated surveillance system. One can analyze the data for the entire city and for each hospital individually, but with 10 separate analyses, the number of false positives would also increase.

Finally, the data can be analyzed geographically. If there were 18 extra cases of ILI in a city, and all lived in the same neighborhood, that would be more informative than 18 cases scattered throughout the city—it would suggest a biological agent released in that area. This is only effective, however, for a geographically focused bioattack, and would not work if terrorists chose to expose people in an office building or at an airport. It is also less likely to detect seasonal or pandemic influenza, which spreads rapidly before symptoms appear

Alternative Applications of Syndromic Surveillance

Since 9/11, the focus of syndromic surveillance efforts has been on early detection of bioterrorist events. The most value, however, may ultimately come from its use in the detection of natural disease outbreaks. More generally, if 21st century syndromic surveillance means effective use of health information technology in identifying cases before they are formally diagnosed, it can supplement traditional public health approaches and improve their effectiveness.

One potential use is in detecting influenza outbreaks. In an "ordinary" year, influenza results in 36,000 or more deaths and more than 200,000 hospitalizations

in the United States alone. In addition to this human toll, influenza-related costs are more $10 billion a year. A pandemic, or worldwide outbreak of a new influenza virus, perhaps evolving from the H5N1 avian flu virus circulating in Asia, could dwarf this impact by overwhelming our health and medical capabilities, potentially resulting in hundreds of thousands of deaths, millions of hospitalizations, and hundreds of billions of dollars in direct and indirect costs. Syndromic surveillance systems feature prominently in federal, state, and local plans to prepare the United States for pandemic flu (Homeland Security Council, 2005).

The Centers for Disease Control and Prevention (CDC) has a number of influenza surveillance systems in place (CDC, 2007), yet they do not provide population-based rates of incidence or prevalence rates on a national level because many infected persons are asymptomatic or experience only mild illness and do not seek medical care. Also, laboratory testing is not common and test results become available late in the course of the illness. Epidemiological characteristics of both seasonal and pandemic influenza, however, suggest that syndromic surveillance and other surveillance systems are likely to make an important contribution beyond the capabilities of existing surveillance systems, and thus enable a more effective public health response. Simulation studies have shown that unless a bioterrorism outlook is exceptionally large, syndromic surveillance detection algorithms take days to be detected (Stoto et al., 2004; Jackson et al., 2006; Buckeridge et al., 2006; Stoto et al., 2006). This time frame is longer than some proponents of syndromic surveillance as a tool to detect bioterrorism suggest is needed (Wagner et al., 2001). Compared to the current influenza surveillance systems, however, a one-week lead time would provide valuable information, and this is likely to be achievable for syndromic surveillance.

Furthermore, a number of studies have demonstrated the potential that syndromic surveillance of ILI offers at the national, state, and local levels. Sebastiani and colleagues (2006) have shown that children and infants presenting to the pediatric emergency department (ED) with respiratory syndromes are an early indicator of impending influenza morbidity and mortality, sometimes by as much as three weeks. Using data from New York City, Lu and colleagues (2006) have shown that monitoring both outpatient and ED data can enhance detection of ILI outbreaks. With similar data, Olson and colleagues (2005) note that age-stratified analyses of ED visits for fever and respiratory complaints offer the potential for more precise quantification of the burden of illness, earlier warning of the arrival of epidemic influenza, and greater sensitivity for detecting the characteristic age shift of pandemic influenza. Comparing unspecified infection cases in Washington, DC, hospitals using optimal detection algorithms to CDC's sentinel physician data for the South Atlantic states for four years in which there was a discernable influenza outbreak, Stoto and colleagues (2007) found that in two of those years, the DC syndromic surveillance based on hospital emergency room data outperformed the other two systems, and in one year it flagged only two days

after the CDC system. Given a built-in delay of about two weeks in the CDC system, this is a substantial advantage.

In normal flu seasons, laboratory analysis to determine whether a case is truly influenza, or to identify the viral strain, is rarely done. Testing, however, is critical for identifying pandemic influenza, in which an antigenic shift results in a new viral strain to which few people are immune by virtue of previous exposure. Syndromic surveillance of flu-like symptoms might trigger more laboratory analysis than is typically done and in this way hasten the public health response. In a normal flu season, Labus (2005) has reported that early identification of the start of the influenza season using syndromic surveillance in Clark County, Nevada, enabled the notification of the medical community. Physicians were encouraged to submit specimens for culture, and the county health department provided kits to help them do this, which allowed for rapid identification of the major circulating strain. In 2003–2004 (a period with a marked increase of early season influenza and deaths in children in other parts of the country) this syndromic surveillance system allowed for better tracking, and provided data for daily reports to decision makers and the media.

Because of their focus on the early detection of bioterrorist events, most syndromic surveillance systems are designed to detect large increases in the number of people with common symptoms such as ILI. As a result, they cannot be expected to detect small numbers of cases, even if very unusual. One reason is that in a small disease outbreak or the early stages of a larger one, each case will be seen by only one physician. The natural tendency of physicians who see only one case, however suspicious it may be, is to discount it. After all, physicians are appropriately taught "when you hear hoofbeats, think horse, not zebra." Some may fear the embarrassment of reporting a case that may turn out to be a false alarm.

Modern health informatics systems provide the potential to identify the presence of small numbers of cases of concern before they are formally diagnosed. For example, automated systems can aggregate data for a metropolitan area, spanning local reporting jurisdictions, to identify, say, cases of rash and fever, which would suggest smallpox. Systems can also be set up to enable and encourage early reporting of cases based on symptoms only. For example, the Syndrome Reporting Information System (SYRIS) system, now operating in Lubbock, Texas, and elsewhere, enables physicians to report suspicious cases to the local health department without waiting for laboratory confirmation, and encourages them to do so by providing feedback in the form of information about practice guidelines and other similar cases (Lindley and Ward, 2007). This can be thought of as a kind of "active syndromic surveillance" or as IT support for astute physicians.

Real-time access to prediagnostic data can also help health authorities respond to public health threats. If person-to-person transmission of avian flu virus is documented in Asia, for example, health departments in Europe and the United States might want to identify and follow up on local cases of people hos-

pitalized with flu-like symptoms, and syndromic surveillance systems could be designed to identify them. If an environmental sensor detects signs of the terrorist agent tularemia, syndromic surveillance systems can be checked for cases with appropriate symptoms. This actually occurred in Washington, DC in 2005, and the lack of cases in area emergency rooms reassured local officials that the alarm was false. Syndromic surveillance systems can also be queried to determine background rates when it is not clear whether a reported cluster of cases is unusual.

The *E. coli* O157:H57 outbreak in the New York City area in late 2006 provides an example of how syndromic surveillance could have been used for case finding. The outbreak came to light on November 17 when the first case was reported to a local health department in New Jersey. By November 27, 11 cases were reported in that jurisdiction. Three days later the Taco Bell restaurant, where people in 9 of the 11 cases had eaten closed voluntarily. On December 1, a similar case (originally attributed to another cause) was reported to a local health department in New York state, and it turned out that this person and three others in that jurisdiction had eaten at a different Taco Bell restaurant. By December 4, all Taco Bells in the New York metropolitan area were closed, and two days later a particular food item, green onions, was identified as the likely source of contamination. By December 9, more than 61 *E. coli* O157:H57 cases in at least four states were reported (CDC, 2006d).

Although a number of syndromic surveillance systems were operating at this time in New York City and the surrounding jurisdictions, there were too few cases in any location to detect. However, once the outbreak was identified in New Jersey, an advanced syndromic surveillance system could have searched emergency department admissions for cases of bloody diarrhea and abdominal cramps in the entire metropolitan area. Cases so identified could have been interviewed to take a food history, and lab samples obtained to test for *E. coli* O157:H57. In addition, health departments could have initiated active surveillance by physicians in the area, searched data from surrounding states to identify additional cases for follow-up and to confirm lack of cases elsewhere. If these steps had been taken, it is possible the restaurant chain and green onions could have been identified and remedial steps taken earlier—either closing the restaurant or removing the green onions. It is also likely that the additional data from syndromic surveillance systems could have resolved the uncertainty about what was happening and thus diminished public concerns.

Using syndromic surveillance—essentially, prediagnostic health information in existing electronic databases—as these examples suggest requires flexible and easily accessible IT systems, as well as a relationship between data providers and health departments that enables the systems to be used when needed. A benefit of developing these relationships may be improved communications between health-care providers and public health, which is essential to responding to any health emergency.

Conclusions

Any careful review of the development of syndromic surveillance in the past five years would have to conclude that much impressive work has been done with respect to information technology, including the real-time integration of many disparate data streams, and analysis—the development of statistical models, detection algorithms, and methods to visualize syndromic data. From a public health practice point of view, however, the value of syndromic surveillance for detecting bioterrorist attacks has not yet been demonstrated. There are two major reasons for this conclusion. First, in statistical terms, there is a relatively narrow window between what can be detected in the first few days and what is obvious. Second, better integration with public health systems is needed before information generated is useful in guiding a public health response. The analysis in this paper, however, suggests that the most important contribution of syndromic surveillance to public health practice may be for natural disease outbreaks, such as seasonal and pandemic flu, and as a tool to monitor outbreaks and guide the public health response. Realizing this potential will require designing systems that focus on these uses rather than being optimized for timely detection of large-scale bioterrorist attacks. Instead of automating the process of detecting outbreaks with statistical detection algorithms, it might be more useful to build flexible analytical tools into syndromic surveillance systems so they can monitor ongoing bioevents and facilitate epidemiological analysis.

IMPLICATIONS OF "REAL TIME" VERSUS "BATCH REPORTING" FOR SURVEILLANCE

Joseph Lombardo, M.S.[3]
The Johns Hopkins University

Introduction

In the context of disease surveillance, there has been confusion promulgated by vendors of systems on the requirement for "real-time" data feeds. The Institute of Medicine requested the author to present material addressing the subject, "Real Time" Versus "Batched" Reporting for Surveillance. The following discussion is based on the author's career of 37-plus years in developing, evaluating, operating, and improving surveillance systems in different domains. Ten of these years have been spent on developing and improving the Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE), a disease

[3]Center of Excellence in Public Health Informatics.

surveillance system being used globally and locally by public health organizations (Lombardo and Buckeridge, 2007).

Definition

The terms "real time" and "batched" for disease surveillance can be used to mean different things by different authors. Any discussion must begin with some formal definition of these terms. The Institute of Electrical and Electronics Engineers' (IEEE's) Computer Society Technical Committee defines real-time systems as those "in which its temporal properties are essential for reliability and correctness; the example applications include embedded systems, control systems, monitoring systems, and multimedia systems" (IEEE-TCRTS, 2007).

Real-time computing systems are required for time-critical applications where the result of a computing process is time critical. Examples with which most everyone is familiar are video games where a split-second delay could change the result of an outcome, or the use of antilock brake systems in cars to provide immediate feedback and response to avoid a collision.

The term "batch" is used in computing much as it is in baking: a set of programs or jobs processed on a computer at one time, like baking a batch of cookies in the oven. The Encarta (Microsoft Encarta, 2007) definition includes:

- **Process items as batch:** To process or assemble items as a batch or in batches.
- **Computer programs processed together:** A set of programs or jobs processed on a computer at one time.

Batched reporting of surveillance data, however, can mean a variety of things. The following are just a few:

- Batched collection of health indicator data;
- Batched processing of indicator data;
- Reporting to health surveillance monitors that one or more rules have been triggered at a periodic time interval; and
- Sending reports for reportable diseases in a group at some specific reporting interval.

The term "reporting" is used when the provider of the data (e.g., hospital, pharmacy, laboratory) sends data to the site where surveillance is being conducted. This is usually the first step in the surveillance process. The term "batched processing" is the processing of several files by applying mathematical algorithms to derive information from the data. These algorithms can be used to convert unstructured text data into structured data, for the identification of abnormal trends in the data, or for transforming data and information to be viewed in

a manner that would permit easy interpretation by a variety of users. Batched reporting is also used to refer to the actions needed to present data and algorithm outputs to the users of surveillance systems. Collection and processing of data do not occur at the same time as when data and results are being made available to the user. Batched health data may be reported to users as soon as it is processed, or it may be delivered at regular intervals, or accessed on demand.

The term "batched reporting" also has been used in the context of providing notification of reportable disease to a higher public health authority. Reports of animal diseases occurred monthly in some jurisdictions for those diseases that are reportable, but do not pose an immediate threat.

Surveillance Context

Data Acquisition and Archiving

Figure 1-10 presents an example of a generic disease surveillance system. Data acquisition occurs on the left of the figure. User interfaces are on the right, and archiving and analytic processes are in the center. Possible sources of early indicators of population health include 911 calls, emergency medical services, emergency department chief complaints, over-the-counter self-medications, etc. Some of the indicator data can be made available in real time while others can not.

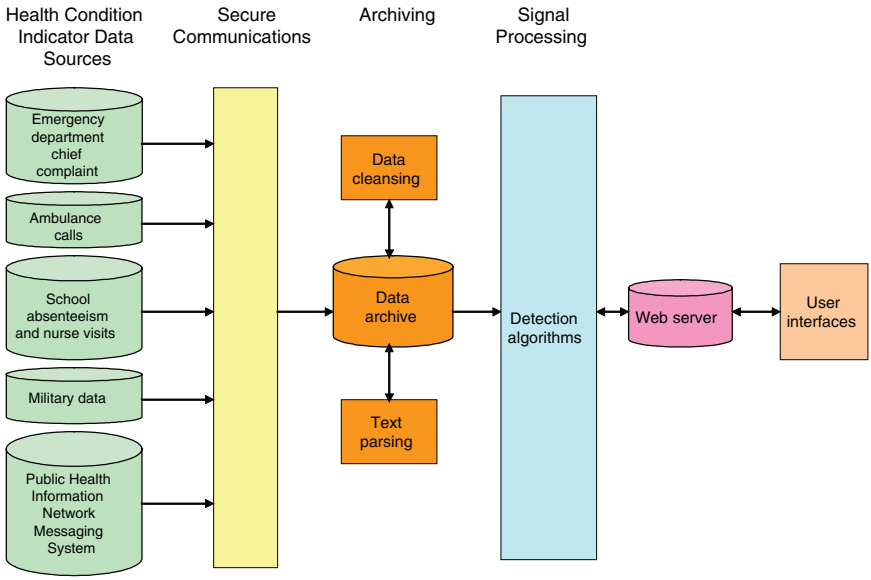

FIGURE 1-10 Electronic health monitoring components.
SOURCE: Lombardo (2006).

Only data that is captured in real time can be made available for surveillance in real time. When a cashier in a large retail chain scans an item the transaction can be captured and transmitted to the company's distribution center. Several large retailers of over-the-counter medications capture their sales in real time so they can keep track of inventory in each store. Schools track absenteeism on a daily basis and not throughout the school day. School nurses could potentially track every student visit as it occurs. Many hospitals now have automated information systems based on the Health Level Seven (HL-7) format. These systems provide a comprehensive framework for the exchange, integration, sharing, and retrieval of electronic health information. Such information includes the instruction of orders; clinical observations and data, including test results; admission, transfer and discharge records; and billing information. HL-7 has become a standard for the interfacing of clinical data for many large hospitals (Health Data Standards: The Players, 2007). Monitoring a hospital's HL-7 message traffic creates a record of activities within the hospital as information is entered and archived. Monitoring an HL-7 data stream provides hospital record data as close to the time they are created as possible.

To preserve the timeliness of HL-7 records, many developers and surveillance system users believe the records need to be transmitted to the automated surveillance system as quickly as they are created. One method for preserving this timeliness is to provide continuous transmission of HL-7 records between the hospital and the surveillance system. The use of a virtual private network (VPN) permits HL-7 records to be transmitted as soon as they appear on the hospital's network.

Another popular mechanism for data transmission uses the File Transfer Protocol (FTP). Records are accumulated and "batched" over some time interval, then sent at a specific time to the FTP site, where they are picked up by the surveillance system for archiving and processing. The Center for Disease Control and Prevention's (CDC's) BioSense program aggregates HL-7 hospital records every 15 minutes, and transfers them to CDC using the Public Health Information Network (PHIN) Messaging System.

Most state and local health departments have varying requirements for the timeliness in which data are provided for surveillance. Many health departments believe that receiving data once a day may be sufficient, while others believe that real time is mandatory. The Department of Health and Human Services for Montgomery County, Maryland, has implemented its data collection surveillance component so it can acquire data at higher rates during times when the department is concerned about a possible health risk.

Data Processing

Once the data are acquired and archived by the surveillance system several processing steps could occur. Initial processing is needed to reduce entry and

transmission errors. The term used in Figure 1-10 to describe these processes is "data cleansing." Separate processing algorithms are needed to convert text data, such as chief complaint, clinical notes, and radiology reports, into a structured data for use in signal analysis. These processes are referred to as "text parsing" in Figure 1-10.

Automated surveillance systems employ a variety of algorithms[4] to process data for early detection of a health event. "Signal processing" is a term frequently used for these processes. If the datasets are large or diverse, or come from many different sources, the signal processing steps can require several minutes to hours of computing time. Certain algorithms, such as those for spatial analysis (e.g., attempting to form spatial clusters across hundreds of ZIP codes) are particularly time consuming; as a result, such cases tend to be processed as batches because they simply cannot be performed in anything resembling real time. Processing is initiated and results are provided after well-defined periods, such as every four hours.

Some surveillance systems are interactive and allow the user to invoke specific processes to get an immediate result. These systems permit the user to analyze and view data as they are being received. ESSENCE provides both options. Data are processed at regular intervals and results available for display, but they are also available for user-defined analysis as soon as they are received, archived, and preliminary processes are completed.

User Interfaces

Many advanced disease surveillance systems take advantage of modern Internet technology. Typically, a user/analyst views a website once a day, but in the event of an emergent health threat, more frequent or ongoing analysis is possible if data are available.

Most modern disease surveillance systems provide outputs to users as soon as the signal processing phase is complete. Users log on to the surveillance system and view the alerts or data. The alerts may be in the form of "flags" indicating that a predetermined "threshold" has been exceeded or an anomalous condition detected; temporal and spatial data displays; or lists of cases that contributed to the alert.

"Real Time" Versus "Batched"

Most modern disease surveillance systems have multiple processes that must be completed before the data are provided to users. Collecting data in real time while processing it in batch due to the constraints in computing time does not make

[4]An algorithm is a set of well-defined rules or procedures for solving a problem in a finite number of steps, or providing an output from a specific set of inputs (Banner Engineering Corp., 2007).

for a real time system. Going through the extra expense of maintaining a VPN to collect HL-7 hospitals as they are being created makes little sense unless these data can be processed and made available to the analyst also in real time However, the question remains whether real time is even needed by public health.

It is hard to conceive of any public health need for the more timely collection of data than that provided by CDC's BioSense program. This program has implemented the collection of "batched" HL-7 hospital records every 15 minutes. The total throughput or time delay of the current BioSense processing steps is not known to the author, but it can safely be estimated to be greater than 15 minutes. The BioSense data feed is batched, but more timely than systems claiming to be real time.

Given constraints on time and resources, one could envision two modes of operation for electronic surveillance systems: one for the routine monitoring of public health, and the other to examine a specific threat based on case definition. For routine monitoring purposes, it will be of paramount importance to keep alert rates to a manageable level. The focused monitoring of perceived threats should be a rare occurrence, but essential information should be obtainable in sufficient time to mount an effective response to an emerging crisis.

Summary

The term "real time" as defined by the IEEE's Computer Society Technical Committee is not appropriate for use in describing modern automated disease surveillance systems. The benefits of real-time data collection are only realized if all other components of a surveillance system satisfy the real-time criteria. Receiving and processing health indicator data several times an hour should be more than adequate for public health needs, even during public health emergencies. The use of the term "real time" is often confused by vendors who misuse the term in an effort to distinguish their product as being better than someone else's. Consumers should attempt to understand the actual system characteristics rather than relaying the misuse of terms by vendors of surveillance systems.

ONE WORLD—ONE HEALTH: WILDLIFE AND EMERGING DISEASE SURVEILLANCE

William B. Karesh, D.V.M.[5]
Wildlife Conservation Society

Outbreaks of avian influenza, severe acute respiratory syndrome (SARS), Ebola hemorrhagic fever, bovine spongiform encephalopathy (mad cow disease),

[5]Director, Field Veterinary Program; Co-Chair, The World Conservation Union (IUCN) Species Survival Commission's Veterinary Specialist Group.

and other emerging diseases are surprising the public, disrupting globalization, resulting in massive economic losses, and jeopardizing business and diplomatic relations. These diseases, which are able to cross the Darwinian divide between animals and people, do not depend on humans for their survival and easily live far from the reaches of most medical interventions. Their competitive advantage in this regard demands that we revisit basic strategies for disease control, including the assumptions from the 1950s declaring the chapter on the threat of infectious diseases closed. Not only was this narrow, urban human health point of view premature, but it diverted resources away from preparedness for dealing with the modern-day world of rapid travel and transportation of both goods and people, higher human population densities, and a growing dependence on intensified livestock production.

Although many in the developed world would hardly recognize meat not wrapped in clear plastic, the vast majority of humans still live in a world like our great-grandparents', buying their food fresh, salted, or smoked in open-air markets, or gathering it themselves. For much of the world, there are no systems of inspections for these markets, and few people have access to good health care, education on hygiene, common vaccinations, or antibiotics. The global transport of animals and animal products, which includes hundreds of species of wildlife (Karesh et al., 2005), also provides safe passage for their bacteria, viruses, fungi, and even the prion proteins that cause insidious illnesses such as mad cow disease and chronic wasting disease of deer and elk. Surveillance of infectious diseases is most useful when it occurs as close to the source as possible, rather than waiting to measure morbidity and mortality in distant lands. This requires a new approach, one that engages people around the world to work together in earnest and share findings in a timely manner.

Currently, no government agency is responsible for, or capable of, the surveillance and prevention of the myriad diseases residing around the world. None are given the responsibility for robustly pursuing the simplest of concepts—*the health of people, animals, plants, and the environment in which we all live are inextricably linked.* The great gains from specialization in the fields of human health, public health, livestock health, and wildlife health have unfortunately resulted in academic hubris and reduced communication across disciplines by the end of the 20th century. Avian influenza serves as the most recent reminder that, in fact, there is only "*one health*." Over the last decade, the Wildlife Conservation Society (WCS) has been working to engage stakeholders in this concept with projects and a series of symposia utilizing the One World—One Health theme in Durban in 2003 (Osofsky et al., 2005a, b), New York in 2004, Bangkok and Beijing in 2005 (Karesh and Cook, 2005), and Brasilia in 2007. The products of these meetings as well as guidelines for future efforts such as the "Manhattan Principles" are openly available.[6] This one health concept is gaining wide

[6]See http://www.wcs-ahead.org and http://www.oneworldonehealth.org.

acceptance and most recently has been endorsed by both the American Medical Association and the American Veterinary Medical Association. However, putting words into action presents the biggest challenge, and the world's agencies and academies devoted to human and animal health were built to support separate sectors rather than to facilitate collaboration.

The U.S. Department of Agriculture (USDA) is mandated and funded to protect the U.S. livestock industry. Radar screens are set to blink when livestock are threatened. Even the more recent concerns of agroterrorism have not done enough to support the global outreach necessary to understanding and reducing diseases overseas before they reach U.S. shores. The wildlife services branch of USDA traditionally was focused on wildlife control and eradication in order to protect livestock. It is rapidly trying to remake itself in a modern world that is recognizing the cultural, ecosystem, and economic value of wildlife itself. But developing an effective program, building a reputation and trust among the wildlife community, and developing expertise in wildlife surveillance will take a long-term commitment that may or may not be on the horizon (or appropriate, in all fairness) for a federal agency focused on agricultural production and markets.

The United Nations' Food and Agriculture Organization's (FAO's) priorities are the production of livestock and crops, with a focus on the urgent needs of developing countries. Traditionally, few resources were devoted to exploring the linkages of the health of wild plants and animals with their domesticated cousins. This has changed since 2005, and a small program was begun in collaboration with the WCS to coordinate responses and investigations of highly pathogenic avian influenza virus in wild birds.

The World Organization for Animal Health (OIE)[7] has a volunteer committee composed of six people who meet for three days per year to address all of the world's wildlife-related disease issues. In the past two years, they have formed a parallel committee to address zoonotic and emerging diseases but the two committees are not linked to one another. The World Health Organization (WHO) is directed at human health, but until the change in the International Health Regulations (IHRs) that took effect this year, they could only respond on official invitation from a country that may or may not know about, or want to reveal, the presence of a disease. The changes in scope will allow for gathering of information without going through official channels. This could help significantly in global response time, but the IHRs are still institutionally entrenched in a world of human disease. The U.S. Centers for Disease Control and Prevention (CDC) has the responsibility to prevent human diseases in the United States, and extend their reach around the world, but also only when invited.

No government agency or multilateral organization is charged with uniting knowledge and efforts that span the diversity of disease threats to people, domestic animals, and wildlife. No one is ensuring that health solutions are based on the

[7]Office International des Epizooties.

input of expertise from human, domestic animal, and wildlife health professionals and equally important, communicated across disciplines in terms that effectively motivate all stakeholders and demonstrate common goals.

Clearly, there is an urgent need for a new health paradigm that not only integrates the efforts of disparate groups, but possibly more important, balances their respective influences to prevent both the gaps and the biases that we are now coming to recognize. The failure to recognize and aggressively address the broad range of diseases that have no respect for hundreds of years of earnest scientific classification, places animals and people in great danger. The immediate effects of the diseases themselves are often the least of the worries. Infectious diseases of people and animals are drivers of poverty and associated civil unrest, disrupt "free" ecosystem services such as drinking water and plant pollination, and can ruin otherwise well-planned and sustainable economic development efforts.

Analyses indicate that more than 60 percent of the over 1,400 infectious diseases currently known to modern medicine are shared between humans and animals (Taylor et al., 2001). From an anthropocentric point of view, most of these infectious agents are labeled zoonotic, or diseases of animals that infect people. Anthrax, Rift Valley fever, plague, Lyme disease, and monkeypox are just a few examples. Receiving less attention is the other group that moves across species boundaries, the anthropozoonotic diseases. These infectious diseases are typically found in humans but can, and do, infect animals. Human herpes virus, human tuberculosis, and human measles are all transmissible to a variety of animal species, with devastating consequences. This traditional division of infectious agents into two groups is convenient for teaching purposes, but lacks the broader and critically important concept that these diseases can move back and forth, and change characteristics in the process. Avian influenza is but one disease that is teaching the medical world about the need for a more holistic point of view.

The consensus of scientific opinion on the origin of HIV/AIDS links it to human consumption of nonhuman primates along with their simian immunodeficiency viruses, estimated to have taken place in Africa late in the first half of the 20th century (Feng et al., 1999). Recent Ebola hemorrhagic fever outbreaks in humans in Africa have a similar history. The disease was first recognized by the western world when it appeared in the Democratic Republic of Congo in 1976, around the Ebola River. The virus infects people, gorillas, chimpanzees, and monkeys (Leroy et al., 2004). It causes severe internal and external hemorrhaging, and can be extremely deadly, killing up to 90 percent of its human victims. Infection spreads quickly, especially via caregivers and by those who flee to escape the illness. Outbreaks have been recorded in Sudan, Gabon, Republic of Congo, Democratic Republic of Congo, Côte d'Ivoire, and Uganda. But it is clear that both people and nonhuman primates suffer equally from the disease. Outbreaks have caused declines in lowland gorillas and chimpanzees in Gabon and the Republic of Congo, and chimpanzees in western equatorial Africa. Other forest animals, such as duikers—small antelopes—and bush pigs may also be

affected. When subsistence hunters discover a sick or dead animal in the forest, they view it as good fortune and bring it home to feed their families and trade with neighbors. The Ebola virus then easily infects those handling the meat, and a chain of contacts and infections ensues. Each human outbreak in central Africa during the late 1990s and the first years of this century was traced to humans handling infected great apes.

The SARS coronavirus has been associated with the trade in small wild carnivores. This disease first appeared to the world in China's Guangdong Province in late 2002. People began complaining of high fever, cough, and diarrhea, and eventually developed severe pneumonia. It was an unknown disease, and it was very contagious. Within a matter of weeks, it spread via a hotel visitor in Hong Kong to five continents. By July 2003, WHO had tallied 8,437 cases, with 813 deaths. Mostly because of a lack of understanding of this "new" disease, global travel and trade were disrupted as fear spread. A coronavirus (a family of viruses found in many animal species) was finally discovered to be the culprit, and it was also detected in masked palm civets that were farmed in the region and sold for human consumption. Later, evidence of the virus was also found in raccoon dogs, ferrets, and badgers in the wildlife markets, as well as domestic cats living in the city and a closely related coronavirus in bats commonly sold in the same markets. Epidemiological studies have concluded that the first human infections did indeed come through animal contact, though the exact species has not been definitively identified (Tu et al., 2004). In the weeks after SARS, the Chinese government responded by closing down live wildlife markets. Within 10 days, nearly a million animals were confiscated, many brought in from other parts of the world with their exotic viruses and bacteria, demonstrating that law enforcement can in fact be used to reduce or control the trade in wildlife and wildlife products. The animals were mixed and matched, exposed to each other's wastes and even fed to each other. If a virus or bacteria was hoping to win the big lottery of jumping among species, going to the markets of Guangdong would be like buying a million lottery tickets. The profits from the wildlife trade in China pale in comparison with the estimated U.S. $50 billion global economic costs resulting from the brief SARS event of 2003 (Newcomb, 2003).

The inadvertent movement of infectious agents due to wildlife handling and trade, as well as domestic animal movement, is not limited to human pathogens, but also extends to those that can devastate native wildlife, which serve as biological linchpins for environmental integrity and provide a range of cultural and quantifiable economic values (Karesh et al., 2005). In 2005, H5N1 Type A influenza virus was isolated from two mountain hawk eagles illegally imported from Thailand in airline cabin carry-on baggage to Belgium (OIE, 2004). Tuberculosis originating from domestic cattle has now infected wild herds of bison in Canada, deer in Michigan and Wisconsin, and Cape buffalo and lions in South Africa. Surveillance of these wild populations is now needed not only to assess risk for humans and livestock, but for the wild animals themselves. In one swift

outbreak of rinderpest, a disease originally introduced to Africa by the importation of domestic cattle, more wild buffalo died in Kenya in 1999 than were killed by illegal poaching during the previous two decades.

Exact quantification of the global wildlife trade is impossible because it ranges in scale from extremely local to major international routes, and much is illegal, or through informal channels. WCS figures compiled from a variety of sources for just the live wildlife trade indicate that each year, roughly 40,000 live primates, 4 million live birds, and 640,000 live reptiles are traded globally (Karesh et al., 2005). Daily, wild mammals, birds, and reptiles flow through trading centers where they are in contact with humans and dozens of other species before being shipped to other markets, sold locally, and even freed back into the wild with new potential pathogens as part of religious customs such as merit release or because they become unwanted pets. Conservative estimates indicate that in east and southeast Asia, tens of millions of wild animals are shipped regionally and from around the world annually for food or use in traditional medicine. The estimate for trade and local and regional consumption of wild animal meat in Central Africa alone is more than 1 billion kg per year (Wilkie and Carpenter, 1999). In Central Africa, estimates of the number of animals consumed by humans annually vary, but a figure of 579 million has been proposed. Estimates for consumption in the Amazon Basin range from 67 to 164 million kg annually, comprising, for mammals alone, between 6.4 million and 15.8 million individuals (Peres, 2000).

Hunters, middle marketers, and consumers make some type of contact with each animal traded. Additionally, domestic animals and wild scavengers in villages and market areas consume the remnants and wastes from the traded and to-be-traded wildlife. These numbers combined suggest that at least some multiple of 1 billion direct and indirect contacts among wildlife, humans, and domestic animals result from the handling of wildlife and the wildlife trade annually.

In addition to the direct health effects of the pathogens on people and animals, animal-related disease outbreaks have caused hundreds of billions of dollars of economic damage globally, destabilizing trade, and resulting in devastating effects on human livelihoods. According to studies performed by Bio-Economic Research Associates, the rash of emerging or reemerging livestock disease outbreaks around the world since the mid-1990s—including mad cow disease, foot-and-mouth disease, avian influenza, swine fever, and other diseases—has been estimated to have cost the world's economies more than $100 billion. The costs are rarely borne by the same individuals that profit from the movement of animals and their pathogens. As mentioned earlier, the cost of SARS alone to the global economy has been put at more than $50 billion (Newcomb, 2003). Wildlife market traders did not bear the costs of the SARS outbreak. The rodent importer in Texas did not reimburse government agencies for the millions of dollars spent on the response to monkeypox in the United States. Hundreds of

millions of public dollars will be spent in attempting to remove tuberculosis and brucellosis from wildlife populations infected by domestic animals.

In early 2003, FAO reported that more than one-third of all global meat trade was embargoed as a result of mad cow disease, avian influenza, and other livestock disease outbreaks. The projected growth of industrial livestock production in developing countries to meet rising global protein demand will increase both the economic and the food security impacts of future disease outbreaks, and the global economic impacts do not adequately reflect the local, direct effects.

Preventing and controlling infectious diseases in the modern world requires a far broader range of expertise than needed for previously isolated systems in highly developed countries. The challenges seen in controlling avian influenza in Asia and Africa are just one example of the multispecies disease dilemma. Most of these diseases threaten local people directly, as well as their livestock and their livelihoods. They decimate wildlife and undermine ecosystem stability and services, and with modern travel and transport, they can quickly pose a threat to any nation. Fear, understandably founded on a lack of information, can drive global responses and economic reactions far beyond the actual cost of disease control.

Currently, it appears that a few people in some of the most remote places on earth, many from nongovernmental organizations (NGOs) and many working at local government levels but unlinked to larger formal networks, are working to fill the intersectorial gaps in health care as they relate to emerging diseases and wildlife. WCS's global health programs are an example of a private-sector effort linked to governmental and multilateral agencies that bring together stakeholders, from civil society and a variety of government sectors, to develop surveillance and information-sharing networks. The work is directed where rare infectious diseases are least understood and local institutions have the fewest capabilities to effect prevention and control. Our staff and partners routinely encounter diseases such as anthrax, avian influenza, monkeypox, and Ebola where they naturally occur. We build local capacity to conduct surveillance and reporting networks at very low costs. When attention was being misdirected at wild birds in efforts to control the current avian influenza outbreaks in Southeast and East Asia, these new, but informally recognized participants in health discussions, were the first to point out that migratory routes and seasonal timings did not correspond with the regional spread of the disease as posited by articles in prestigious scientific journals—it was the largely uncontrolled movements of domestic birds that were spreading this disease, not wildlife. Control efforts would be needlessly misdirected without this simple input to decision makers.

Building bridges across disciplines to solve health problems can have simple but significant synergistic effects. Studies in South America have shown that, contrary to common opinion, livestock diseases pose more threats to wildlife than the other way around. In much of the world, reducing disease in domestic animals would benefit several industries, improve human health and livelihoods, and help protect wild animals from livestock and other domestic animal diseases.

In Central Africa, gorillas and chimpanzees have little to no immunity to common human diseases. Local people and tourists threaten wild populations with these illnesses, which could be simply avoided by implementation of good preventive health programs and practices in villages. People and wildlife both benefit. WCS's work with Ebola hemorrhagic fever in gorillas and chimpanzees has shown that when investments are made for working not just in the cities but in the forests, natural resource managers can help to detect the presence of the disease in wildlife months before the first human cases—providing the lead time to warn villagers not to hunt or handle the animals that are the source of infection.

Over the past two years, the WCS network of local villagers and hunters, park managers and staff, government public health officials, and regional laboratories has detected outbreaks of Ebola in great apes and notified local communities. For the first time, known human outbreaks resulting from the disease in animals have not occurred. This broader, one-health approach is much more effective and inexpensive than the traditional "quarantine and stamping out" efforts after an outbreak has begun. A set of guiding concepts on these themes, called the Manhattan Principles, was developed by human and animal health specialists in conjunction with wildlife conservation professionals.[8]

Another large-scale example of a worldwide private–public collaborative effort is the Global Avian Influenza Network for Surveillance (GAINS) of wild birds. The U.S. Agency for International Development (USAID), CDC, and USDA are providing support to WCS to develop and administer the wild bird GAINS program. GAINS is a smart and targeted investment in the U.S. government's fight against avian influenza, because wild birds around the world can serve as sentinels for the early detection of the virus's presence.

Awareness of and interest in the GAINS program continues to grow. Working relationships with local institutions are being built in more than 28 countries, with many more anticipated. This network of partners builds a "window on the world" and has helped GAINS bring timely and pertinent information that will help combat the threats posed by highly pathogenic avian influenza to both humans and animals.

The GAINS program has made significant progress in its global implementation since receiving start-up funding in summer 2006. Collaborations have been established between WCS and U.S.-based and international organizations—including governments, NGOs, and universities—to work together to improve our understanding of the dynamics of avian influenza, and to evaluate disease risks for people, biodiversity, and domestic poultry. WCS staff have been in active discussions with colleagues from USAID, CDC, Department of Homeland Security (DHS), Department of Defense (DoD), U.S. Geological Survey (USGS), USDA, National Institutes of Health (NIH), Department of State (DoS), WHO, FAO, as well as university and private-sector experts to address integrated approaches to

[8]See http://www.oneworldonehealth.org.

global disease information management issues. Together with FAO, WCS has conducted training efforts in Eastern Europe, Latin America, and the Caribbean, and a recent agreement with USDA will expand training and bird monitoring in Latin America. WCS is providing technical expertise related to health monitoring of wild birds and capacity-building activities around the world.[9]

GAINS fieldwork also enables the isolation of new viral strains, which can contribute to vaccine development and help guide preparedness in the United States and abroad. One of the primary purposes of GAINS is to share international disease information through an interactive, publicly accessible web-based database, a working prototype of which has already been made available on the GAINS website. The database is starting to map sample collection sites, flyways, and results of biological surveillance. The goal is to alert decision makers about disease occurrence rather than waiting for traditional scientific journal publication.

From Afghanistan to Zimbabwe, field surveillance for avian influenza is currently underway. Our work in Mongolia illustrates the field methodology being used in many sites. Mongolia has been a hot spot for avian influenza outbreaks in the past two years and is a country where wild birds appear to be of particular importance to the ecology of the disease. Last year WCS staff collected more than 3,500 samples at 42 sites across the country. WCS staff collected an H5N1 strain of avian influenza virus from wild birds that have been selected by WHO to be used in human pandemic vaccine development and testing. Working with WCS staff in Mongolia, USGS scientists fitted whooper swans from the region with satellite transmitters (supplied by FAO) in early August, and some have been tracked to China, Korea, and Russia. These types of data may shed light on possible viral transmission routes across Asia.

The early successes with the Wild Bird GAINS program has led to expansion of the program to a broader range of infectious diseases and species. Named the Wildlife Global Animal Information Network for Surveillance (Wildlife GAINS), the effort is designed to establish a comprehensive, worldwide wildlife health surveillance system to enhance preparedness for and awareness of emerging infectious diseases. This nongovernmentally managed network would connect a wide variety of U.S. government agency partners, multilateral agency partners, conservation organizations, veterinary and medical schools, and other national and international partners. The unique strengths and capacities that NGOs such as the Wildlife Conservation Society have to work with developing country governments and scientific colleagues must be harnessed to develop and enhance surveillance mechanisms that are of great importance to human security and well-being.

Workers in the fields of health and global governance need to find ways to focus skills and expand resources to make the entire world safer from infectious

[9]See http://www.gains.org.

disease. The financial costs of disease outbreaks are currently borne by the global economy and will only serve to slow economic development where it is needed the most. There is an obvious need to break down barriers among health disciplines to prevent any one of them from restricting funding to their area of interest, and there is an urgent need to build bridges among the government agencies and the privately operating individuals and organizations around the world that now take responsibility with only scarce resources. Immediately, before the next global pandemic, trade in wildlife needs to be dramatically reduced and, like the livestock industry, properly regulated. Finally, global health will not be achieved without a philosophical shift from the "expert dictates" paradigm inherent to both science and medicine, to a broader, multistakeholder approach, based on the understanding that there is only "one world and one health."

AGRICULTURAL BIOSECURITY: THREATS AND IMPACTS FOR PLANT PATHOGENS

Jacqueline Fletcher, Ph.D.[10]
Oklahoma State University

James P. Stack, Ph.D.[11]
Kansas State University

Plant Vulnerability to Disease

Plant resources in the United States, including crops, rangelands, and forests, are vulnerable to endemic, introduced, and emerging pathogens (American Phytopathological Society Public Policy Board, 2002; Casagrande, 2000; Madden and Wheelis, 2003; Wheelis et al., 2002; Whitby, 2002). An estimated 65 percent of U.S. crop losses, valued at $137 billion, are attributed to introduced pathogens annually (Pimentel et al., 2000). Increasing globalization and international trade activities create a strong likelihood that many other exotic plant pathogens will arrive in the United States in the coming years.

The vulnerabilities of U.S. agricultural production to emerging diseases result from a number of factors. Huge acreages are planted with grains and forage crops, or are covered with grasslands or forests. Because it is impossible to regularly or frequently monitor such extensive areas for disease symptoms, long periods are likely to pass between the time a pathogen is introduced and when it is detected. A second source of vulnerability is the lack of genetic diversity in our plant resources; most of our nation's production is centered on just three

[10]National Institute for Microbial Forensics & Food and Agricultural Biosecurity, and Department of Entomology and Plant Pathology.

[11]Biosecurity Research Institute.

crops: wheat, corn, and soybeans. Within these and other crop species, certain genotypes conferring attributes important for yield and quality are preferentially grown over large areas, increasing the chance that a pathogen detrimental to that cultivar will have serious impact.

More than 50,000 plant diseases occur in the United States (Madden, 2001; Madden and Wheelis, 2003), caused by a variety of pathogens, including fungi, viruses, viroids, bacteria, nematodes, and parasitic plants. These organisms are disseminated by various means, including wind, water, agricultural equipment, seeds or propagative plant parts, insect vectors, animals, or farm workers. For any given region and crop, producers may deal with up to 10 to 15 serious plant diseases that can cause severe economic repercussions (Pinstrup-Andersen, 2001). About 65 percent of U.S. crop losses are due to nonindigenous (introduced) pathogens, amounting to an estimated cost of $137 billion annually (Pimentel et al., 2000). All crop pests (pathogens, arthropods, and weeds) combined caused preharvest losses of 42 percent and an additional 10 percent loss after harvest. Of these, 13 percent were due to plant pathogens, 15 percent to arthropods, and 13 percent to weeds. Worldwide, losses for the eight major crops that comprise half of the global croplands were estimated at $300 billion in 1988–1990 (Oerke et al., 1994).

A number of pathogens that occur elsewhere in the world are of significant concern to U.S. plant production, should they arrive. Most past introductions of plant pathogens to the United States have been unintentional. Many pathogens not yet in the United States would pose significant threats to our current crops. Because eradication of plant pathogens is rarely physically or financially feasible, the only effective approach is to manage the disease so that its impact falls below an economic threshold—the point at which management costs exceed the profits associated with production.

The use of microbes, such as the anthrax bacterium, against human targets is a highly visible act with immediate consequences. Directing pathogens toward agricultural targets may be less visible, and effects may not be apparent for some time. However, such actions, which effectively target the nation's food supply—from its production in the field to its place on the plate—may have serious and long-range impacts (Adam, 2006). Many plant pathogens can be acquired readily by those wanting to use them intentionally for purposes of harm. Furthermore, they may be attractive agents for nefarious applications because they can be handled, grown, transported, and disseminated with little technical expertise or equipment, and pose little or no danger to the health of the handler. The Institute of Medicine (IOM)/National Research Council (NRC) Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats recently concluded (2006) that the increasing accessibility and simplicity of technological information related to pathogens increase the likelihood that rogue states or individuals may use such knowledge in a criminal manner.

History of Biological Warfare

Biological warfare has been targeted to agricultural systems in the past. Around the world, state-sponsored programs supported research to enhance the suitability of microorganisms for use as weapons (Casagrande, 2000; CIDRAP, 2003; Madden and Wheelis, 2003; Wheelis et al., 2002; Whitby, 2002). Before the Biological and Toxin Weapons Convention outlawed state programs on biological weapons in 1972 (IOM/NRC, 2006), U.S. research programs had focused on the pathogens causing anthrax, foot-and-mouth disease, and rice blast. Germany had bioweapons programs during World Wars I and II, the former Soviet Union during World War II and the Cold War, and Iraq at the time of the Iran–Iraq War. Islamic militants in Afghanistan were involved in weaponization of the fungus *Puccinia graminis,* causal agent of wheat rust. Canada, France, Japan, and the United Kingdom also considered the use of bioweapons against agricultural targets.

Despite knowledge of such research activity in multiple countries, no reports of the deliberate use of pathogens against crops or other plants have been published. Yet, indicators of increasing likelihood of such use point to the need for preparedness. The United States must develop the capabilities and knowledge to ensure the safety and security of our food at all levels, and at all points of production—the distribution pathway from farmers' fields to the consumer. Rapid action is critical if we are to have these capabilities in place before they are needed for a devastating incident.

Impacts of Plant Diseases

Past incidences of the impacts of crop diseases on human health and society may be helpful in illustrating the potential damage of plant pathogens. The Irish potato famine (1845–1846), caused by the plant pathogen *Phytophthora infestans,* led to extensive famine and resulted in the deaths of a million people and the emigration of another 1.5 million Irish, many to the United States (Large, 1940; Carefoot and Sprott, 1969; Schumann, 1991). During the same timeframe, the severe impact of a rust fungus on coffee production in Ceylon (now Sri Lanka), the prime supplier of coffee to Great Britain, forced much of British society to turn to tea as their primary hot beverage (Large, 1940; Schumann, 1991). Weather conditions in both the United States and Europe during World War I were favorable for the development of plant diseases in wheat and potatoes, crops essential for nourishing the troops on both continents. The critical food shortages that ensued were factors in the movement and strength of the troops and changed the course of the war. Brown spot of rice contributed to the Great Bengal Famine of 1943, and in the United States, a 1970 epidemic of corn leaf blight destroyed about 20 percent of the $1 billion crop (Rogers et al., 1999).

U.S. agricultural infrastructure is strong, diverse, and resilient. Temporary unavailability or elimination of a certain food product because of plant disease

is unlikely to result in significant nutritional hardship for Americans. The same cannot be said for all countries, however; a serious rice disease in Southeast Asia, for example, could lead to malnutrition and hunger, destabilizing social infrastructures in affected areas.

Deliberate introductions of plant pathogens to crops and other plant resources in the United States could have serious non-nutritional impacts (Budowle et al., 2005a, b; Murch et al., 2003; Fletcher et al., 2006). Likely impacts of crop diseases in the United States include losses in the quality and quantity of our food, increases in consumer food prices, costs of growing crops that are less desirable, and costs of management strategies, both short term (crop destruction, pesticide application, or redirecting use of the crop) and long term (development of resistant varieties) (Casagrande, 2000; Madden and Wheelis, 2003; Wheelis et al., 2002; Whitby, 2001, 2002). Several plant pathogens can also infect humans; these are primarily opportunistic pathogens of greatest concern to immunocompromised patients, the very young, or the old. Some plant pathogenic fungi produce mycotoxins that can pose important health risks for humans, and other species produce spores that are allergenic. There also can be important indirect impacts on human nutrition, as well as on the agricultural community, if plant products used for livestock feed are lost.

The most significant impacts of deliberate plant pathogen introductions, however, are likely to be economic in nature. Imposition of quarantines and embargoes on U.S. agricultural products not only affect producers, but have downstream effects on the commercial enterprises that harvest, store, package, transport, add value, and market the commodity. Perhaps more importantly, there could be a loss of trading partners and markets worldwide. Furthermore, knowledge of intentional targeting of the food supply by those intending harm would lead to a loss of public trust in our food and in the ability of government to ensure its safety. Ultimately, rural communities that rely on agricultural production may be destabilized and grower livelihoods threatened.

At the other end of the food system continuum, there has been an alarming rise in the incidence of foodborne illnesses due to microbial contamination of fruits and vegetables. A recent survey by the U.S. Food and Drug Administration (FDA) of samples from major distributors showed that 1.6 percent of domestic produce was contaminated with human pathogens (FDA, 2001). Recent incidents of contamination of leafy greens and peanut butter with the human pathogens *E. coli* O157:H7 and *Salmonella spp.* demonstrate the devastating impact that may result from the introduction of microbes into fresh food plants. Today's mass food production operations and national distribution systems have caused a significant increase in the scope of such foodborne illnesses (Maslanka et al., 2002). Once primarily local events, with local response, food contamination incidents are now far more widespread. In the fall 2006 *E. coli* outbreaks, 205 victims in 26 states suffered severe disease and 3 died. As a result, consumers changed their buying

habits, producers of the affected crops suffered significant economic losses, and downstream enterprises were negatively impacted (FDA, 2007).

High-Consequence Plant Pathogens and Diseases

In 2004, the U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS), as designated in 7 C.F.R. Part 331 of the Agricultural Bioterrorism Protection Act of 2002, first established a list of plant pathogens of high consequence to be designated as Select Agents[12] (Table 1-3). Although this list is similar in nature to the Select Agent lists for human and zoonotic diseases, there is one important difference. Plant pathogen Select Agents are, at the time of their placement on the list, exotic microbes not endemic or established in the United States. This contrasts with the policy of listing indigenous human and animal pathogens on their respective lists. The fact that, by definition, plant Select Agents are not indigenous within the United States necessitates the imposition of strict regulations, registrations, restrictions, and security[13] on any research or possession of these microbes.

Originally consisting of 10 plant pathogens, the recent removal of 2 pathogens (Plum pox virus and *Phakopsora pachyrhizi,* the causal agent of soybean rust) after their arrival and establishment in the United States has left the list with 8 agents. A mandated biannual review and possible revision of the plant Select Agent list is underway at the time of this writing.

Citrus Canker: A Recent Example of Significant Disease Impact

Florida produces about 80 percent of the citrus grown in the United States, and most of the state's fruit is processed for juice. The industry is worth about $1.4 billion per year. Although *Xanthomonas axopogonis* pv. *citri*, the bacterium that causes the devastating citrus canker disease, is not on the Select Agent list, it has occurred in Florida citrus-growing areas several times since the turn of the century, each time causing brown, necrotic, raised scars or cankers on leaves, stems, and fruit.

Canker is a quarantine disease; fruit from affected areas cannot be moved across state lines or sold in the world market. Because the disease was not considered established in the United States, an eradication strategy has been in place for many years. This approach was successful in Florida in the early 1900s and again in the 1980s. APHIS and the Florida Department of Agriculture and Consumer Sciences adopted that same strategy for the most recent outbreak, which was first detected in 1995. However, the latter outbreak presented new challenges.

[12]See http://www.apsnet.org/online/feature/BioSecurity/ and http://www.cdc.gov/od/sap/docs/salist.pdf.

[13]See http://www.aphis.usda.gov/programs/ag_selectagent/index.html.

TABLE 1-3 U.S. Select Agent List for Plants

• *Liberobacter africanus*	Citrus greening (African)
• *Liberobacter asiaticus*	Citrus greening (Asian)
• *Ralstonia solanacearum* R3 Bv2	Potato bacterial wilt
• *Xanthomonas oryzae* pv. oryzicola	Rice bacterial leaf streak
• *Xylella fastidiosa*	Citrus variegated chlorosis bacteria
• *Peronosclerospora philippinensis*	Philippine downy mildew of corn
• *Sclerophthora rayssiae var zeae*	Brown stripe downy mildew of corn
• *Synchytrium endobioticum*	Potato wart fungus
• **Pathogens not yet established in the United States*	
• Pathogens recently removed from Select Agent list	
• *Phakopsora pachyrhizi**	Soybean rust
• *Plum pox virus*	Pox of stone fruits

*Also spelled pachyrhizae.
SOURCE: Fletcher (2006).

First, the initial eradication guidelines called for elimination of the diseased tree, plus any citrus trees within a 125-foot radius of the symptomatic plant. Although this policy was not popular, it was relatively well accepted. However, in the late 1990s, these measures failed to prevent disease spread. Further research led to an eradication strategy modification requiring the elimination of all citrus trees within a 1,900-foot radius of any infected tree. Complicating matters was the fact that the 1995 outbreak was not confined to commercial groves. It also was widespread in residential areas of Miami where landowners objected, some filing lawsuits to stop the eradication campaign. While the legal issues were debated in court, the disease continued to spread. The eradication plan eventually was upheld by the courts and the program was reinstated (Gottwald et al., 2002); overall, $200 million was spent and more than 10 million trees were destroyed (Brown, 2001). However, the occurrence of several hurricanes in Florida in 2005 spread the pathogen far beyond its previous locations and eliminated hope of eradication. In 2006, USDA APHIS revised its approach to focus on managing the disease.

Arrival of Two Plant Pathogen Select Agents

Two plant pathogens on the Select Agent list have arrived in the United States in the past two years. Were we ready for them?

Soybean rust, caused by the fungus *Phakopsora pachyrhizi,* affects a major U.S. crop that is grown over 75 million acres and is worth more than $18 billion a year (USDA-ERS, 2007). In areas where the rust is endemic, such as Asia and South America, yield losses commonly range from 10 to 30 percent, but can be much higher. U.S. producers, who grow 74 million acres of soybeans/year (accounting for about $15.7 billion), feared that the arrival of the fungus would

severely impact the industry. U.S. epidemiologists had been monitoring the global movement of the pathogen for several years in an effort to provide warning for its inevitable arrival to U.S. territory. The disease was first detected in the United States in fall 2004 (Schneider et al., 2005). The first diagnosis, in Louisiana, was quickly followed by detection in several other states, but because the disease arrived after the soybean crop had been harvested there was no impact on production that year. Indeed, the 2005 and 2006 growing seasons were characterized by weather patterns unsupportive of *P. pachyrhizae* infection and disease, so actual losses have not yet approached the damaging levels anticipated. This has been good news for producers, but ironically, has prompted a sense of security that may be unfounded in future years when conditions may be more conducive to pathogen establishment.

Regardless of the seriousness of soybean rust to date, the fact that the pathogen was distributed widely—again likely by hurricane winds in 2005 (Stokstad, 2004)—and the fact that it establishes easily and overwinters in a variety of hosts, including an extremely invasive vine called kudzu, means it is now considered to be established in the United States (Pivonia and Yang, 2004). Since the plant Select Agent list contains only exotic pathogens, APHIS removed *P. pachyrhizae* from the list in 2006. "Delisting" has several implications, both positive and negative. Federally mandated response to, and management of, a Select Agent is extremely expensive for both federal and state agencies. In addition, the extensive and expensive policies, certifications, permits, and containment requirements for scientific research on Select Agents are significant disincentives for plant pathologists to work on the pathogens of greatest concern. The removal of *P. pachyrhizi* from the list will facilitate research, but it also changes the responsibility of federal agencies in their response to the disease.

The bacterial pathogen *Liberobacter asiaticus,* a Select Agent that causes a disease officially known as "huanglongbing," or citrus greening, was discovered in Florida in fall 2005 (APHIS, 2007). Its possible arrival had been a concern for at least two years, after it was learned that its insect vector—the citrus-feeding Asian citrus psyllid, *Diaphorina citri*—had arrived in the state and would be likely to spread the pathogen quickly should it arrive. Like citrus canker, huanglongbing was more damaging than anticipated because it, too, occurred during the 2005 hurricane season, when extensive wind dissemination of inoculative vector insects quickly resulted in the pathogen becoming endemic in the state. The question of whether *L. asiaticus* will or should be removed from the Select Agent list is complicated by the fact that, although the bacterium may be established in Florida, it is not yet known to occur in citrus-growing regions of Texas, California, and other southern states.

Components of a Strong Plant Biosecurity Strategy

A robust system of preparedness for threatening exotic or emerging plant diseases will require the following elements:

- Early detection and diagnostic systems
- Epidemiological models for predicting pathogen spread
- Reasonable but effective strategies and policies for crop biosecurity
- Distributed physical and administrative infrastructure
- A national system for strategic planning and response coordination
- Microbial forensic capability: validated technology and investigative capability

Before 2001, our national capability in plant disease diagnostics and recovery was fragmented, poorly supported. and of limited effectiveness due to declining resources. In the past five years, however, significant improvements in infrastructure will help to ensure preparedness for a serious plant pathogen introduction event. In 2004, President George Bush issued Homeland Security Presidential Directive 9 (HSPD-9), which mandated a National Plant Disease Recovery System (NPDRS). The USDA Office of Pest Management Policy, assigned by the Secretary of Agriculture to develop the NPDRS, has worked to develop specific Recovery Plans for each of the Select Agents as well as for several other plant diseases of high consequence. Their approach, which is well underway at this time, has been to bring key experts from federal agencies, private industry, and academia together for the development of each plan, and to partner with the American Phytopathological Society (a 5,000-member professional society dedicated to plant health) to ensure broad-based community input and participation. Another important initiative has been the establishment—by USDA-Cooperative State Research, Education, and Extension Service (CSREES)—of the National Plant Diagnostic Network, an interconnected system of diagnostic laboratories affiliated with land grant universities and/or state departments of agriculture in each state (Stack et al., 2006).

At this writing, it is clear that many individual improvements and initiatives have enhanced our nation's ability to prevent and prepare for emerging plant diseases and pathogens. Individual efforts within federal agencies concerned with agricultural biosecurity (USDA APHIS, CSREES, and Agricultural Research Service [ARS]; Departments of Defense and Homeland Security; Environmental Protection Agency; and Food and Drug Administration) also have enhanced our preparedness. However, significant gaps remain.

Preparedness for events involving intentional introductions of plant pathogens, whether for purposes of bioterror or biocrime, must include a strong national security plan that encompasses microbial forensics and criminal attribution. However, U.S. crop producers, consultants, and agricultural scientists, unaccustomed to considering the possibility of intentional pathogen introduction, traditionally focus disease management strategies on prevention, rapid eradication, or long-term management. A recent study (Fletcher et al., 2006) assessed currently available information, technologies, and resources, developed for peaceful applications, which can be utilized for plant pathogen forensics. The authors also prioritized activities and resource expenditures needed to enhance our plant

pathogen forensics capabilities. Strategies needed for a comprehensive national microbial forensic capability, to determine the source of the pathogen and provide evidence for attribution, include (1) assuring high stringency of investigative technologies (validation, confidence, statistical significance, consistency); (2) tracing pathogen origin and movement; (3) identifying the timing and site of initial introduction; (4) identifying the perpetrators; (5) collecting evidence for criminal attribution; and (6) forming linkages with the law enforcement and security communities.

One of the most pressing gaps, because it impacts all the others, is the need for greater communication, cooperation, and coordination between and among federal agencies, academic institutions, and industry. Each of the agencies and entities contributing to national agricultural security has a unique mission and specific goals for which it is accountable to its stakeholders, and each is responsible for different elements of an outbreak response. Currently, there is no single entity, such as the Centers for Disease Control and Prevention (CDC) or a national center, to ensure strategic planning for future preparedness and the most effective and efficient response to a plant pathogen emergency. To be effective, this coordinating function should be established at a level above individual agencies. The coordinating entity would not duplicate or unnecessarily overlap the diverse elements of a robust national biosecurity plan because most of these responsibilities are charged to existing components of government. It would focus on strategic planning, program reviews, and coordination of activities among federal agencies, private entities, and academia; prioritization of research and education needs for allocation of limited resources; database and pathogen collections; and coordination of public relations.

Conclusions

Our nation's agricultural industry is strong and our food supply is among the safest in the world, but vulnerabilities do exist. Recent initiatives in various branches of government, academia, and industry have enhanced the security of our plant resources, but gaps and needs remain. Fortunately, the actions needed to sustain and protect our plant resources from intentional pathogen introduction, and to recover from deliberate plant disease outbreaks, will also enhance the effectiveness and productivity of normal U.S. agricultural enterprises. For example, in addition to the threat of intentional introductions of exotic plant pathogens and pests, new pathogen species or races emerge naturally. Globalization of markets, unprecedented international travel, and changes in climate from various causes all contribute to an increased likelihood that pathogens will move across national borders and employ adaptive strategies in response to exposure to new environments. Let us use the opportunities provided by these challenges to strengthen our agricultural production systems, and ensure that our nation continues to lead the world in providing food that is abundant, reliable, nutritious and safe.

PLANT BIOSECURITY INFRASTRUCTURE FOR DISEASE SURVEILLANCE AND DIAGNOSTICS

James P. Stack, Ph.D.[14]
Kansas State University

Jacqueline Fletcher, Ph.D.[15]
Oklahoma State University

Introduction

The vital role of plants in society is not well understood by the general population or by most policy makers. Healthy plant systems are a prerequisite to the health and welfare of human and animal systems, and are essential to the economies of developed nations. Human, animal, and plant systems are intricately linked; the intersection of these three systems forms the basis of our economy, our culture, and our standard of living. The emerging one-medicine concept of holistic health that encompasses animal and human systems is rational and obvious when we consider the value inherent in these systems and the impact that zoonotic diseases have had over the past 50 years (Dudley, 2004; Karesh and Cook, 2005; Potter, 2004). However, we must expand that holistic one-medicine concept to include plant systems.

When we assess value within our primary living systems, it is appropriate that human systems have the most value, animal systems second, and plant systems third. However, plant systems are the foundation of all three. Plants generate the oxygen we breathe. They are the food we consume directly and the feed we provide to the animals we consume. They are the fibers that clothe us and the timber that shelters us, and they are becoming the fuels that power the technologies associated with our high standard of living. They stabilize our ecosystems and beautify our landscapes. Plants have great aesthetic value and great economic value. Healthy plant systems are vital to our national economy and consequently to our national security. The stability of societies and economies depends on the health of plant systems (Diamond, 2005). Therefore, we must protect our natural and agricultural plant systems to ensure the sustainability of our food production systems and ultimately our society.

A Biosecurity Framework

A national strategy for plant biosecurity must be comprehensive with respect to science and policy and must address issues of infrastructure, technology, and

[14]Biosecurity Research Institute.

[15]National Institute for Microbial Forensics & Food and Agricultural Biosecurity, and Department of Entomology and Plant Pathology.

education. One conceptual approach to the development of plant biosecurity infrastructure is based on a simple outbreak model. In its simplest form, this model includes the following components: the source of the outbreak agent; the introduction of the agent into some new environment; the detection of that agent at some point after the introduction event; the accurate diagnosis of the new agent at some point after the detection event; the response to the outbreak; and the resolution of the outbreak. Each component requires a unique strategy for preparedness: potential introductions require a prevention strategy; detection requires a surveillance strategy; diagnosis requires a technology strategy; response requires a communications and mitigation strategy; and resolution requires a recovery strategy.

Prevention

The U.S. Departments of Agriculture (USDA) and Homeland Security (DHS) share responsibility for preventing the introduction of new plant pathogens and insect pests that threaten our plant systems. This is accomplished through the activities and programs of Customs and Border Protection (CBP) and USDA's Animal and Plant Health Inspection Service Plant Protection and Quarantine (USDA-APHIS-PPQ). Due to the extremely large and increasing volume of imports of plants and plant products, port and border inspections can never be 100 percent effective in preventing the accidental or intentional introduction of new agents. The increase in Internet-based commerce further adds to this challenge by providing a means to circumvent the inspection and quarantine process associated with interstate and international trade. Consequently, we must anticipate the introduction of agents that threaten our plant systems, whether accidental due to global trade, intentional due to terrorism or crime, or natural due to weather events (e.g., hurricanes).

A prevention strategy should include the capability to intercept those agents with a high probability of introduction and establishment. Several lists of high-consequence pathogens and pests have been generated by government agencies and scientific societies. One such list identified more than 500 plant pathogens and nematodes and over 700 insects and mites that pose threats to U.S. plant systems (Huber, 2002). We lack the resources necessary to develop specific plans for over 1,200 organisms. Because there is no defining set of characteristics to determine which threat agent will become established and cause significant damage, a prioritization process is needed to identify those high consequence agents with the greatest potential to cause persistent, wide-scale damage such that specific interception protocols are required. For example, if a new race of a pathogen emerged with the potential to destroy over 50 percent of the U.S. wheat crop, its characteristics indicate that the pathogen will establish and spread, there are no effective management tools, and pathways for pathogen introduction exist, then a comprehensive preparedness, response, and recovery strategy should be developed for that specific pathogen.

Surveillance, Detection, and Diagnosis

An Institute of Medicine study identified six critical elements necessary to a food safety system (IOM, 1998). These same six elements would provide the framework for biodefense against threats to national food security (King, 1999). Among those elements was a comprehensive surveillance and monitoring system. This element is as important for plant-based systems as it is for human and animal systems.

For the purposes of this paper, surveillance is the process of searching, detection is the process of finding, and diagnosis is the process of determining and/or verifying what is found. The National Plant Diagnostic Network (NPDN) was established by USDA in 2002 to provide the necessary critical infrastructure to facilitate early detection and rapid diagnosis of disease and pest outbreaks in natural and agricultural plant systems (Stack et al., 2006). This is accomplished through the primary mission areas of building infrastructure for diagnostics and communications and through training and education programs that target first detectors and diagnosticians.

Surveillance and detection We should assume that introductions will continue to occur as a result of global trade and the increasing threats of intentional introductions due to bioterrorism and biocrime. If the projections for increased trade and climate change are accurate, it is quite possible that the frequency and severity of introductions will increase.

Our current surveillance and detection systems vary significantly according to plant system, target pathogen or pest, and geographic region. Funding for surveillance of plant systems is most often allocated for specific target agents; consequently, those programs are executed only in areas at risk. Because of limited funding, general surveillance at the field level is minimal. For some plant systems, industry has implemented very effective surveillance programs, and the data are provided to APHIS. Mechanisms to share data are being explored.

Among the major limitations to an effective surveillance system is not having enough trained personnel in the field. Unlike human and animal systems, in which doctors and veterinarians are distributed throughout rural and agricultural areas, few plant doctors with diagnostic expertise operate at the local level with plant-based systems. NPDN, in collaboration with Cooperative State Research, Education, and Extension Service (CSREES), APHIS, the Extension Disaster Education Network, and the Regional Integrated Pest Management (IPM) Centers, has developed a training and education program targeting first detectors at the local level. Its registry of trained first detectors may serve as a resource for outbreak management.

Diagnosis NPDN was established to provide a triage system for the rapid and accurate diagnosis of introduced plant pathogens and insect pests. Because of a decline in national and local support for plant diagnostics over many years, state labs varied tremendously in diagnostic infrastructure and experience. With

funding from USDA, NPDN has rebuilt and enhanced much of that infrastructure and implemented programs to train diagnosticians in the latest diagnostic technologies (Stack et al., 2006).

Morse identified three elements for an effective early warning system; clinical recognition, epidemiological investigation capability, and laboratory capacity (Morse, 2002). NPDN has become an integral component for early warning and NPDN labs provide surge diagnostic support during outbreaks.

NPDN has created a national database for the diagnostic data collected at the network labs. An NPDN epidemiology group is developing data analysis tools that include syndromic analysis. Many of the issues and challenges associated with syndromic surveillance in human systems (Stoto, 2005; Stoto et al., 2004) also apply to plant systems. Because there are many natural introductions in plant systems, syndromic surveillance might prove to be a useful approach. Coordination and communication among all the disciplines will be important.

Response

Response to plant disease outbreaks resulting from new pathogen introductions is a responsibility of USDA APHIS. For most introductions, APHIS provides the leadership for a coordinated response that often includes APHIS-led rapid deployment teams, state departments of agriculture, industry, and in some cases, land grant university diagnostic labs. An elaborate structure exists within APHIS for the development of response plans to high-consequence pathogens and pests.

NPDN, in partnership with APHIS and state departments of agriculture, has developed and implemented a training exercise program to facilitate preparedness for outbreak response. All 50 states have participated in at least one exercise involving local, state, and federal governments, as well as state, regional, and national diagnostic labs. The exercise scenario makes clear the roles and responsibilities of all participants. After the exercise scenario, action reports are analyzed to identify areas in need of improvement.

Recovery (A Superficial Treatment)

Recovery, which follows response, is the strategy by which to return a system to the preevent mean or to a new, but stable, mean. An effective recovery strategy will be comprehensive in nature and include short-term plans that address the transition from response to the new system mean, while long-term plans will need to address prevention and recovery from subsequent introductions. The scope of recovery plans vary as a function of the scale of the outbreak and the ripple effects throughout the national and global economies. While response revolves around outbreak delineation, containment, eradication, and management, recovery is focused on local and system-level issues, including ecological impacts,

production shortfalls, effects on transportation systems, impacts on trade agreements, market reentry strategies, and replacement markets or systems.

Mandated by Homeland Security Presidential Directive 9 (HSPD-9), the National Plant Disease Recovery System (NPDRS) was established within the USDA Agricultural Research Service. NPDRS has involved other federal agencies (e.g., APHIS and CSREES), state departments of agriculture, scientific societies, and universities in the development of national response plans for the Select Agents and other high-consequence pathogens.

Among the challenges of an effective plant disease recovery strategy will be to find cost-effective solutions for low profit margin systems. Deriving a cost–benefit premium that achieves sustainable plant systems without significantly raising the percentage of the U.S. income spent on food or without causing irreversible ecosystem damage will be challenging. One goal for such a strategy would be establishing mechanisms for national cooperation *among public and private sectors and international cooperation that facilitates collaboration* without compromising trade. The true cost of risk reduction is not known. More effective predictive models for invasiveness, impacts, and recovery outcomes will be needed.

To date, NPDRS has focused on response plans. The challenge for NPDRS will be to transition into the development of recovery strategies in the face of increasing introductions that call for more response plans.

Challenges

The Select Agent Paradox

The Select Agent program includes a requirement for the identification of high-consequence plant pathogens and toxins having a reasonable potential to cause significant ecological or economic damage and the potential for deliberate introduction. Once a pathogen is designated as a Select Agent, strict laws regulate its possession, handling, and dissemination. Responsibility for managing a plant disease outbreak caused by a Select Agent resides with APHIS. If it is suspected or determined that the introduction was intentional, then the Federal Bureau of Investigation would share primary responsibility.

The original Select Agent list for plant pathogens included 10 pathogens (see Fletcher and Stack earlier in this chapter). Since its adoption, at least four of these agents have been introduced into the United States either accidentally as a result of trade (*Ralstonia solanacearum*, *Liberobacter asiaticus*, Plum pox virus) or naturally as a result of a weather event (*Phakopsora polysora*) (Stokstad, 2004). Two of those agents are now considered to be endemic and were removed from the Select Agent list. Once removed from the list, the management of the threat agent shifted from primarily a federal responsibility to primarily a state and local responsibility.

The utility and effectiveness of the Select Agent program should be reviewed. At best, it reduces the potential for an accidental escape from a domestic lab and impedes the illicit acquisition of a viable culture or toxin preparation from a domestic lab or commercial culture collection. At worst, it precludes achieving a state of preparedness at the state and local levels. Pathway analyses indicate that for most of the Select Agents, there is an equal or greater probability of being introduced accidentally or naturally than intentionally. If these agents are truly the organisms of greatest concern, we should be encouraging many of our scientists to conduct the research necessary to ensure that we can detect them quickly, diagnose them correctly, and respond effectively to minimize the potential negative impact. If working with these agents is too difficult for U.S. scientists then we will not be building the necessary expertise for the organisms that pose the greatest threat to the country. A reevaluation of the goals and effectiveness of the Select Agent Rule should be executed with specific reference to the unintended consequences that impair preparedness and response.

Animal and Plant Health Inspection Service

The authority for regulating high-consequence plant pathogens and insect pests resides within APHIS. Responsibilities include providing emergency response to outbreaks; issuing permits for interstate transport and international importation of pathogens and pests; coordinating national and regional pest surveys; providing training programs; and developing and validating diagnostic protocols. Most of these tasks are time sensitive and resource intensive, sometimes with significant legal ramifications. Yet, among the USDA agencies, APHIS has historically received the least funding. Its level of support seems disproportionate to its responsibility. If we are to develop and maintain a national state of preparedness in the face of increasing plant pathogen and pest introductions, increased support within USDA for APHIS and increased support within APHIS for plant programs will be necessary.

Sampling

Sampling underpins the successful implementation of every strategy on which a successful biosecurity program depends. A sampling protocol depends on the characteristics of the target agent, the environment in which it exists, and the matrix from which it is to be sampled. Consequently, much effort should be applied to the development and validation of the methods deployed. However, the extremely large number of potential threat agents in plant systems precludes implementation of a comprehensive sampling strategy for each agent. Therefore, more general sampling strategies are needed that increase the probability of interception for a wide array of agents.

Formulating and implementing a national strategy for recovery from single or multiple introductions to plant systems is a challenge beyond the mission of any single agency or department. It will require the coordination of several government departments at the local, state, and federal levels; public and private educational institutions; and the many industries that support plant systems in the United States. As has been identified for zoonotic disease surveillance (Dudley, 2004), a central body with responsibility for plant disease health that would develop a national strategy does not exist.

Summary

There are many challenges to achieving plant biosecurity within the United States and across the world. The success of U.S. agriculture has made possible a high standard of living with a safe, inexpensive, and dependable food supply system. But it has also left us complacent with respect to food production. Educational programs are needed to increase awareness among the general population and among policy makers regarding the interdependence of plant, animal, and human systems. Appropriately, human systems have the greatest value in society and require the greatest investment of our time and resources. Sustenance of healthy human and animal systems requires healthy plant systems. Having less value does not mean having little value.

The world at the beginning of the 21st century is vastly different than it was at the beginning of the 20th century. Among the challenges to sustainable living systems are globalization, climate change, population growth, and bioterrorism/biocrime. There is neither a single strategy nor a single technology that will ensure the security of our living systems. The benefits of globalization are tremendous, but so too are the risks if we do not prepare for the consequences with respect to emerging diseases of humans, animals, and plants. Consequently, all nations must be secure if any nation is to be secure. Through modern transportation systems and international commerce, some of the natural barriers (e.g., oceans) to the dispersal of pathogens have been circumvented or eliminated. Most plant pathogens once took decades to disperse naturally around the world. Through normal commerce it may now take only a few days to a few weeks. Two introductions of the Select Agent *Ralstonia solanacearum* r3b2 in 2003 and 2004 from Kenya and Guatemala, respectively, are good examples. The threat of intentional introduction could reduce that dispersal interval to one day.

Historically, pathogens have moved naturally and accidentally among nations around the world. However, the rate of their border crossings has increased dramatically, resulting in drastically reduced time to prepare for an introduction. International cooperation is essential to achieve plant biosecurity. The importance of global management of disease outbreaks to minimize large-scale impacts was justified effectively for animal and human diseases (Karesh and Cook, 2005).

The same case can be made for plant diseases. Many of the plant pathogens that have caused epidemics in North America over the past 150 years were introduced from Africa, Asia, Europe, and South America. Intuitively, the health and stability of plant production systems in the United States depends on good plant surveillance systems in other parts of the world. Improved cooperation among nations is required for prevention and rapid outbreak intervention.

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2

Surveillance Networks

OVERVIEW

As several of the contributors to this chapter note, clinical surveillance of infectious disease is inadequate in much of the developing world due to limited funding for public health infrastructure. Because many impoverished regions are also at high risk for emerging disease threats, alternative methods of surveillance are crucial to global health. The papers collected in this chapter describe a variety of electronic surveillance networks, designed to gather and integrate information on infectious disease from a variety of nontraditional sources (e.g., Internet sites, news outlets, observers with little or no medical training) and to disseminate alerts broadly and rapidly.

The chapter begins with a description of the first infectious disease surveillance network, ProMED-mail. Stephen Morse, one of the network's founding members, provides a brief history of the free, nonprofit, noncommercial, moderated e-mail list that today serves over 37,000 subscribers in more than 150 countries, as well as anyone with Internet access. Since it began as an experimental system in 1993, ProMED-mail has helped to demonstrate the power of networks and the feasibility of designing effective, low-cost global reporting systems. It has also encouraged the development of additional electronic surveillance networks—such as the Global Public Health Information Network (GPHIN) and HealthMap, described in subsequent contributions to this chapter—and the World Health Organization's (WHO's) "network of networks," the Global Outbreak Alert and Response Network, or GOARN (see Summary and Assessment).

The chapter's second paper, by presenter Abla Mawadeku and coauthors from GPHIN, offers descriptive comparisons of that network along with ProMED-mail

and the European Commission's Medical Intelligence System (MedISys), which is available only to European Union member states. GPHIN, a primary source of electronic surveillance for WHO, also serves a host of government institutions, nongovernmental agencies and organizations, academic institutions, and private companies, who pay between 30,000 and 200,000 Canadian dollars per year in subscription fees, depending on the specific services provided.

HealthMap is a freely accessible, automated network that collects information from multiple web-based data sources on infectious outbreaks (currently news wires, Really Simple Syndication (RSS) feeds, ProMED mailing lists, and EuroSurveillance and WHO alerts). The network then organizes and displays this information in real time as graphic "maps" featuring geography, time, and infectious disease agent. In their contribution to this chapter, workshop presenter John Brownstein of Harvard Medical School and his colleagues at Children's Hospital Boston discuss their efforts to evaluate the HealthMap system with reference to four characteristics that have been used to evaluate syndromic surveillance systems: data acquisition; information characterization; signal interpretation; and dissemination. The authors' preliminary evaluation of HealthMap according to these criteria appears to demonstrate that the aggregation of multiple sources of data—each potentially biased or otherwise flawed—increases the sensitivity and timeliness of alerts while reducing false alarms.

The concluding paper of the chapter describes a different sort of electronic surveillance network: one powered by cell phones, enabling observers in some of the world's most remote and impoverished communities to report disease outbreaks. The authors are workshop speakers Pamela Johnson of Voxiva, a company that provides information technology to establish surveillance networks in low-resource settings, and David Blazes, of the U.S. Naval Medical Research Center Detachment in Lima, Peru, which used an Internet- and cell phone-based electronic system developed by Voxiva to support disease surveillance by the Peruvian navy along that country's coast and remote rivers. This experience is presented as a case study in surveillance and evaluated according to the Centers for Disease Control and Prevention (CDC) guidelines for public health surveillance systems. The authors also share lessons gleaned from six years of building surveillance systems, based on cell phones and other cost-effective information technologies, for use in low-resource environments.

Workshop participants raised a series of issues in response to the presentations upon which the papers in this chapter are based. A detailed account of this discussion appears in the Summary and Assessment section, "Considerations for Surveillance Networks." Discussants were especially concerned about the potentially devastating economic consequences to a country—particularly a developing country—of being labeled (accurately or inaccurately) as harboring a feared infectious disease. In his contribution to Chapter 4, speaker Will Hueston assesses the tradeoff between health and development inherent in the release of surveillance information such as HealthMap's geographic depictions of outbreak reports.

GLOBAL INFECTIOUS DISEASE SURVEILLANCE AND EARLY WARNING SYSTEMS: PROMED AND PROMED-MAIL

Stephen S. Morse, Ph.D.[1]
Columbia University

A number of emerging infections have appeared throughout the world in recent years (Morens et al., 2004; IOM, 1992, 2003; Morse, 1995). Or, in the words of Marci Layton (New York City Department of Health and Mental Hygiene), we must learn to expect the unexpected. It is widely agreed that one of the most important measures for both emerging and existing infectious diseases is an effective early warning system, that is to say, global infectious disease surveillance. Here, I will discuss ProMED, the nonprofit international Program for Monitoring Emerging Diseases, and its best known progeny, ProMED-mail (PMM). ProMED itself was founded in 1993 to design and help implement global surveillance systems that could detect both known and emerging infections (Morse et al., 1996).

A Brief History of ProMED and ProMED-Mail

ProMED had its roots in the same Institute of Medicine (IOM) report that led to the development of the Forum on Microbial Threats (IOM, 1992). The Committee that developed the 1992 IOM report was chaired by Joshua Lederberg and the late Robert E. Shope. After the report was released, there was considerable concern about maintaining the momentum. Many of the original Committee members (including me) believed the problem required long-term attention. In addition, for specific reasons the charge to the IOM Committee and consequently the report were limited to the United States. However, there was a clear need to consider these infections as global threats that would require international solutions. In an attempt to fill what many (including this author) saw as the fragmentation of disease surveillance systems and the lack of global capacity, ProMED was begun in 1993 under the auspices of the Federation of American Scientists (FAS).[2]

Several years earlier, I had been asked by Barbara Hatch Rosenberg, then chairing a working group on biological nonproliferation issues at FAS, to provide technical advice for her working group. After the 1989 National Institutes of Health (NIH) meeting on emerging viruses and the 1992 IOM report, Rosenberg and I discussed the possibility of developing an initiative for global infectious

[1]Mailman School of Public Health.

[2]An article on the early history and activities of ProMED is available at http://www.fas.org/faspir/pir1293.html, with an update at http://fas.org/promed/announce.htm. Additional materials are available at http://fas.org/promed/.

disease surveillance, with start-up resources from FAS. Dorothy Preslar served as the project staff at FAS.

The group held a small initial organizational meeting in February 1993 at The Rockefeller University in New York. In addition to Rosenberg, and myself as Chair, among those present at that meeting were Ruth Berkelman (then at the Centers for Disease Control and Prevention, or CDC), Scott Halstead (then at the Rockefeller Foundation), D. A. Henderson (then at Johns Hopkins and the U.S. Department of Health and Human Services), James M. Hughes (then at CDC), John LaMontagne (then at NIH's National Institute of Allergy and Infectious Diseases, or NIAID), and Shope (then at Yale). At that time, it was decided that a conference would be held in Geneva in fall 1993, that the group's purview should include animal and plant diseases in addition to human disease (a view especially advocated by Berkelman), and that the group should be named ProMED (Shope suggested the name).

The next activity was a conference, cosponsored by FAS and the World Health Organization (WHO) and held on September 11 and 12, 1993, at WHO headquarters in Geneva. Part of the challenge at that time was that the then-Director General of WHO did not believe that surveillance for infectious diseases was part of the organization's core responsibilities. Unfortunately, many clinicians and most of the lay public naïvely believed otherwise, and thought that WHO was already doing it.

The September 1993 ProMED meeting, co-chaired by Francis Nkrumah of Ghana and myself, was held in the WHO Executive Board Room, and included as speakers a number of people who had been influential in WHO affairs, including Jan Kostrzewski, a former chair of the WHO Executive Board, Henderson, and a number of members of the World Health Assembly. At that event, 60 prominent scientists and public health officials working on human, animal, and plant health from all parts of the world met, unanimously endorsed the concept of global surveillance, and formed ongoing working groups to assess present capabilities and develop and implement plans for a suitable global program that could address both known and emerging infections. We also invited John P. (Jack) Woodall (then at WHO) onto the Steering Committee, and James LeDuc (then at WHO, seconded from CDC) agreed to serve as a special consultant.[3]

One would think it should be fairly simple to strengthen and network regional centers of excellence to augment official systems and develop mutual cooperation, whether through WHO (preferably) or through regional intergovernmental organizations. On the other hand, if diseases can emerge anywhere, how can one get early warning from literally everywhere? The latter seemed the harder task, so we decided to try tackling what everyone considered the easier one first. At meetings in Geneva and elsewhere, we recommended developing a coordinated

[3]The list of the early Steering Committee members can be found at http://fas.org/promed/about/steering.html.

system of regional centers and a minimum set of capabilities to identify and respond to unusual disease outbreaks. A plan was subsequently published (Morse et al., 1996), in part elaborating on the system Henderson had proposed at the 1989 NIH/NIAID meeting on emerging viruses (Henderson, 1993). The strategy developed was vigilance for unusual clinical presentations of special concern (e.g., encephalitis or acute respiratory distress with fever in adults); a minimum set of microbiological capabilities at each site to identify common diseases; and a system to refer unidentifiable samples to successively more sophisticated reference laboratories, through the network, for possible identification. The plan also included epidemiologic capacity, which could be provided rapidly through the network if needed (Morse et al., 1996).

The effort continued with meetings at other places. At a Steering Committee meeting in June 1994 at Airlie House in Virginia, we realized that our members from all over the world had no reliable means to communicate with one another. Nkrumah of Ghana, for example, had a Telex, which in any major American city usually required a trip downtown to a special office building to send, but no fax machine. In Russia, they had fax machines but no fax paper because of a lack of money. We decided to try to put everyone on a common communications system. Charles Clements, then at a nonprofit organization called SatelLife, which specialized in inexpensive e-mail connections for remote and underserved areas through satellite radio links, had been invited to the meeting. I appointed Woodall as head of a new Communications Task Force. By the end of the meeting a plan had been developed to connect everyone by e-mail. SatelLife provided connectivity for places without e-mail connections, for example (at that time) in Africa, China, and Russia. The rest of us learned how to use the existing e-mail systems at our institutions (quite an ordeal in those days). Thus ProMED-mail was born. Although only about 10 years ago, it was another era technologically.

As the system developed and people started using e-mail for communications, we realized it could also be used as an international outbreak reporting system. (So much for deferring those "more challenging" goals, such as how to get reports from everywhere.) Woodall and I served as the initial moderators (or "editors"), a time-consuming task. Woodall deserves tremendous credit for his dedication and enormous contributions to the subsequent development of the system. Since 1995, the system has been available on the Web,[4] as well as by e-mail subscription. The partnership between ProMED and SatelLife continued fruitfully until 1999, when the ProMED reporting network was transferred to the International Society for Infectious Diseases (ISID), headquartered at Harvard's Channing Laboratory in Boston. The communications network was renamed ProMED-mail, to distinguish it from other ProMED activities then underway.

[4]See http://www.promedmail.org.

ProMED-Mail: A Prototype Infectious Disease Reporting System

Many people think of PMM as synonymous with ProMED, as it has taken on a robust life of its own. PMM was designed as an open reporting and discussion system. It is a nonprofit, noncommercial e-mail list that now has some 40,000 subscribers, with over 165 countries represented. Not all of them, of course, send in reports because the editors would be overwhelmed, but many subscribers do read the e-mails on a regular basis. Although numbers vary, incoming e-mails (roughly 100 a day) generate an average of 7 to 10 reports every day.

The e-mail listserv is moderated, which means that messages coming in are first read by people with scientific or medical expertise. Originally this was Woodall and at times me until I left for government service in 1996. As the list grew, a number of other moderators were recruited in various specialty areas, and the system is fortunate to have a number of distinguished experts as moderators.

In principle, subscribers send in reports and information. Rapporteurs take additional responsibility to report regularly in their own geographic or special interest areas. Rapporteurs report from Russia, China, and a number of other places as well as within the United States. When someone sends in a report from somewhere (one of the earliest reports of Ebola in Kikwit, Zaire, now the Democratic Republic of Congo, came from a medical missionary who had a radio e-mail link), the report is assigned by the editor-in-chief or someone acting in that capacity, to the appropriate moderators for editing and, if appropriate, posting to the list. The moderator reads the report for scientific plausibility. If the report looks credible, the moderator edits and formats as needed, probably adds comments to put the item in context, and send it out as a posting to the list. All subscribers are free to comment or add information after reading the posting.

In addition to the full list, which includes outbreak reports and discussions on human, veterinary, and plant diseases, there are several sublists for those who want only certain parts of this information. It is possible to subscribe to the animal and plant disease lists separately. The human disease list includes both human and animal disease. This causes occasional complaints from physicians, but we have believed strongly from the beginning that it is essential to improve the connections between animal and human health. Justifying this is the fact that many emerging infections are zoonotic. Those who are interested in getting only the breaking news, without the ensuing discussion, can subscribe to the Emerging Disease Reports (EDR) sublist. I get EDR on my BlackBerry wireless device.

In recent years sub-lists have been developed in Portuguese, Spanish, and Russian, and there is interest in developing other foreign language lists as well. Some of the regional reports of wide interest are translated into English.

The PMM architecture is simple. Technically, the e-mails are 7-bit ASCII text, the most basic format. When the system was started in August 1994, people in developing countries had very limited bandwidth. It is amazing how much

this has changed in the past decade, with broadband Internet cafes now even in remote areas.

The editors also search the Web and press reports, an increasingly important source of information. This strategy was originally adopted by GPHIN (the Canadian government's Global Public Health Intelligence Network), which is described in another chapter. GPHIN was started in 1999 and is based largely on news sources from the Web. Unfortunately such material was not available when PMM was started. Since then, the explosive growth of the Web and of improved methods for searching have made such strategies very effective.

Perhaps one of the most important value-added features of PMM is the distinguished and hard-working team of moderators or editors (for this chapter, I am using these two terms interchangeably). Although they are essentially volunteers, all are subject-matter experts. The moderators also have their own e-mail lists and personal networks for follow-up, which demonstrates the power of networking. Larry Madoff is the current editor-in-chief of PMM, while Woodall (now associate editor) remains as active and involved as ever. He has had a critical role in developing PMM into what it is today. Eduardo Gotuzzo, in addition to being a member of the IOM Forum, is Chair of the PMM Policy Committee.

All this is probably obvious to anyone who has read PMM. Anyone can contribute; data come from clinicians (those proverbial astute clinicians in the field all over the world), public health officials and epidemiologists, lab scientists, or medical missionaries, but also journalists and interested laypeople.

There was a concern initially that the method of obtaining data would give rise to many rumors that health authorities would then have to verify, expending valuable resources. This has not turned out to be a major problem. Of course, sometimes information is incorrect, but in general the reliability turns out to be more than 95 percent, according to figures that Madoff tabulated. However, PMM has developed several mechanisms to deal with the possibility of erroneous reports. One is personal follow-up by moderators. The moderators, experts in their fields and generally well connected, can use their own personal networks to try to get more information to include. Second, an uncertain report could also be posted as a request for information (RFI), an inquiry which is simply a way of asking people if they have more information they can contribute. Others on the network may also spontaneously add to or correct a posting if they have additional facts.

Subsequently, WHO, in response to information from PMM and GPHIN, developed a very effective mechanism of its own, called the Outbreak Verification List. WHO sends this list out regularly to a limited group of public health officials and scientists to try to follow up on various outbreak reports. It is a sign of WHO's increasing capacity and interest that the reports increasingly are coming from WHO's own country and regional representatives. WHO has developed its own network of networks, the Global Outbreak Alert and Response Network (GOARN), which includes a number of formal and informal sources. It should

be noted that the situation at WHO has greatly improved in the last few years, thanks to the concerted efforts of a number of people, including James LeDuc in the early days, and notably David Heymann more recently.

One particularly interesting aspect of a system like PMM is that it can be used to compare reports from a number of places. In addition to outbreak reporting, it provides the ability for people to recognize that what they are observing may be happening elsewhere, too. An initial report may encourage others to contribute local information that may help to estimate the extent and numbers of an infectious disease outbreak, and to monitor spread. One example was a 1995 outbreak of meningococcal meningitis occurring simultaneously in several states and in the United Kingdom. The outbreak became evident when the reports from various places appeared on PMM.

PMM has been available on the Web since the Ebola outbreak of 1995 in Kikwit, when it partnered with and later incorporated an independent effort called "Outbreak." As the Web itself grows, the website has had an increasing presence. If one prefers not to receive e-mail alerts, it is a simple matter just to search the website and read any of the reports. The Web archives include some of the earliest reports, such as the first reports of Ebola in Kikwit. Among other PMM "firsts" was Venezuelan equine encephalitis, coincidentally in Venezuela. It was originally denied by the government; when it was verified it led to the resignation of the health minister. West Nile virus in 1999 was another event PMM extensively covered. During this period, Ian Lipkin generously wrote in to offer reagents for people internationally. Other firsts include reports of H5N1 influenza in Indonesia in November 2003 and fatalities in China in 2005 attributed to *Streptococcus suis.*

The first report of severe acute respiratory syndrome (SARS) that appeared on PMM was a rumor about an unusual outbreak in south China with unexplained deaths. Steve Cunnion picked this up, and information was posted on February 10, 2003. Shortly after that, China officially reported the disease, and WHO was able to release information officially. By that time, China reported 305 cases. SARS had actually been infecting people for at least several months (IOM, 2004). SARS then spread to Toronto, where it was originally called "atypical community-acquired pneumonia" and was reported on PMM.

Madoff has tabulated the PMM disease reports over the past 10 years. Dengue, which is quite common, is one constant, as are a number of others. Many are known conditions, but at least 209 are not. Some will eventually be added to the known category. There have also been reports of CDC Category A agents, normally more closely associated with bioterrorism or biowarfare. However, anthrax exists naturally throughout the world in livestock. In developing countries, there may be thousands of cases of gastrointestinal anthrax from contaminated meat. More than 200 cases of anthrax in livestock were reported on PMM before the intentional anthrax attacks of fall 2001. Botulism and tularemia are also natu-

rally occurring diseases, which reminds us that many of the classic bioweapons, including the Category A agents, are zoonotic agents.

PMM was developed as a prototype, and continues to evolve. There have been increasing efforts since then. GPHIN and WHO's GOARN have already been mentioned. A later paper, by Pamela Johnson, will discuss Voxiva, which uses the power of networks with another technological base, the cell phone network.

PMM has also elicited some kind comments. Henderson referred to CNN and PMM as the major sources of information for infectious diseases. Steven C. Joseph (formerly New York City Health Commissioner, Dean of the Minnesota School of Public Health, and Assistant Secretary of Defense for Health Affairs) referred to PMM as "the CNN of infectious diseases" (Personal communication, S. C. Joseph, June 1995). Perhaps the most intriguing characterization comes from Steven Johnson, in his book *The Ghost Map*, about cholera in Victorian London. A sentence in the book caught me by surprise as I was leafing through it:

> The popular ProMED-mail e-mail list offers a daily update on all the known disease outbreaks flaring up around the world, which surely makes it the most terrifying news source known to man (Johnson, 2006).

For an infectious disease surveillance system, that seems high praise indeed.

Since PMM was started as an experimental system more than a decade ago, it has helped to demonstrate the power of networks and the feasibility of designing widely distributed, low-cost reporting systems, and it has encouraged the development of additional systems using additional technologies. All these efforts help to begin building the heavily networked surveillance systems that will be needed to deal with threats in an increasingly globalized and unpredictable world.

Acknowledgments

Sincere thanks to Jack Woodall and Larry Madoff for their hard work and helpful discussions, and to all the editors/moderators and funders of ProMED-mail for their dedication and good work.[5] Stephen S. Morse is supported by CDC cooperative agreements A1010-21/21, U90/CCU224241 (Centers for Public Health Preparedness), and U01/CI000442, the Arts & Letters Foundation, and by NIH/NIAID cooperative agreement 5U54AI057158 (Northeast Biodefense Center RCE).

[5]A list of current PMM personnel is at http://www.promedmail.org; click on "Who's Who."

GLOBAL PUBLIC HEALTH SURVEILLANCE: THE ROLE OF NONTRADITIONAL SURVEILLANCE TOOLS

Abla Mawudeku, M.P.H.[6]
Public Health Agency of Canada

M. Ruben, M.D., Ph.D.[7]
Public Health Agency of Canada

R. Lemay, B.Sc., M.B.A.[8]
Public Health Agency of Canada

Introduction

In a world deeply interconnected by traveling and trade, the spread of infectious agents is inevitable. Regions once isolated are now integrated into the global community and have the risk of being exposed to infectious agents that they previously were unexposed to, as well as sources of old and new agents, and even new pandemics. Therefore, there is global concern about surveillance and control of diseases (particularly infectious diseases) around the globe.

Any global surveillance system has to overcome several challenges; basically, it requires a good system for communications to and from the field to get timely collection, analysis, and dissemination of data, and to be able to force political decisions and allocation of resources. However, susceptibility to infectious diseases and increased risks of infection are usually associated with poverty, and poverty is more frequent in those countries where epidemiological and laboratory surveillance is defective or nonexistent (Heymann and Rodier, 2001). In addition, while several countries, particularly in the Western world, have already national surveillance systems to monitor for potential public health threats, in many circumstances these systems are inadequate, fairly erratic, or too disease specific to identify new diseases early (Butler, 2006). Also, countries have been reluctant to report outbreaks due to the perception of a negative impact of such news on the country's economy (trade and tourism). Public alarm, sometimes fueled by the press, has resulted in many occasions in important losses for the countries, which then try to hide or delay the recognition of the presence of human or animal diseases (Cash and Narasimhan, 2000). Nevertheless, the electronic era, in which press reports and the Internet keep societies informed and interconnected, have begun to break down all attempts of "secrecy."

Currently there is no comprehensive global public health surveillance system. The World Health Organization (WHO) is the only organization that has the mandate to monitor and respond to global public health threats, as established

[6]Chief.
[7]Scientist.
[8]Senior Surveillance Officer.

in the International Health Regulations (IHRs). WHO not only uses information gathered from traditional surveillance systems but also uses information from nontraditional surveillance systems to leverage in order to capture a more comprehensive outlook of the situation about potential public health threats occurring worldwide. The use of nontraditional surveillance systems has contributed to the improvement of epidemic intelligence used for the early detection of potential public health threats. This has enabled WHO and other public health organizations such as the European Center for Disease Control (ECDC) to better assess, investigate, and respond to events of concern (Figure 2-1).

A revised version of these regulations, IHR 2005, will be implemented in June 2007. These new IHRs will strengthen WHO's authority in surveillance and response because they include more demanding surveillance and response obligations and apply human rights principles to public health interventions (Baker and Fidler, 2006). The new regulations require that member countries report to

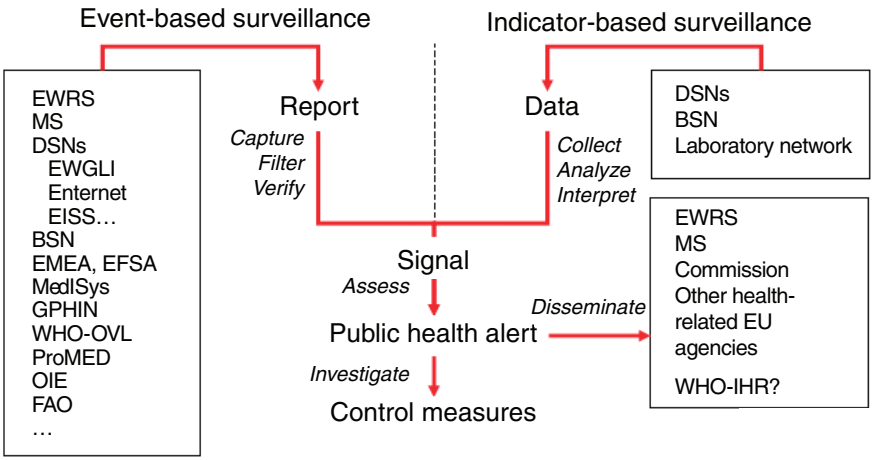

FIGURE 2-1 Epidemic intelligence framework.
EWRS = Early Warning Response System; MS = messaging system; DSN = disease surveillance network; EWGLI = European Working Group for Legionella Infections; EISS = European Influenza Surveillance Scheme; BSN = Basic Surveillance Network; EMEA = European Agency for the Evaluation of Medicinal Products; EFSA = European Food and Safety Authority; WHO-OVL = Outbreak Verification List; OIE = Office International des Epizooties (World Organization for Animal Health); FAO = Food and Agriculture Organization; EU = European Union; and Enter-net is an established and thriving EU-wide network for the laboratory-based surveillance of human Salmonella and Verocytotoxin-producing *Escherichia coli* (VTEC) infections.
SOURCE: Based on Kaiser et al. (2006).

WHO "all events which may constitute a public health emergency of international concern" (i.e., unexpected or unusual public health events that might include communicable and noncommunicable disease events, whether natural, accidental, or intentionally created). IHR 2005 also requires from member countries (if practicable) to report to WHO all public health risks identified outside their territories that might cause international disease spread (Baker and Fidler, 2006). They also give WHO more autonomy from the governments of member countries; WHO can now use nontraditional surveillance information (i.e., data from the news media) and ask the countries about "rumors" of circulating infectious agents.

Several innovative nontraditional surveillance systems leverage the advancements in modern Internet and information technologies to efficiently and rapidly gather information about events of public health concern. The Global Public Health Intelligence Network (GPHIN), the Program for Monitoring Emerging Diseases (ProMED), and Medical Intelligence System (MedISys) are examples of such systems that are commonly used by the public health community. All these surveillance systems disseminate relevant reports to the public health community in a timely manner.

Global Public Health Intelligence Network

GPHIN is an early warning system that takes advantage of existing information technology to continuously scrutinize news media sources through news aggregators who have contracts with newspapers around the world, as well as with health and science websites. The multilingual system gathers information by monitoring global media on a 24/7 basis and in nine languages, including Arabic, Chinese (simplified and traditional), English, Farsi, French, Russian, and Spanish. More recently, Portuguese has been added. In addition, and with the help of automated translation software, non-English articles are translated into English, and English articles translated into French, Portuguese, Spanish, Russian, Chinese (simplified and traditional), Farsi, and Arabic. The translations give the essence of the news report.

The system, which has automated and manual components, searches for information on disease outbreaks and other emerging and reemerging public health threats (e.g., contaminated food and water, bioterrorism, chemical or radiological threats, natural disasters) and then generates timely alerts (Figure 2-2). The automated process helps to organize and prioritize the relevant news media reports that are reviewed and analyzed by a team of analysts who are multilingual and multidisciplinary (Figure 2-2). The analysts work in shifts and provide analytical coverage on a 24/7 basis. The analysts have the responsibility of identifying events that may have serious public health consequences, and of flagging them as alerts following preestablished criteria. The analysts also review, periodically, the items kept in the database as irrelevant, to ensure that none of these items represents a potential alert. In addition, the analysts are responsible

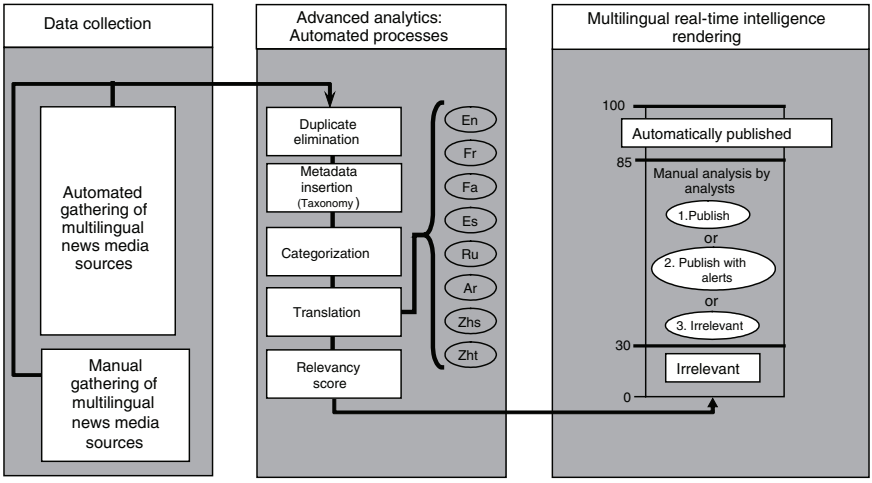

FIGURE 2-2 Global Public Health Intelligence Network (GPHIN) flow of information. SOURCE: Public Health Agency of Canada.

for identifying trends or relationship of events, checking clarity of machine translations, and updating search syntaxes and keywords used to monitor and gather relevant news media reports. The users are also able to interact with the analysts to request assistance or to provide feedback.

GPHIN is currently one of the primary sources of information for WHO. Other GPHIN users include government institutions, nongovernmental agencies and organizations, as well as academic institutions and private companies that conduct public health surveillance worldwide. Users have access to GPHIN through a password protected website and also receive e-mail alerts (Mykhalovskiy and Weir, 2006).

ProMED-Mail

ProMED[9] offers a free public website and an e-mail list that has subscribers from around the world (currently more than 37,000 subscribers from over 150 countries). Its mission is "to provide early warning, 7 days a week year around, of outbreaks of emerging infectious diseases and episodes of acute toxicity, and the spread of antibiotic and disease vector resistance, worldwide, free of charge by e-mail" (Woodall, 2001; Woodall and Calisher, 2001). The system distributes information about outbreaks often early on, before it is confirmed by WHO;

[9]ProMED-mail, International Society for Infectious Diseases, http://www.isid.org.

therefore, it complements the global surveillance done by WHO and countries (Woodall, 2001).

It allows communications by e-mail all over the world, and includes sublists of reports in Spanish, Portuguese, and Russian, with some of the most interesting local reports translated into English. ProMED publishes media reports, personal reports, and summaries; it presently covers not only human diseases, but also animal and plant diseases, and it is also available on the Web (Woodall, 2001). Most data published by ProMED comes from individuals (clinicians, public health officers, epidemiologists, laboratory scientists, and lay individuals) or from academic or official organizations worldwide.

ProMED has several moderators who cover their own geographic areas (e.g., Russia, China) and search the Web and press reports for relevant news. These moderators are subject-matter experts and provide their expertise as volunteers (Mykhalovskiy and Weir, 2006); they also have their own e-mail lists and personal networks to follow up the reports, and they frequently add their comments and their knowledge to the news.

MedISys

MedISys is a near real-time news alert automated system managed by the Directorate General Health and Consumer Affairs of the European Commission.[10] MedISys covers emerging and reemerging public health issues related to communicable diseases and bioterrorism. It monitors on a 24/7 basis approximately 800 Web sources (news and medical sites) daily in 25 languages, including the languages of European Union (EU) member states, Arabic, and Chinese. Access to MedISys is limited to EU member states.

Conclusions

The continuous proliferation of emerging and reemerging pathogens able to infect humans, domestic animals, plants and wildlife seems to have increased in the past years, helped by the increased and faster movement of people and goods. This has generated international concern and increased efforts to improve the early warning capacity to detect potential public health threats worldwide in order to control and prevent the spread of diseases (Heymann and Rodier, 2001; Formenty et al., 2006).

Today's advancements in communication technology (e.g., blogs, wikkies), and information technology are used liberally by the news media and the public; this makes possible the rapid dissemination of worldwide news about events of public health concern. Such proliferation of information has made it challenging for the public health community, with limited resources, to be aware of and

[10]See http://medusa.jrc.it/medisys/homeedition/all/home.html.

analyze all the data available in an efficient and effective manner. Current early warning tools, such as GPHIN, MedISys, and ProMED also find it challenging to keep abreast of all the sources of information available. Therefore, the most feasible and cost-effective solution would be to establish a network of nontraditional early warning surveillance systems in order to leverage the expertise provided by each system. GPHIN, MedISys, and ProMED, which are complementary, could then strengthen the mutual abilities of monitoring, gathering, analyzing, and disseminating information about events of public health concern.

In such a collaboration, ProMED's team of experts would provide reports of relevant events; GPHIN's would add a team of multilingual, multidisciplinary analysts plus its technical capacity to process high volumes of disparate multilingual data; and MedISys would add its capacity to monitor the Internet for news in more than 20 languages, improving the gathering of information about potential public health threats in remote areas. In addition, this collaboration would make possible the dissemination of synthesized information (from the numerous news sources) about relevant events, highlighting major points and strengthening epidemic intelligence. Furthermore, visualization features, like the ones provided by the Geographic Information System (GIS), could also facilitate the epidemiological analysis of public health threats.

For such a comprehensive and ambitious network to be effective, and to reach the entire planet, it would also need the support of the public health community and wildlife, animal, and agricultural experts, when possible (Jebara, 2004; Butler, 2006). It also would need technologic and economic support from the private sector. It is expected that a network like this could adapt to the needs of the different customers, and provide support to all countries, worldwide, to strengthen their surveillance systems and be able to accomplish the mandate of the IHR guidelines. These guidelines anticipate that each member state should assess its capability to strengthen and maintain core surveillance capacities by 2009 and develop a plan to accomplish this (Hardiman, 2003; Baker and Fidler, 2006).

HEALTHMAP: INTERNET-BASED EMERGING INFECTIOUS DISEASE INTELLIGENCE

John S. Brownstein, Ph.D.[11]
Harvard Medical School

Clark C. Freifeld, B.S.[12]
Children's Hospital Boston

Ben Y. Reis, Ph.D.[13]
Children's Hospital Boston

Kenneth D. Mandl, M.D., M.P.H.[14]
Children's Hospital Boston

Although many developed countries are strengthening their traditional clinically based surveillance capacities, the required health information infrastructure is lacking in parts of the world that may be most vulnerable to emerging health threats. At the same time, an enormous amount of information providing situational awareness about infectious diseases is found in web-accessible information sources, such as Internet-based discussion sites, disease reporting networks, news outlets, and blogs. These data also exemplify unprecedented potential for increasing public awareness on public health issues prior to their widespread recognition. Despite the growing use of these unstructured information sources for monitoring emerging infectious diseases, there has been little, if any, formal evaluation of their utility, accuracy, coverage, or timeliness. Building on established evaluation approaches for public health surveillance systems, we present a surveillance framework that defines important challenges and critical research questions that define a research agenda. The framework is informed by evaluation of the performance of HealthMap, a freely accessible, automated system for real-time monitoring of online information about emerging diseases. This chapter highlights the value of a robust research agenda, continued organic evolution of existing and new technologies, and scrutiny through a rigorous evaluation framework to help ensure that the global public health enterprise maximally leverages

[11]Instructor, Department of Pediatrics, Harvard Medical School, Children's Hospital Boston, 1 Autumn St, Room 541, Boston, MA 02215. Phone: 617-355-6998. Fax: 617-730-0267. E-mail: john_brownstein@harvard.edu.

[12] Research Software Developer, Children's Hospital Informatics Program at the Harvard–MIT Division of Health Sciences and Technology, Children's Hospital Boston, 300 Longwood Ave., Boston, MA 02115.

[13]Instructor, Children's Hospital Informatics Program at the Harvard–MIT Division of Health Sciences and Technology, Children's Hospital Boston, 300 Longwood Ave., Boston, MA 02115.

[14]Associate Professor, Children's Hospital Informatics Program at the Harvard–MIT Division of Health Sciences and Technology, Children's Hospital Boston, 300 Longwood Ave., Boston, MA 02115.

new electronic sources for surveillance, communication, decision making, and intervention.

Introduction

Real-time public health surveillance represents a critical tool for controlling infectious diseases, an effort that requires a timely and global approach addressing the complex and dynamic interactions among infectious agents, animals, and the environment (Heymann and Rodier, 1998, 2001; Woodall, 2001). Although many developed countries are strengthening their traditional clinically based surveillance capacities, the required health information infrastructure is lacking in parts of the world that may be most vulnerable to emerging health threats (Butler, 2006). The existing network of traditional surveillance efforts by health ministries, institutes of public health, multinational agencies, and laboratory and institutional networks has gaps in geographic coverage and often suffers from poor information flow across national borders.

At the same time, an enormous amount of information providing situational awareness about infectious diseases is found in web-accessible information sources, such as Internet-based discussion sites, disease reporting networks, news outlets, and blogs (Heymann and Rodier, 2001; Grein et al., 2000; M'Ikanatha et al., 2006). Even web-based clickstream and keyword searching aggregated across Internet users can provide important insights (Eysenbach, 2006). These resources provide valuable and highly local information about disease outbreaks and related events, even from areas relatively invisible to daily global public health efforts (Woodall, 1997). In fact, the majority of outbreak verifications currently performed by the World Health Organization's (WHO's) Global Outbreak Alert and Response Network (GOARN) initially begin as reports from informal electronic data sources such as mailing lists and local news media (Heymann and Rodier, 2001; Grein et al., 2000).

While these web-based data sources can facilitate early detection of outbreaks, they may also support increasing awareness of public health issues prior to their formal recognition. Through low-cost and real-time Internet data mining combined with open-source and user-friendly technologies, participation in global disease surveillance is no longer limited to the public health community (Keystone et al., 2001; Petersen, 2005). Furthermore, the availability of web-based media across national borders greatly ameliorates the potentially suppressive effects of political influence on the spread of information.

The HealthMap Project

Though valuable, electronic sources of emerging infectious disease news are not well organized or integrated. We sought to develop HealthMap, a freely accessible, automated approach to organizing data about infectious outbreaks accord-

ing to geography, time, and infectious disease agent (Figure 2-3) (Holden, 2006; Larkin, 2007; Captain, 2006). HealthMap is a multistream real-time surveillance system that aggregates multiple Web-based data sources (currently news wires, Really Simple Syndication (RSS) feeds, ProMED mailing lists, and EuroSurveillance and WHO alerts). Information is acquired automatically through screen scraping, natural language interpretation, text mining, and parsing to obtain disease name and geocode the location of the outbreak. HealthMap also addresses the computational challenges of integrating multiple sources of unstructured online information in order to generate robust meta-alerts of disease outbreaks. Through this approach, we achieve a unified and comprehensive view of current global infectious disease outbreaks in space and time.

System Challenges

Despite the success of Internet-based surveillance systems such as HealthMap, important technological and methodological challenges remain. Four principal development and deployment issues are as follows:

(1) Value. Though there is an abundance of disparate electronic resources, none is comprehensive. Each has gaps in coverage of certain geographic areas, population sectors, medical expertise, and availability.

(2) Standards. No universal standards exist for capturing, processing, reporting, interpreting, or sharing structured data. Such standards would greatly facilitate the communication and use of information by computationally based systems.

(3) Performance. Metrics for systematic evaluation of these data sources and the performance of these systems are still needed. Though there has been some description of individual data sources (M'Ikanatha et al., 2006; Cowen et al., 2006), there is still limited understanding of their value for spatial and temporal detection and monitoring of disease outbreaks.

(4) Accessibility. Important issues require attention to system ownership, target audience, restrictions, cost, and sustainability.

Surveillance Framework

A good starting point for design of a surveillance framework is the one currently used for the syndromic surveillance systems that have evolved over the past eight years (Mandl et al., 2004a; Buehler et al., 2004; CDC, 2000). The anthrax attacks of 2001 gave rise to large-scale surveillance efforts directed at early detection of an outbreak, prior to confirmed diagnosis (Perkins et al., 2002). These novel surveillance systems also use data that are not diagnostic of a disease, but that might indicate the early stages of an outbreak, often earlier than might otherwise be possible with traditional public health methods. The ideal syndromic surveillance system has the following traits: it acquires data automati-

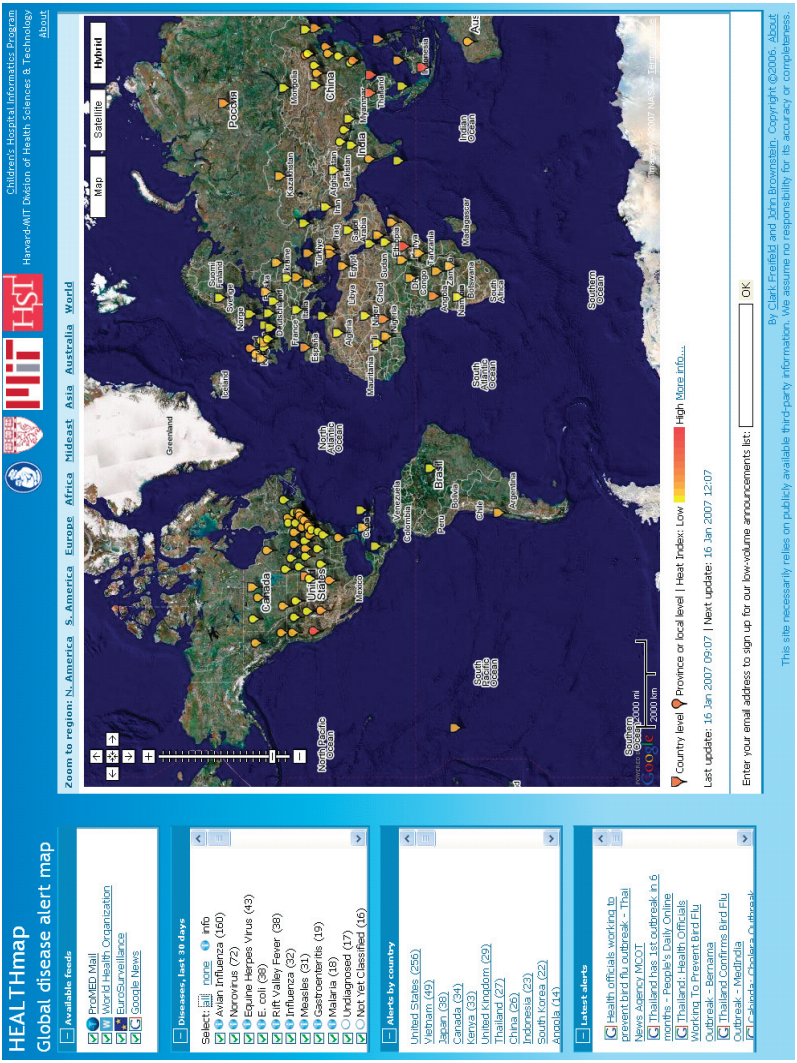

FIGURE 2-3 Screenshot of the HealthMap system.
SOURCE: http://www.healthmap.org.

cally; collects ongoing data in real time or near real time; electronically stores and transmits data to an analytic module; has sufficient demographic, geographic, and temporal coverage to support anomaly detection; captures data in standard formats across data sources; protects private information and patient confidentiality; and scans for outbreaks, correctly distinguishing an abnormal pattern from a normal or expected one (Mandl et al., 2004a). While Internet-based surveillance represents a paradigm shift from indicator-based to event-based sources of information, the existing framework is designed to support the evaluation of all public health surveillance systems. The standard set of evaluation metrics used to interpret data quality and signal detection should apply across both traditional and Internet-based surveillance approaches (Mandl et al., 2004a, b; Buehler et al., 2004; Wagner et al., 2001). Both Internet-based surveillance and traditional syndromic surveillance require four stages: (1) data acquisition, (2) information characterization, (3) signal interpretation, and (4) dissemination and alerting (Figure 2-4).

Here we present a summary of initial evaluation efforts based on this surveillance framework. To help inform our evaluation, we analyzed the HealthMap alert data stream, over a 20-week period (October 1, 2006, through February 17, 2007),

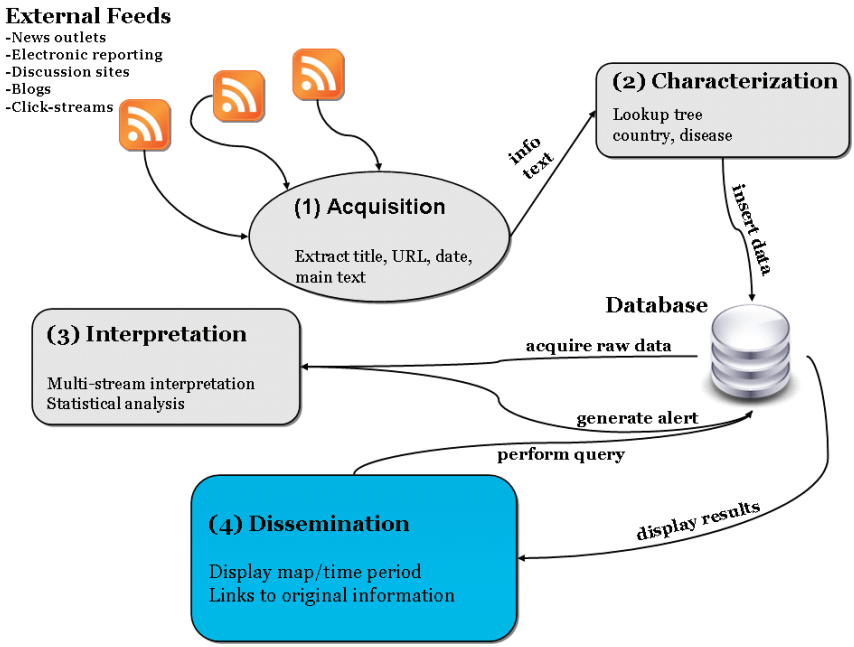

FIGURE 2-4 Framework for Internet-based surveillance.
SOURCE: Brownstein (2006).

applying standard evaluation metrics (volume, geography covered, diseases captured, timeliness, sensitivity, and specificity). Over this period, HealthMap found 3,194 news reports of infectious disease outbreaks (a mean of 22.8 per day, 95 percent confidence interval, 20.6–25.0).

Data Acquisition

Data can be acquired by search either of the open Web or of specific restricted or open websites. The choice of data sources has critical implications for early outbreak detection and disease monitoring across all metrics. Here data sources are evaluated across three dimensions: quality, cost, and availability.

Data Quality

The ideal information sources would be sensitive to even the smallest aberrations. However, as in all surveillance activities, there is an inherent tradeoff between the timeliness and specificity of a system. For example, local news sources may report on strange incidents involving a few cases that would not be picked up at the national level. However, local news reports may be less reliable, reporting stories without adequate confirmation. Information is not always validated, and the credibility of the sources is not always vetted. Thus, without proper filtering, these local news sources may be responsible for substantial noise in the system and increasing the overall false alarm rate. Furthermore, other biases may be introduced for political reasons, resulting either in disinformation (false positives) or censorship (false negatives). In the case of ProMED, its hierarchical curation structure helps minimize false positives. However, while expert review does increase specificity, the required manual processing delays alert reporting.

Data Cost

Internet-based surveillance data have been limited largely to automated mining of information from news aggregators. An important question is whether paid subscription sites provide more value than freely available information. For example, news aggregators such as LexisNexis®, Factiva®, and Magenta News® may all be useful sources of information, especially for local news in a substantial number of languages. However, free online news aggregators, such as Google News and Yahoo News, potentially integrating up to 10,000 sources, may have almost equal value.

The use of free data means that these systems may be provided at minimal cost to the public and to countries that lack the resources to pay high subscription rates. For paid data, cost-effectiveness of various data sources becomes an important issue. Data for HealthMap are acquired strictly through free news

sources. Whether these data sources differ substantially from paid sources is the subject of future evaluation.

Data Availability

The time interval at which these sites are updated can have critical implications for the efficacy of the public health response. Ideally the source should provide timely reports. In reality, media reporting may be guided by external factors such as a weekly health/science section or unrelated news events that might delay reporting. For example, news volume is strongly affected by day of the week, with high volume on Fridays and low volume on Sundays.

News media reports may also be subject to bias about which diseases are covered. Our evaluation found that the richness of pathogen reporting across news sources was substantial, with 66 unique infectious diseases reported through Google News in the 20-week period (Table 2-1). However, we found that distribution of reports across pathogens (or pathogen evenness) was low, with a substantial skew toward reporting of outbreaks of avian influenza and norovirus. The more skewed distribution in the news sources is expected given the tendency for the media to focus and sustain reporting on stories of public interest. We also

TABLE 2-1 Top Infectious Disease Alerts from the HealthMap System, October 1, 2006–February 16, 2007

Disease Reported	Total Number of Reports
Avian influenza	661
E. coli	492
Norwalk-like virus	242
Salmonellosis	217
Influenza	169
Dengue fever	133
Herpes	118
Cholera	81
Undiagnosed	78
Gastroenteritis	46
Pertussis	52
Rift Valley fever	46
C. difficile	33
Staphylococcal disease	32
Diarrhea	29
Legionellosis	28
Tuberculosis	28
Malaria	26
Chickenpox	25
Measles	25

SOURCE: http://www.healthmap.org.

found that news outlets often picked up more common seasonal and endemic conditions (e.g., epidemic influenza, dengue, *E. coli*, *Salmonella*). This is in contrast to the ProMED system that explicitly avoids reporting on endemic infections—such as tuberculosis and HIV—or vaccine-preventable diseases (Madoff, 2004).

Geographic coverage of data sources also merits quantitative evaluation (Figure 2-5). During the evaluation period, 88 countries had reports of infectious disease outbreaks, with the greatest reporting from the United States (n=1,346), Canada (n=235), and the United Kingdom (n=226). Given that the analysis included only English-language news sources, the skew toward English-speaking countries is not surprising. However, it is also clear there is a bias toward reporting from countries with larger populations (e.g., China), numbers of media outlets, public health resources, and availability of electronic communication infrastructure (approximated by number of Internet hosts).

Future Work in Data Acquisition

Gaps in population and geography covered by news sources need to be understood and adjustments need to be made. For example, important gaps in media reporting exist in tropical areas, which also have the greatest burden of infectious diseases. Monitoring other Internet-based sources such as blogs, discussion sites, and listservs could complement news coverage. In particular, the use of clickstream data and individual search queries is a promising new surveillance source (Eysenbach, 2006). Ultimately, informal news-based sources should be considered as part of a comprehensive multistream surveillance system that provides an integrated view of global health information.

Characterization

Although free and unrestricted websites have large quantities of useful information about infectious diseases, the information is not well organized. News media output usually comes as unstructured free text, making analysis of the geographic and temporal relationships between different reports and data sources difficult. Automated disease and geographic location grouping is usually accomplished through natural language interpretation and automated text mining and parsing. Search criteria can include disease names (scientific and common), symptoms, keywords, and phrases. Once gathered, automated approaches for initial filtering often require human verification.

Classifying Information

Extracting a pathogen name from a free text report presents a number of formidable challenges. In HealthMap, we draw from a continually expanding

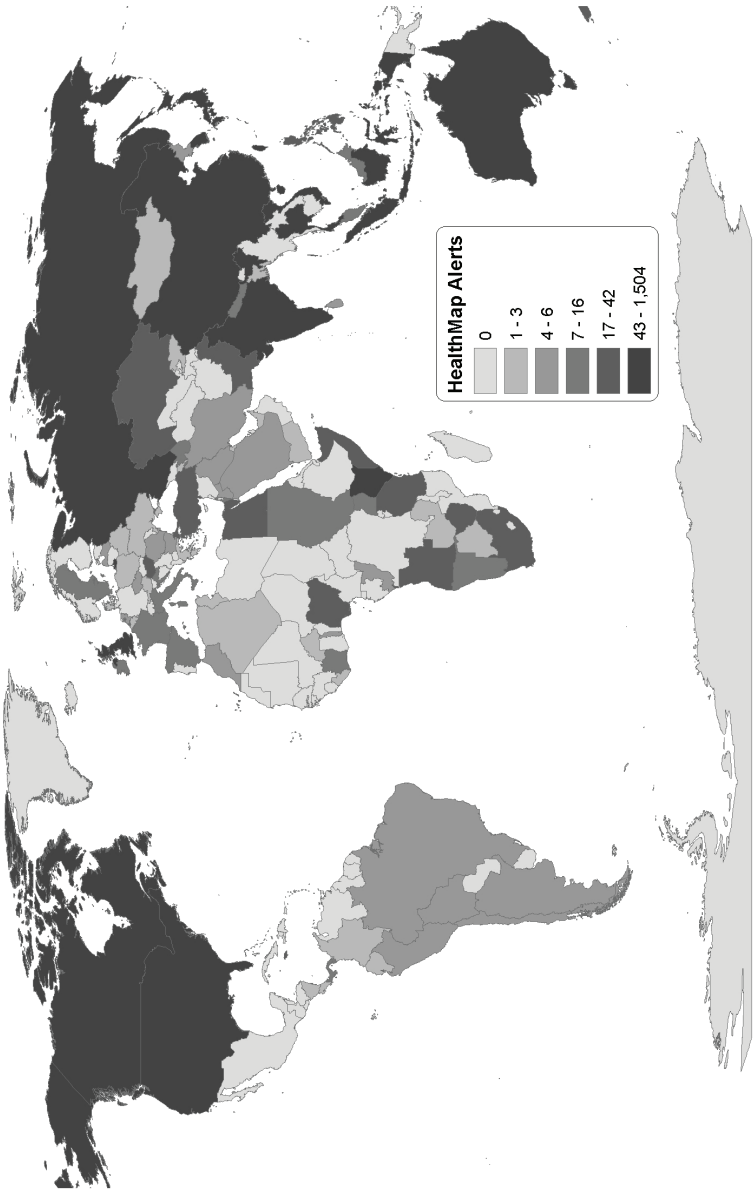

FIGURE 2-5 HealthMap geographic coverage, October 1, 2006–February 16, 2007.
SOURCE: Brownstein (2006).

dictionary of pathogens (including both human and animal diseases) to organize unstructured and semistructured disease outbreak alert information. Locations are extracted by matching geographic names with a master table of latitude and longitude coordinates of centroids of certain geographic areas, including countries, provinces/states, and cities. In addition to reasonable performance and scalability, a key advantage to this pattern dictionary approach is that it is translated relatively easily to other languages: A different dictionary can be plugged in easily to the existing architecture. A language expert is needed to perform the initial translation, refine the pattern library, help with capitalization and punctuation subtleties, and provide other adaptations, but the basic approach can be re-applied without major changes to the system. Furthermore, the language expert needs to have minimal technical knowledge with respect to natural language syntax or software development to contribute to the library.

Although effective for rapid matching, a number of hurdles need to be overcome. First, in the case where a word may have multiple spellings, for example, diarrhea (common in the United States) and diarrhoea (common in the United Kingdom), we stock the dictionary with multiple patterns for a single pathogen. While look-up time does not increase substantially with the addition of patterns to the dictionary, the disadvantage of the dictionary approach is that it requires *a priori* knowledge management and allows identification only of locations and diseases already present in the database. Similar challenges exist for identifying the precise geographic location of an outbreak, as geographic names and borders are subject to change. The expansion and editing of the database requires extensive and careful manual data entry. Another limitation of the look-up engine is that it ignores pattern context. A good illustration is the use of "plague" in reports—often news articles use it metaphorically, such as "Problems continue to plague New Orleans cleanup effort." If the look-up engine matches the word "plague" alone, it will mark this alert as an outbreak of *Yersinia pestis* in Louisiana. We mitigate this problem by including "to plague," "a plague," and other similar strings as null patterns in the library so that the classifier will mask them.

Rating Information

Clearly, the article text contains the best indicators about the locations and diseases of the event in question. However, blindly searching the text, while increasing sensitivity, leads to excessive false positives. To mitigate this problem, we process the input in stages: If the classifier cannot identify location and disease from the initial input provided by the feed, namely the modified headline, it can request more text from the feed. For example, in the case of the Google News aggregator, the system examines the headline, then the description, which usually consists of the first one or two sentences of the article, and finally the publication name. Frequently, a publication in one area refers to events in another area, making the publication name and location an unreliable source for the location

of the alert. However, articles that do not refer to a well-known location, such as "Suburban school closed after flu outbreak," generally refer to a location near the publication headquarters. By processing the input in stages, we reduce the false positives of the first case while including more of the true positives of the second case.

Future Directions in Data Characterization

Future work must focus on improving natural language processing capability to clearly identify the pathogen, filter nonpertinent reports and duplicates, and enhance the spatial resolution of location. Ideally improvements in how the source information is reported would vastly enhance characterization. For example, structured annotation on the attributes of an outbreak by the article author or source publication would remove the problems inherent with natural language processing. However, given that data standards for news reporting are not likely to be implemented in the short term, advanced text processing methodologies such as fuzzy matching and neural networks could have an important role in enhancing current systems. Furthermore, reliance on an external geocoder with consistently updated databases of geographic locations may be a better solution (Croner, 2003). Although machine learning techniques are undoubtedly important, human analysis still has tremendous value, as exemplified by the Global Public Health Intelligence Network (GPHIN) (Mawudeku and Blench, 2006) and ProMED (Madoff and Woodall, 2005). The success of Wikipedia has shown that leveraging collaborative human networks of trained public health professionals (such as ProMED subscribers and international groups of experts) could be an ideal mechanism for classification, severity assignment, conflict resolution, geocoding, and confirmation of reports on outbreaks of rare or even infectious diseases of unknown identity (Giles, 2005).

Interpretation

While issues of acquisition and characterization have been addressed by many systems, methods for interpreting these data are for the most part underdeveloped. Current systems aggregate Internet-based news resources, but are limited in terms of analytical tools available to the user. Development has been geared toward knowledge management, where news on infectious disease is aggregated and reorganized. Because of the magnitude of information collected, users could, over time, become overwhelmed with an increasing number of false alarms. Thus, there is a need to move from simple knowledge reorganization to an analytic approach for disseminating timely yet specific signals. A number of strategies are available to reduce the false alarm rates in these inherently noisy data sources.

Multistream Interpretation

False alarms often can be reduced by thorough aggregation and cross-validation of reported information on a particular disease outbreak. The motivation for such a meta-alert is based on the idea that multiple sources of information on an incident can provide greater confidence in the validity or reliability of the report than any one source alone. In HealthMap, the severity of a meta-alert is calculated as a composite score based on: (1) the reliability of the data source (e.g., increased weight to WHO reports and less weight to local media reports); and (2) the number of data sources, with increased weight to multiple types of information (e.g., discussion sites and media reports on the same outbreak).

For evaluation of multistream surveillance to be effective, basic characteristics such as sensitivity, specificity, and timeliness of different news source types need to be quantified (Wagner et al., 2001; CDC, 2001; Reis and Mandl, 2003a; Brownstein et al., 2005b; Bloom et al., 2007). In our evaluation, we used officially confirmed outbreaks obtained from WHO Outbreak News, available in the public domain, as a "gold standard" indicator of an infectious disease outbreak (WHO, 2007). We measured key detection characteristics of Google News reports for 12 focused outbreaks over the 20-week period. Mean timeliness for Google News, defined as the time between detection by the surveillance source and report by WHO, was 12 days. However, actual timeliness varied widely from 102 days earlier to 59 days after the WHO report. For example, a diarrheal outbreak in Ethiopia was detected by the media nearly three weeks before the WHO report. In contrast, a plague outbreak in the Democratic Republic of the Congo and a Chikungunya outbreak in India were only reported in the media once the official WHO report was released. Sensitivity, defined as the proportion of WHO alerts detected by news data, was moderate, with 58 percent of the alerts reported in the news. In contrast, we identified 267 unique alerts (country–disease pairs) from Google News, revealing a high volume of reporting. Given that only a subset of outbreaks is posted to WHO Outbreak News, the specificity of news data could not be calculated given the current data sources. Without a better gold standard of validated outbreaks, assessing false positives is difficult.

Statistical Interpretation

The value of news reports can be measured similarly to traditional surveillance data sources used for outbreak detection, where the goal is to distinguish an abnormal pattern from a normal or expected one. Statistical methods for outbreak detection include temporal pattern models such as statistical process control (SPC) (Hutwagner et al., 1997) and autoregressive moving average models (ARIMA) (Reis et al., 2003), spatial models for geographic cluster detection (Kulldorff and Nagarwalla, 1995; Brownstein et al., 2002; Olson et al., 2005), and spatiotemporal patterns for detecting space-time interactions (Kulldorf et

al., 2005). To apply these to monitoring Internet news sources, we must define the baseline patterns and thresholds of reporting for which no action is required. In this case, we expect a baseline level of random noise in news media reports generated by case definitional issues, surveillance bias, and overreporting. The generation of statistical signals therefore can be based on a set threshold of report volume defined by modeling this baseline. Models can include factors such as cyclical patterns (day of week, month, seasonal effects) and autocorrelation (Reis and Mandl, 2003b; Brownstein et al., 2005a), as well as geographic and temporal biases of news reporting. Thresholds would be set by evaluating the tradeoff between signal quality and timeliness.

Future Directions in Data Interpretation

Future work in modeling and data integration should also be directed at improving risk assessment. For example, signals from unstructured online information sources can be integrated with other health indicator data to provide a broader context for the alert. Pertinent datasets include mortality and morbidity estimates, population density and mobility, and pathogen seasonality and transmissibility (Wilson, 1995; Altizer et al., 2006; Dowell and Ho, 2004; Grassly and Fraser, 2006; Fraser et al., 2004). With the increasing importance of vectorborne and zoonotic diseases (Gratz, 1999; Dobson and Foufopoulos, 2001; Brownstein et al., 2004), consideration also should be given to inclusion of ecological data such as distribution of arthropod vectors and animal host reservoirs, as well as environmental predictors including climate and vegetation (Brownstein et al., 2003; Colwell et al., 1998; Kitron, 1998). Combining these informal sources with clinical and laboratory surveillance data should also be an important next step. Such integration could yield a relevancy score for the report, define populations at risk, and predict disease spread.

Dissemination

An important final consideration is how information from Internet-based systems should be disseminated. Clearly a critical audience is public health officials interested in real-time updates of infectious disease status in their geographic region. However, whether these systems should be freely available and open to the public is an area of active debate. Travelers, for example, may have a keen interest in up-to-the-minute knowledge about infectious disease activity at their destination. For the general population, obtaining integrated real-time coverage of a disease emergency is particularly challenging given disparate news and alert sources. An unrestricted sentinel system dedicated to the aggregation and geographic display of current outbreaks could fill this information gap.

On the other hand, unrestricted access to this information could have severe

economic impacts on the countries affected by the disease alerts. The risk is especially elevated with fully automated systems that may not have the benefit of informed human judgment. However, even with careful controls, any system can generate spurious alerts. User restrictions may be the only way to guard against unwarranted damage (Cash and Narasimhan, 2000). Furthermore, an open access model might not be economically sustainable. GPHIN depends on subscription fees to make any necessary improvements to the system. In contrast, HealthMap is based on freely available data and is open to the public. However, a tiered approach such as the one used by MedISys (Medical Intelligence System) where general information is provided to the public based on free resources and more detailed information pertinent to public health officials (including geographic detail) is provided by paid subscription may represent a reasonable compromise. Information access is a key consideration for the future development of these systems.

Another critical question is who ultimately should oversee these systems and manage the information collected, especially given that issues of trust and reliability are paramount. At the moment, systems are being developed by international organizations, governments, and academic institutions. The current linkage between surveillance by GPHIN and public health response by WHO's GOARN presents a very appealing approach. An initiative at Google.org, called the International System for Total Early Disease Detection (INSTEDD) project, aims to develop a system that increases the number of languages and data sources available through GPHIN (Delamothe, 2006). INSTEDD could become a transparent and publicly available resource independent of any government agency. How such a system would be linked with existing public health infrastructure should be an area of active consideration.

Conclusions

The growing use of informal electronic information sources highlights an important paradigm shift in disease surveillance, expanding beyond traditional public health systems. Although Internet-based informal sources on outbreaks are becoming a critical tool for global infectious disease surveillance, important challenges still need to be addressed. In particular, an unavoidable pitfall of a system-of-systems approach is that it is inherently subject to the limitations of the primary data collected by the individual component systems. Our preliminary evidence-based evaluation of HealthMap suggests that aggregation of multiple sources may counter this limitation by increasing sensitivity and timeliness while reducing false alarms, in that assessments are not based on any single news outlet alone. Because many of the places with the least technological adoption also carry the greatest infectious disease burden, future system development should also specifically address the digital divide to achieve more uniform and comprehensive global coverage. A robust research agenda, continued organic evolution of existing and new technologies, and scrutiny through a rigorous evaluation framework

will help ensure that the global public health enterprise maximally leverages new electronic sources for surveillance, communication, decision making, and intervention.

Acknowledgments

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USING CELL PHONE TECHNOLOGY FOR INFECTIOUS DISEASE SURVEILLANCE IN LOW-RESOURCE ENVIRONMENTS: A CASE STUDY FROM PERU

Pamela R. Johnson, Ph.D.[15]
Voxiva

David L. Blazes, M.D., M.P.H.[16]
Naval Medical Research Center Detachment

Summary

Basic routine health surveillance has been largely unachievable in most of the developing world because of inadequate funding and public health training, especially in resource-limited parts of Africa, Asia, and Latin America. Considering that many emerging diseases with pandemic potential first occur in the developing setting (e.g., severe acute respiratory syndrome, or SARS and H5N1 avian influenza), enhanced surveillance systems in these countries must become high priorities for safeguarding global public health. This presentation reports on an innovative model using a cell phone- and Internet-based reporting system that has been developed and tested to extend disease surveillance by the Peruvian Navy along the coast and remote rivers of Peru. Alerta DISAMAR—the name given to the system refers to the Health Department of the Peruvian navy—has been fully operational in Peru since 2003. More than 600 individuals have been trained and have used an Internet- and cell phone-based electronic system developed by Voxiva to report routinely from 42 land-based sites and 19 ships. More than 80,000 cases and 31 outbreaks have been reported. Alerta DISAMAR represents a sustained, large-scale effort that leverages cell phones and related tech-

[15]Co-founder and Executive Vice President.
[16]Director, Emerging Infections Program, Lima, Peru.

nological innovations to strengthen disease surveillance. Because mobile phone networks are expanding so rapidly across the developing world, this model has important lessons for strengthening disease surveillance in other low-resource environments.

Background

The low-resource environments of most developing countries pose a particular challenge to global efforts to establish effective infectious disease surveillance and detection. There is little question that these countries are important to global surveillance. "Out of every 100 persons added to the population in the coming decade," Zlotnik wrote, "97 will live in developing countries" (Zlotnik, 2005). Figure 2-6 shows countries sized in proportion to their populations. It shows how significant the share of the world's population is in China, Brazil, Nigeria, sub-Saharan Africa, and other countries in the developing world.

Infectious disease is disproportionately represented in these countries. Many new and emerging infectious diseases—including SARS, H5N1, HIV/AIDS—trace their origins to these often densely populated environments. However, despite their demographic and epidemiologic significance, most developing countries, where microbial threats to global health are most likely to emerge, also possess the weakest surveillance systems. The Government Accountability Office (GAO), in a global review of surveillance systems, noted that:

> Developing country systems are a weak link in the global surveillance framework. Surveillance systems in industrialized and developing countries suffer from a number of common constraints, including a lack of human and material resources, weak infrastructure, poor coordination, and uncertain linkages between surveillance and response. However, these constraints are more pronounced in developing countries, which bear the greatest burden of disease and are where new pathogens are more likely to emerge, old ones to reemerge, and drug-resistant strains to propagate. Weaknesses in these countries thus substantially impair global capacity to understand, detect, and respond to infectious disease threats (GAO, 2001).

Over the past decade, a number of important efforts have been made to use information technology to strengthen surveillance systems. Most have taken place in developed countries where computers and Internet connectivity are readily available. In addition, e-mail and the Internet have had a major impact in facilitating the growth of global networks such as the World Health Organization's (WHO's) Global Outbreak Alert and Response Network (GOARN), ProMED-mail, and a number of global disease-specific surveillance networks (Heymann and Rodier, 2004).

Despite the evident importance of information technology (IT) in these

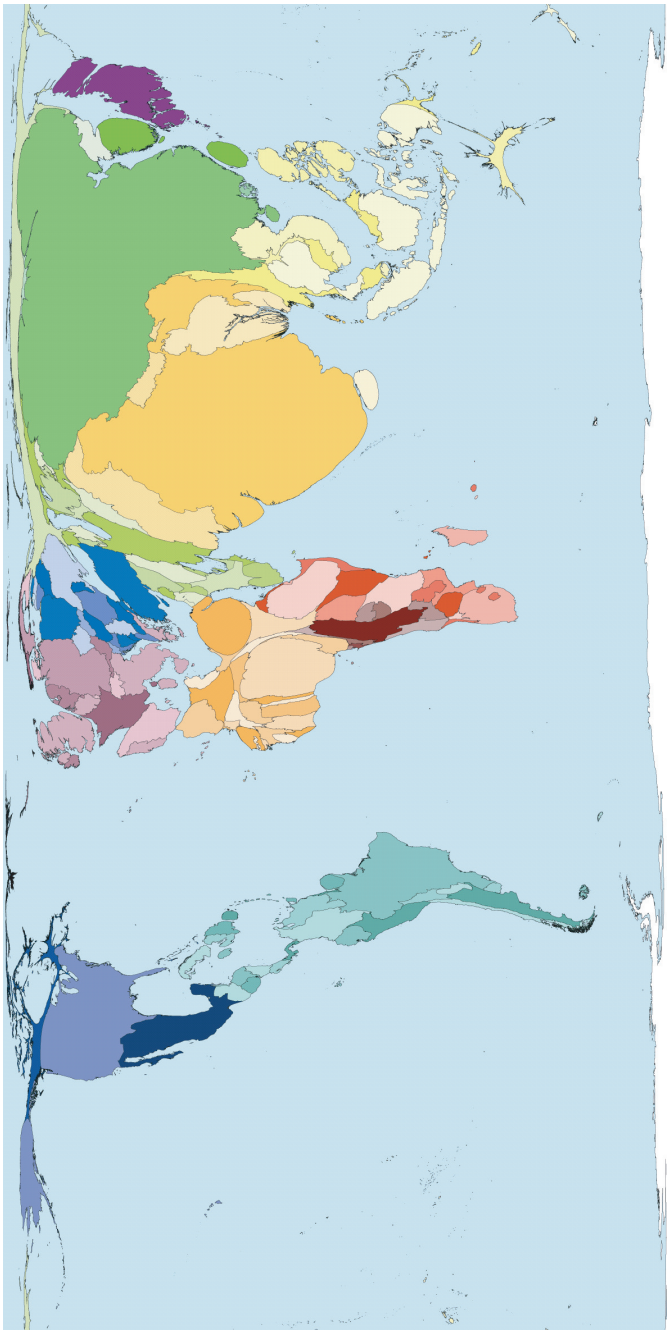

FIGURE 2-6 Distribution of the earth's population.
SOURCE: Worldmapper (2007). See http://www.worldmapper.org. Reprinted with permission. © Copyright 2006 SASI Group (University of Sheffield) and Mark Newman (University of Michigan).

examples, IT has yet to realize its full potential for strengthening the surveillance systems of countries in the developing world. Even where computers exist, inadequate power and lack of Internet coverage outside major towns and cities has meant that in most developing countries routine surveillance systems are still largely paper based, and transmission is slow. Health officials in capital cities and towns may be easily linked to global networks and colleagues in other major cities, but communicate less easily with health facility staff in their own countries.

Until recently, there was no practical, measurable way to bridge the digital divide between the cities and the poor and rural areas in these countries, where most of the population lives. Nonetheless, a major recent review of disease priorities led by The World Bank holds out a vision of the future of disease surveillance:

> Public health agencies, ministries of finance, and international donors and organizations need to transform surveillance from dusty archives of laboriously collected after-the-fact statistics to meaningful measures that provide accountability for local health status or that deliver real-time early warnings for devastating outbreaks. . . . Information technology and informatics can help in attaining this vision . . . technology can facilitate the collection, analysis, and use of surveillance data, if data standards are developed and compatible systems are established. . . . technology such as cell phone-based systems could accelerate collection of key data (for example, occurrence of a viral hemorrhagic fever outbreak) (Nsubuga et al., 2006).

The explosive growth of mobile telephone networks in the developing world is already a dramatic success story. According to the International Telecommunications Union (ITU), Internet connectivity is growing at a good pace, but the reality is that cell coverage is growing much faster. In the developing world there are 1.2 billion phones and a million new mobile phone subscribers every day. Approximately 80 percent of people who live today are within reach of a mobile phone signal, according to the ITU. Half of all households will have phone access in the next decade, and 90 percent of the world will be covered by 2010. In Latin America, there are more than 270 million mobile phone users today. The industry estimates that within the next 3 years, 75 percent of people in Latin America will own a cell phone. Africa shows the most dramatic growth. Over the past 5 years, growth has averaged nearly 60 percent a year, with nearly 76 million subscribers at the end of 2004.

Voxiva was founded in 2001 to find practical ways of using information technology for health and development in low-resource environments. We reviewed a variety of pilot projects that were seeking to extend the benefits of the Internet using a variety of individual devices, including personal digital assistants (PDAs) and satellite dishes. However, we did not find any practical, measurable, and sustainable strategy to support data collection and communication with points

of service. It was and in many countries remains a paper-based world, with few benefits of IT reaching large scale.

Voxiva's founders recognized the potential of the growth of cellular networks to develop a measurable, sustainable approach that could support public health and development. Working with a variety of public health agencies, including health officials in the U.S. and Peruvian navies, Voxiva developed innovative software that allows health professionals to enter and access data using the Internet, a cell phone, or other devices. The software makes it possible to write a survey and to make that survey available in multiple formats so users can use the tools they have and the most convenient, cost-effective means to respond.

Figure 2-7 illustrates the approach that Voxiva has taken to optimize the use of the existing infrastructure of personal computers (PCs), Internet, cell phones, fixed phones, pay phones, PDAs, smart phones, and paper to create networked data collection and communications surveillance systems in low-resource environments.

Over the past six years, we have learned a number of lessons for building IT systems for use in low-resource environments, leveraging cell phones and other forms of information technology.

Building on Available Infrastructure

The global mobile phone network is increasingly the most important globally deployed communications infrastructure that covers the developing world. As fast growing and highly successful local businesses, telecommunications companies provide global infrastructure for data transmission and communication that is inherently sustainable. As a result, the health sector no longer needs to build and maintain its own infrastructure to transmit data and support communication with its network of health facilities.

Hardware is also increasingly available. Health ministries, states or provinces, and increasingly districts have computers and at least intermittent Internet access. In addition, the dramatic expansion of mobile phone usage has put a simple "terminal" within the reach of many if not most health workers—one that can be used to enter data, respond to surveys sent by text messages, and send and receive alerts. Providing a toll-free number that people can call with their own mobile phones is a quicker and cheaper approach to expanding a surveillance network than buying, equipping, maintaining computers, and paying for power and Internet access for all health facilities.

By building on this global telecommunications infrastructure and available hardware, it is possible to rapidly create large-scale integrated networks that can do basic reporting without large-scale new investments in acquiring, installing, and maintaining technology. Over time, the infrastructure will grow—but most countries already have enough hardware to begin.

As one example, Voxiva was able to support the national scale-up of

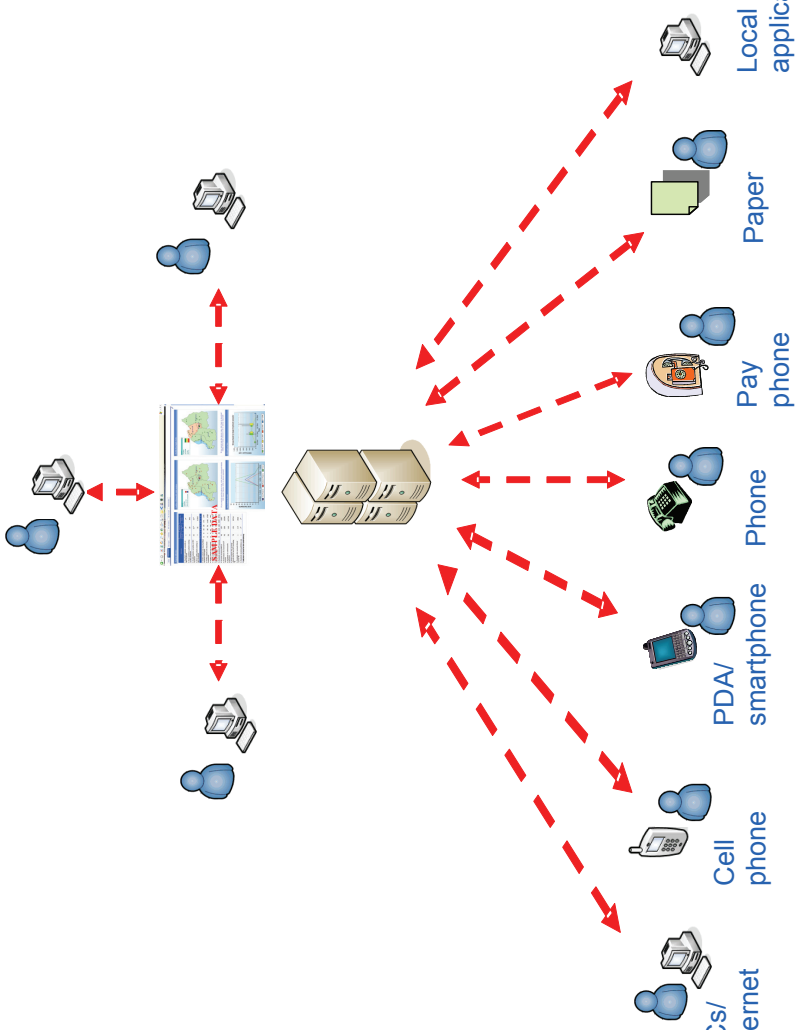

FIGURE 2-7 Being able to enter and access data from any available communications channels can optimize the use of existing infrastructure.
SOURCE: Voxiva. Reprinted with permission of Voxiva.

Rwanda's national HIV/AIDS program with a monitoring system that allows health facilities to report program indicators and register new patients. Without any new investment in hardware, Rwanda was able to rapidly increase its electronic reporting system from 12 facilities to 146 sites. Ninety percent of the sites report program indicators and register patients using the phone. They use their own cell phones, call a toll-free number—the first in Rwanda—log in using their password, and enter basic data digitally using the keypad. Over time, more and more sites will get computers and Internet connectivity, but the program was able to reach national coverage rapidly without waiting.

Multiple, Redundant Technologies

We have found that no single solution or hardware works in all environments, for a variety of reasons. Power is a major constraint, especially in the most remote environments and poorest countries. The cost of connectivity remains high in many countries. Maintenance and support for computer hardware and software are costly and in short supply. Actual needs for bandwidth and analytic power vary depending on how users are using the data collected. For many needs, paper records will be the base system. Having the choice of different electronic devices means that one can optimize the use of available hardware and allows health professionals to enter and access data using the access means they have. This also creates redundancy: If the Internet is not available, it is still possible to do basic reporting via the phone.

Electronic Data Capture at the Source

Paper systems rely on copying information at the source, relaying it, then entering and aggregating information at higher levels; this system of data transmission is error prone and makes it difficult to trace data and cases back to their source. If data can be entered and confirmed at the source, this in itself can enhance quality. If data can be transmitted to a central database, reviewed and approved at higher levels (e.g., at the district level), and also be made rapidly available to others who need it, the burden and risks associated with entering data multiple times are reduced.

Rapid Transmission of Data

Most surveillance systems rely on physical transmission of data via mail or "sneaker net" with people bringing the forms to a monthly meeting or on a periodic visit. More urgent information is transmitted via individual phone or radio calls and recorded centrally. Electronic transmission data can cut the time and cost required for transmission dramatically. Although this is important for routine surveillance, it is even more vital for an event, such as a serious outbreak

or pandemic, when the situation on the ground could change rapidly. Electronic submission of data in near real-time information could help decision makers make much better decisions about allocation of resources in a situation of rapid change.

Shared Database, Role-Based Access

If data are collected at the source and transmitted to a core database, organizations can make that data available to authorized users according to the specific roles they play. For example, the same set of data could be viewed in a variety of ways:

- Health staff can get confirmation that their report has been received, notification of cases of interest from neighboring locations, and results of a case investigation;
- A district health official could see reports from health clinics and posts immediately—then edit or approve them;
- Senior health officials could review aggregate data;
- Surveillance officers could get lists of nonreporting sites; and
- Outbreak investigation teams or vaccination teams could get short message service (SMS) or e-mail alerts about suspected cases of measles or potential outbreaks.

Data, collected once and transmitted to a central database, can be used many times. Furthermore, data can be presented in standard templates, basic reports, and maps or exported for additional analysis.

Communication Plus Feedback

An extended electronic network can also facilitate communication and feedback that is vital to the supervision and motivation of a distributed network. Automated messages can be sent by multiple means—e-mails, text messages, voice mails, alerts—and accessed through the available technology.

Build Human Capacity

Information technology alone is no silver bullet. Building a surveillance system in *any* environment requires an investment in the training staff at all levels. Well designed information systems can help, with tools such as validation rules, reminders, and online access to guidelines and training materials. Such tools could be even more helpful in situations where health staff are not well trained. However, the best designed system cannot detect disease or respond to

an outbreak without the right processes and people; at its core, a surveillance system will always be about the people who use it. The role of technology should be to empower networks of clinicians, nurses, and other health workers to fully participate in this important enterprise of global disease surveillance.

The same technological approach leveraging cell phone technology is being used for a variety of purposes. It has been used for syndromic surveillance in schools in San Diego and Washington, DC. It has been tested in the Canete Valley in Peru and in Baghdad and Basra, Iraq, and is being developed with the Ministry of Agriculture in Indonesia to create a system to strengthen animal surveillance. In Latin America, it is being used to monitor national HIV/AIDS programs, track adverse events, and support public safety (Olmsted et al., 2005; Curioso et al., 2005).

Alerta DISAMAR: A Case Study in Infectious Disease Surveillance

Background

In fall 2001, at a time when other events in the world raised awareness of microbial and other threats, there was an outbreak of *P. falciparum* malaria at a remote naval base in the Amazon jungle basin of Peru that led to several deaths. As in some other countries, the existing surveillance system was underdeveloped and primarily paper based; it was not unusual for reports to take a month to get to authorities in Lima.

Primed by these events, the Peruvian navy, the U.S. Naval Medical Research Center Detachment in Lima, and the Peru-based office of Voxiva developed a joint project. In January 2003, they initiated Alerta DISAMAR, a novel electronic disease surveillance system. This experience in implementation has been exciting to observe from the ground up, and this case study describes some of the lessons learned during deployment of this surveillance system in Peru.

Pandemics by definition involve the global dissemination of disease. Military populations historically have been involved in the dissemination of a number of infectious diseases, including their well-documented role in the spread of H1N1 influenza in 1918–1919 (Oxford et al., 2005). There are also examples from antiquity of troop movement roles in the spread of smallpox, cholera, measles, syphilis, and plague (McNiel, 1977). More recently, high rates of HIV infection have been seen in sub-Saharan African militaries, and this population certainly contributes to ongoing transmission (Whiteside and Winsbury, 1996). Despite the known risks of disease transmission among highly mobile armed forces, these groups remain among the most poorly tracked populations in many developing nations. The combination of undersurveilled military populations and dangerous transmissible diseases seems the perfect recipe for a pandemic.

Military personnel are a very good population to place under surveillance for

emerging infectious diseases (Chrétien et al., 2007). They serve as ideal sentinel populations due to their expeditionary mission, their frequent travel to remote locations, and their interactions with local populations.

A number of challenges exist in implementing an electronic disease surveillance system, some cosmopolitan and some unique to resource-limited settings. The dubious observer may even ask if conducting surveillance in a resource-limited setting is even feasible when the potential pitfalls and challenges often seem insurmountable. The first challenge is to create a system that is complementary and not duplicative of existing surveillance systems. Creation of parallel surveillance systems can paradoxically lead to the failure of both the established and the new systems because limited funds and effort can be diluted between the two systems with neither functioning effectively (Nsubuga et al., 2006). Second, one must convince the stakeholders in the population under surveillance that their efforts are useful and their valuable time is not wasted. To accomplish this, one must make sure that meaningful data are returned to the end users of the system, and in a timely fashion so that consequential action may be taken to limit the effect of a disease or condition. An example might be the timely detection of an influenza outbreak in a closed facility where case isolation, enforcement of hand/cough hygiene, and antiviral chemoprophylaxis may limit the spread of this contagious illness.

Additionally, a disease surveillance system in the developing setting must be cost-effective, with few recurring expenses in order to assure sustainability. Many countries in the developing world have limited funds to spend on public health, and these are often exhausted in responding to crises rather than invested in preventive strategies. Finally, a disease surveillance system in the developing setting must be able to function in remote locations and austere conditions.

With regard to the situation in the Peruvian navy, we focused our attention on a population that was not under surveillance, and applied novel technology in the attempt to create a model that could be disseminated to other resource-limited settings worldwide. Furthermore, in establishing this surveillance system, we have attempted to change the culture within this population to approach disease characterization and transmission from a broader perspective, that of epidemiology and public health.

The System

The Alerta electronic disease surveillance system uses a countrywide network of health-care facilities that encompasses more than 95 percent of the population of the Peruvian navy and its civilian dependents in most regions of Peru (over 120,000 people). Some of these sites are tertiary care facilities in the capitol city of Lima, but the majority are smaller, more remote, and less capable clinics that exist throughout the country. Figure 2-8 shows a typical clinic site in one of the austere areas where this system functions.

FIGURE 2-8 Health-care personnel collect data.
SOURCE: Jose Quispe, Peruvian Navy. Reprinted with permission from NMRCD.

The network consists of 43 fixed sites throughout Peru and 19 ships both on the coast and on rivers in the jungle (Figure 2-9). The sites use a diverse range of reporting techniques, with 12 sites routinely reporting by radio relay, 27 by telephone, 15 by Internet, and 8 by telephone or Internet.

Data flow from individual clinics to the central operations hub in Lima. The actual data flow from the field is described in Figure 2-10. Data are collected on standard clinical forms during patient encounters, then entered into the system by nurses or physicians via cell phones, toll-free public telephones, or by Internet if accessible. Several extremely remote sites are beyond the cellular footprint, and in these, the Peruvian navy personnel use a radio phone to relay data to the next nearest site that has either a cell phone or access to public phones or the Internet. Occasionally, satellite phones are used if they are available to enter data through the toll-free telephone system.

The data collected through this system are often the only systematic representation of the epidemiology of diseases within the Peruvian navy. This has allowed baseline levels of disease to be set, and allocation of scarce resources to be assigned based on rational data rather than assumptions. The system collects rates of the 29 reportable illnesses for the Peruvian Ministry of Health (MoH) as well as some militarily relevant cases such as training-related injuries. The data generated by this system are invaluable to both the Peruvian navy and the MoH

FIGURE 2-9 Alerta network.
SOURCE: Dr. Carmen Mundaca, Naval Medical Research Center Detachment (NMRCD). Reprinted with permission from NMRCD.

because they report disease rates from areas of the country where the MoH does not have a significant presence.

The data are captured and displayed in real time on a web-based platform. Several automated outputs are generated so that feedback is given almost immediately to the stakeholders in this process, either by electronic mail or short message service (SMS) messaging to cellular phones. Features include automated outbreak detection via algorithms, graphical representation to assist clinicians, and baseline trends.

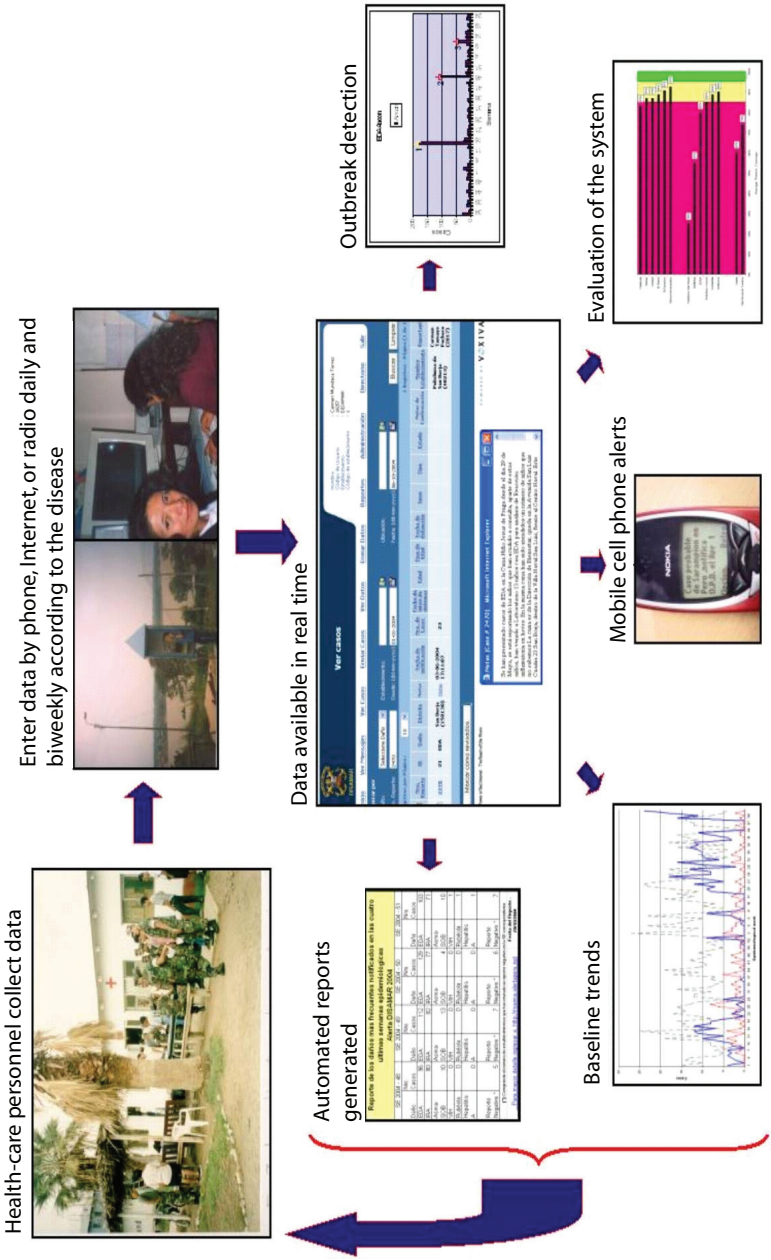

FIGURE 2-10 Data flow from the field.
SOURCE: Dr. Carmen Mundaca, NMRCD. Reprinted with permission from NMRCD.

Discussion

A complete evaluation of the ALERTA surveillance system was performed for the period from January 2003 to November 2006, and is the subject of a separate publication (Mundaca et al., 2005). This evaluation focused on three phases: implementation (first year), consolidation (second year), and expansion (third and fourth years). The methods for this evaluation are based on the Centers for Disease Control and Prevention's (CDC's) Updated Guidelines for evaluating public health surveillance systems (CDC, 2001). The tasks involved in evaluating this system are adapted from the steps in program evaluation in the Framework for Program Evaluation in Public Health (CDC, 1999), as well as from the elements in the original guidelines for evaluating surveillance systems (CDC, 1988). This assessment was based on information from several data sources, including the main database generated by the system platform, quarterly morbidity reports from the Peruvian navy, outbreak reports, information from Voxiva personnel, focus groups, training evaluations, and surveys applied to stakeholders. Highlights of this evaluation are included below, and include usefulness, sustainability, stability, and flexibility.

The Alerta system has been invaluable to the Peruvian navy. Since its implementation through November 2006, 80,747 events have been reported, including 3,789 in 2003; 9,454 in 2004; 25,246 in 2005; and 42,258 through November 2006. The Peruvian navy has embraced Alerta DISAMAR and the culture of epidemiology surrounding it. As one example, the Peruvian military leadership asked all the services for the number of cases of dengue fever in the past year. The navy was the only group that could provide a number and distribution within the week. They searched Alerta DISAMAR's database and were able to provide the information rapidly. Since this incident, the other branches of the Peruvian military have decided to implement Alerta. Reports such as these have allowed baseline levels of disease to be determined, and for the first time have identified outbreaks of disease in a timely fashion so that diagnoses can be made and interventions enacted.

One of the most important questions to ask in evaluating a system is whether that system is doing what it was intended to do. Over the past four years, we have detected more than 31 outbreaks, including diarrhea, dengue, influenza, and tuberculosis. The outbreak of diarrhea depicted below is an example of an outbreak reported using the system (Figure 2-11), and there have been several outbreaks of acute respiratory infections that have initiated outbreak responses at recruit training camps. One of these identified outbreaks (mumps) led the Ministry of Health (MoH) to conduct active community surveillance that uncovered an ongoing outbreak in the civilian population that mirrored that found in the Peruvian navy.

Timely detection of outbreaks of disease allow accurate laboratory diagnoses to be made, and with a firm diagnosis, a viable response can be fashioned

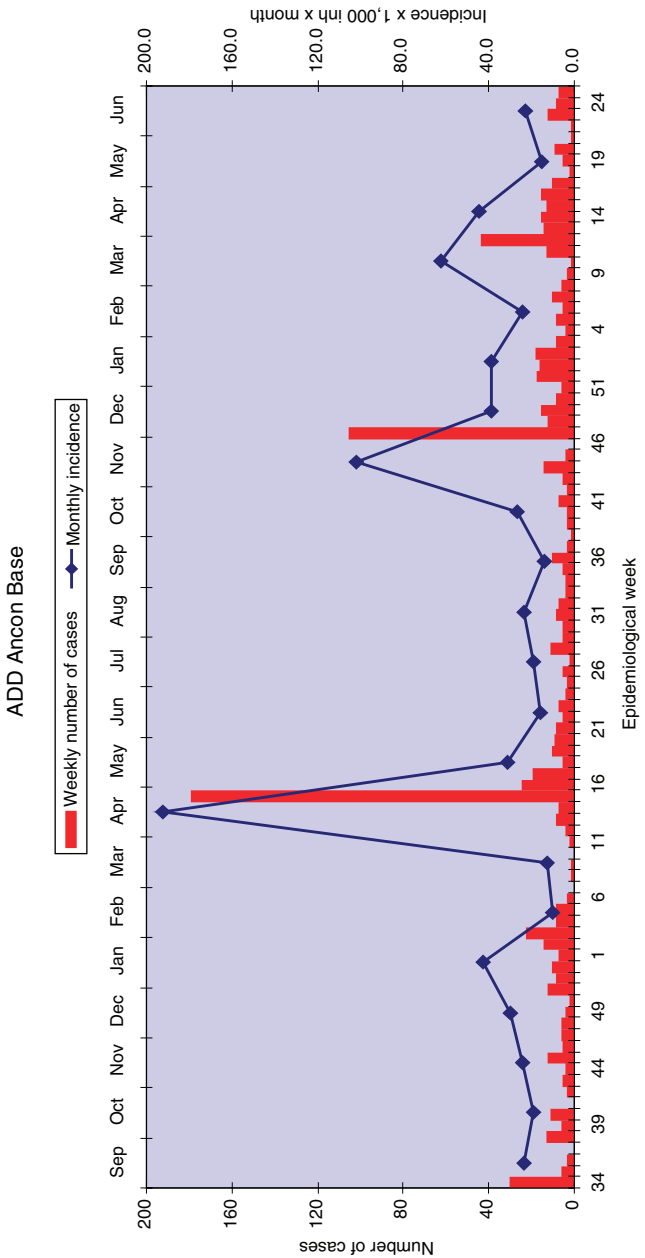

FIGURE 2-11 Outbreak of diarrhea as reported by the system.
SOURCE: Dr. Roger Araujo, NMRCD. Reprinted with permission from NMRCD.

that hopefully will attenuate the outbreak. The Naval Medical Research Center Detachment (NMRCD) has been able to marry Alerta to molecular and microbiologic diagnostics in a number of these outbreaks, including the use of rapid antigen detection testing for influenza.

In addition to outbreak response, we have also provided training in basic epidemiology and more advanced field epidemiology. We have trained more than 600 public health personnel in the Peruvian navy in basic epidemiology and the use of this electronic disease surveillance system. Throughout South America, we have also trained more than 1,300 epidemiologists in the basics of outbreak detection and management. The objectives for these courses and the entire curriculae in Spanish and English are available at no cost on the Web (Lescano et al., 2007).

The following attributes of the Alerta system were included in the evaluation process:

- **Simplicity:** Description of the data flow; estimated time for the reporter to collect information and analyze the data; staff training requirements; and time spent on the maintenance of the electronic platform.
- **Flexibility:** Number of reporting sites added per year; cost and time required to add new sites; ability to add new diseases to the reporting template.
- **Data quality:** Reporting rate (percentage of sites that report per total number of sites); percentage of complete reports; error rate (number of errors/number of reports); error rate per site (number of errors/total number of sites per week).
- **Acceptability:** Personnel surveys after training courses; number of personnel who report per site; mean time after training to achieve a timely report.
- **Representativeness:** Coverage (percentage of Naval population covered by the system); characteristics of the population.
- **Timeliness:** Percentage of sites that report on time and percentage of outbreaks detected on time; average of days to report.
- **Stability:** Number of system failures; percentage of time that the system is fully operational; actions involved with repairs in the system.
- **Sustainability:** Joint responsibilities; relationship with the Peruvian navy; incentives; costs assumed by each part; problems and requirements to sustain the system.

Overall, the Alerta electronic disease surveillance system has been embraced by the Peruvian navy and has transformed public health preparation and response in this population. Both the Peruvian navy and the NMRCD laboratory have contributed personnel, resources, and significant time to ensure optimal performance. The implementation of this system has not been without pitfalls, and many challenges persist. However, the significant progress illustrates how horizontal partnerships and small projects can generate measurable improvements in epidemiologic capability.

This quote from a U.S. navy physician sums up the experience in Peru:

> The introduction of Alerta has led to early outbreak identification/response, timely case management, and increased review of clinical procedures within reporting units. . . [It is a] working model for similar larger scale international programs Alerta is a simple, near real-time disease surveillance model for countries in all stages of communications technology development (Lescano et al., 2003).

Clearly, to respond to and control a potential pandemic, all regions of the world need fully functional public health systems. These systems require careful networking of many components, including reliable disease surveillance, accurate local diagnostics, rapid medical response capability, and fluid cooperation and communication among local and international partners.

Some components of successful public health strategies are present in the U.S. Department of Defense Global Emerging Infections Surveillance and Response System (DoD-GEIS). This system is a decade-old DoD program initiated in response to President Clinton's directive in 1996 that mandated the development of a global system to track, control, and respond to potential pandemic infections. It generated, among other things, the electronic disease surveillance system described above (White House, 1996). GEIS serves as just one component of a growing network of public health assets that are increasingly being used to control infectious diseases with pandemic potential, complementing many global public health community efforts (Chrétien et al., 2006).

The Alerta model implemented in Peru has a number of dimensions that have contributed to its success:

- Committed leadership in all parties;
- A regulatory regime that specified reporting requirements;
- A practical use of information technology that maximized the use of available telecommunications and computing infrastructure;
- Real-time data collection from points of service and automated reports and notification;
- Live database for continuous analysis and investigation;
- Links to laboratory and investigation capacity;
- Training and support of a distributed network of clinicians and other health workers; and
- Mobile technology accessible to virtually everybody in Peru—if not individually then through a Navy command with cell phones and Internet access.

The approach that was developed and tested in Peru is now being expanded with support from the U.S. DoD Southern Command to five neighboring countries: Bolivia, Colombia, Ecuador, Paraguay, and Uruguay. In addition, Voxiva is part of a public–private partnership with the GSM Association, the largest asso-

ciation of mobile phone operators (more than 650 mobile phone operators and 2 billion subscribers worldwide) to extend the benefits of this network in service to public health. Hopefully this can provide not only a model of working in the field, but also a model of cooperation between public and private entities.

Acknowledgments

The results reported derive from the common vision and hard work of a number of individuals in the Peruvian and U.S. navies and Voxiva as well as the support of the DoD-GEIS program. Key individuals include Drs. Carmen Mundaca, Roger Araujo, Tanis Batsel, Rafael Elgegren, Ernesto Gozzer, Patrick Kelley, Andres Lescano, Monica Negrete, and Mario Ortiz.

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3

Detection and Diagnostics

OVERVIEW

Workshop presentations on infectious disease detection and diagnostics surveyed current capacity, needs, and challenges; anticipated forthcoming developments; and imagined a future in which diseases can be diagnosed prior to the appearance of symptoms (see Summary and Assessment).

Diagnostics for Developing Countries

The session began with a reminder from Mark Perkins of the Foundation for Innovative New Diagnostics (FIND) that while emerging diseases and bioterrorism threaten public health, infectious diseases such as tuberculosis and malaria have long imposed a severe burden on the developing world. In their contribution to this chapter, Perkins and Peter Small of the Gates Foundation discuss the need for rapid, accurate, inexpensive, robust diagnostics in developing countries—a need that could be met by recent advances in genomics, proteomics, and materials science if there was a profitable market. To fill this gap, FIND guides the development and adoption of novel diagnostic products for diseases of the developing world in much the same way as public–private partnerships have been established to produce drugs and vaccines for low-resource settings. With FIND's support, companies that produce low-cost diagnostics for use in developing countries realize sufficient cost savings (in manufacturing, approval procedures, and marketing) to sustain profits.

Rapid Diagnostics

Soldiers at risk of contracting infectious disease—either from the natural environment or from bioweapons—need diagnostics that are rugged, rapid, and easy to use, according to speaker Mark Wolcott of the Diagnostic Systems Division at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). In their contribution to this chapter, Wolcott and co-authors discuss the rationale, design, and development of rapid diagnostic assays for infectious diseases. They offer brief, comparative descriptions of a variety of platform technologies that in the future may be combined to produce comprehensive, integrated diagnostic systems—perhaps in the guise of miniaturized "labs on chips" that process samples, perform assays, and automatically report their results. "As technologies mature and new technologies are developed, rapid infectious disease diagnostics will become available and practical," the authors predict.

Rapid diagnostic tools are also improving infectious disease surveillance in animals. Workshop presenter Alex Ardans, who directs the California Animal Health and Food Safety Laboratory System, described the development of polymerase chain reaction-based (PCR-based) assays to screen for diseases that have caused devastating outbreaks in livestock, such as exotic Newcastle disease (END) in poultry and foot-and-mouth disease (FMD) in cattle. California also developed a highly efficient tuberculosis testing program after the disease was detected in several of the state's large dairies.

Based on such experiences, Ardans argued that the state's laboratory system plays its most crucial role when recognizing and responding to unusual disease events. For example, following a recent END outbreak among fighting cocks, whose handlers worked in and spread the disease to commercial poultry operations, the laboratory optimized an existing real-time PCR assay for END that was used to perform more than 85,000 tests (Crossley, 2005). Such emergencies present unique opportunities to improve disease diagnosis, Ardans said, although not necessarily with the latest technology. He noted that laboratory researchers, in pursuit of the source of *E. coli* O157:H7 following a recent outbreak in spinach, discovered that a gauze swab used to sample irrigation waters for contaminants performed better than newer concentration devices.

Emerging Diagnostics

Although Koch's postulates remain diagnostic standards, adapting them to a vastly expanded understanding of disease states has become increasingly problematic, observed presenter Ian Lipkin and co-author Thomas Briese of Columbia University's Jerome L. and Dawn Greene Infectious Disease Laboratory. Their paper discusses contemporary problems in proving causality, and illustrative case studies that reveal how these challenges are shaping pathogen surveillance and discovery. The authors also provide a taxonomy and comparative guide to proven

and proposed methods for characterizing infectious agents without recourse to cultivation, including two platforms of their own creation: MassTag PCR and the GreeneChip. In the future, Lipkin and Briese predict, substantial advances against chronic disease will occur "not from technical improvements but from investments in prospective serial sample collections and an appreciation that many diseases reflect intersections of genes and environment in a temporal context."

Pre-Symptomatic Diagnosis

Imagining a future in which bioterrorism agents are continually reengineered to elude standard detection and diagnostic methods as well as therapeutics, speaker and Forum member Stephen Johnston offers a model of diagnosis for exposure to a pathogen before symptoms appear: a host-based detection system, capable of analyzing hundreds to thousands of components in samples of blood, sputum, or urine, and thereby capable of detecting any type of engineered or natural threat agent. In the final paper of this chapter, Johnston discusses the feasibility of developing such a system and its potential not merely to detect biothreats, but to "convert standard health practice from one that treats symptoms to one that detects disease very early—even presymptomatically."

PARTNERING FOR BETTER MICROBIAL DIAGNOSTICS[1]

Mark D. Perkins, M.D.[2]
Foundation for Innovative New Diagnostics

Peter M. Small, M.D.[3]
Bill and Melinda Gates Foundation

Timely and accurate diagnosis is critical to the global efforts to prevent and treat infectious diseases. And yet, those on the front lines of this battle struggle to make do with inadequate and antiquated testing technology. For example, a 100-year old test is used to diagnose tuberculosis, a disease that kills someone every 16 seconds, and precious new antimalarial drugs are being rolled out with the same diagnostic imprecision that currently mistreats several hundred million cases every year. The tragic reality is that diagnostic uncertainty exacts a huge toll in morbidity and mortality. Reliance on underperforming diagnostic technologies limits the control of the world's greatest killers, especially in settings with high

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[2]Chief Scientific Officer.

[3]Global Health Program.

human immunodeficiency virus (HIV) prevalence. We contend that innovative mechanisms are needed to produce, develop and deploy new and better diagnostic tools for infectious diseases in developing countries.

Global Public Health Goals at Risk

Acknowledging the impact of the global tuberculosis epidemic in the early 1990s, the World Health Assembly of the World Health Organization (WHO; Geneva) declared tuberculosis a global emergency and ratified goals for case detection and cure under the DOTS (directly observed therapy shortcourse) strategy by the year 2005. Although important successes in fighting tuberculosis have been achieved in recent years, reliance on weak diagnostic tools has slowed progress. Case detection targets for smear-positive tuberculosis have not been met, and fewer than 25 percent of all cases are now detected and reported as smear positive (WHO, 2004). The data available suggest that the Millennium Development Goal of halving tuberculosis prevalence by 2015 also cannot be achieved universally without improved methods for diagnosing tuberculosis (Dye et al., 2005).

The weaknesses of standard diagnostic tests for tuberculosis are well documented. Even in controlled research settings, the average sensitivity of sputum microscopy for pulmonary tuberculosis is only 60 percent in immunocompetent populations, and it is substantially lower among people infected with HIV. Conventional culture methods are so slow that testing often loses clinical relevance, and the poor predictive value of the tuberculin skin test renders it essentially worthless in disease-endemic areas. The weaknesses of the available diagnostic technologies are only amplified in high-burden countries, which typically have insufficient infrastructure and inadequate staffing.

Reliance on inadequate diagnostic tools cripple TB control efforts. Because of limited access to diagnostic services and the low sensitivity of conventional testing, patients in many high-burden countries remain undiagnosed for three to six months (Madebo and Lindtjørn, 1999; Liam and Tang, 1997). These delays result in increased morbidity and mortality, mounting costs combined with loss of work, and continuing tuberculosis transmission to families and communities.

Unlike tuberculosis, which requires months of treatment to cure, malaria can be treated with a few doses of unsupervised treatment. This dramatically reduces the motivation to confirm the diagnosis. Microscopy for malaria is notoriously difficult, and experienced microscopists give substantially different results on up to a third of all slides. In most settings where malaria is endemic, quality microscopy is poorly available and malaria treatment is given by default to almost all patients with fever. Fever is an exceedingly common symptom in the tropics, and an estimated 800 million malaria treatments are given each year for fevers, the great majority of which are not caused by malaria (Amexo et al., 2004). This massive mistreatment of hundreds of millions of people results in

the fatal under-treatment of other diseases, such as pneumonia and sepsis, which present with similar symptoms.

Having watched at least two generations of malaria medicines fall to mounting drug resistance, the international malaria community has called for greater diagnostic accuracy before treatment, especially as expensive artemisinin-based therapies are introduced. In 2004, the WHO recommended that malaria should be confirmed by parasitologic examination before treatment in all patients older than five years of age. In this setting, the development of simple and rapid diagnostic tests (RDTs) that can detect circulating *Plasmodium* antigens in a drop of finger-prick blood is a key recent development.

The success of RDTs in improving the targeting of drug therapy, and their acceptance in malaria management by remote health workers and patients, will depend on the reliability and accuracy of the tests. There are now more than three dozen manufacturers of such tests, many of which show inadequate sensitivity, thermostability and geographic applicability. Though RDTs are now in wide use in some areas, the lack of true performance data on most of these tests, the variability in published performance of others and the lack of a global quality assurance mechanism has generated chaos and confusion with regard to test selection and has resulted in many end-users rejecting test results in favor of presumptive treatment.

The lethal convergence of these diseases and HIV exacerbates the negative impact of weak diagnostic tools. The rise of HIV in tuberculosis-endemic settings dramatically increases tuberculosis incidence, the number of symptomatic individuals and the pressures on already overburdened health systems. HIV coinfection decreases the sensitivity of microscopy for TB at the same time that it increases the urgency for rapid diagnosis and treatment. From South Africa to Brazil (Pronyk et al., 2004; Gutierrez et al., 2002), 30 to 50 percent of HIV-infected people die with undiagnosed tuberculosis, and *Mycobacterium tuberculosis* is now a leading cause of bacteremia in febrile patients visiting emergency rooms in sub-Saharan Africa (Archibald et al., 1998). Fever in HIV endemic areas cannot be assumed to be benign if nonmalarial. Thus, for many countries burdened by HIV, the need for improved diagnostic tests is increasingly urgent.

New Opportunities

Recent trends in science and technology, and in the diagnostics industry, indicate that there may be important new opportunities to improve diagnostic tests suitable for developing countries. Availability of the complete genomic sequence of *M. tuberculosis* allows a comprehensive assessment of potential diagnostic targets. Massive investment in biodefense has generated a range of diagnostic technologies intended for front-line use. The growing diagnostics industry can develop new diagnostic tests at a fraction of the cost and time needed to bring drugs and vaccines to licensure.

Motivated primarily by the small but significant market in industrialized countries, the tuberculosis diagnostics industry has produced several new tests in recent years. For example, shortcuts around the slow growth of *M. tuberculosis* using phage-based or molecular methods allow tuberculosis detection and screening for rifampin resistance within 48 hours (Albert et al., 2002; Johansen et al., 2003). Other new tests exploit tuberculosis-specific proteins to detect latent infection with much improved specificity, especially in BCG (BacilleCalmette Guérin)-vaccinated populations (Lalvani et al., 2001; Mori et al., 2004). Likewise, for malaria diagnosis, several rapid immunochromatographic tests detecting *Plasmodium* antigens in blood have been developed over the past 15 years, and they now reach a market of some 25 million people.

Forging a Public–Private Initiative

Market forces alone, however, will not yield the diagnostic tools needed to improve global health. Private companies often avoid developing products that will primarily be used in developing countries out of skepticism about the return on their investment. Developing countries have little capacity to pay the higher prices typically attached to new products, even when these costs result in overall savings to health care systems. The processes by which these countries license, purchase, and distribute products are often inadequately developed and poorly understood by industry.

The drive to develop new diagnostics for the developing world is unlikely to succeed without the private sector, with its expertise in product development, manufacturing capacity, product distribution and quality control. Unless measures are put in place to address current market dynamics, the number of companies engaged in diagnostics development will likely remain limited, and most will continue to tailor their products to markets in industrialized countries. The resulting products, such as the molecular amplification systems and automated systems for early detection of mycobacterial growth—which have markedly improved the diagnosis of tuberculosis in industrialized countries—may be little used in developing countries and thus have no impact on the global tuberculosis problem. Most of the companies manufacturing rapid malaria tests are small and do not have the resources to redevelop their assays to address important deficiencies in sensitivity and shelf life, especially at tropical temperatures.

Goal-driven public sector action is needed across the development pathway to forge a strong and sustainable partnership with industry to generate new diagnostics (Figure 3-1). Public sector actors must be prepared to sponsor basic research, partner equitably with industry on product development, evaluate products in a regulatory-quality fashion (Small and Perkins, 2000), demonstrate the efficacy of implementation, change technical and financial policies to foster new diagnostics, and actively facilitate the latter's distribution and use. In pursuit of these goals, the public sector should explore such innovative approaches as the

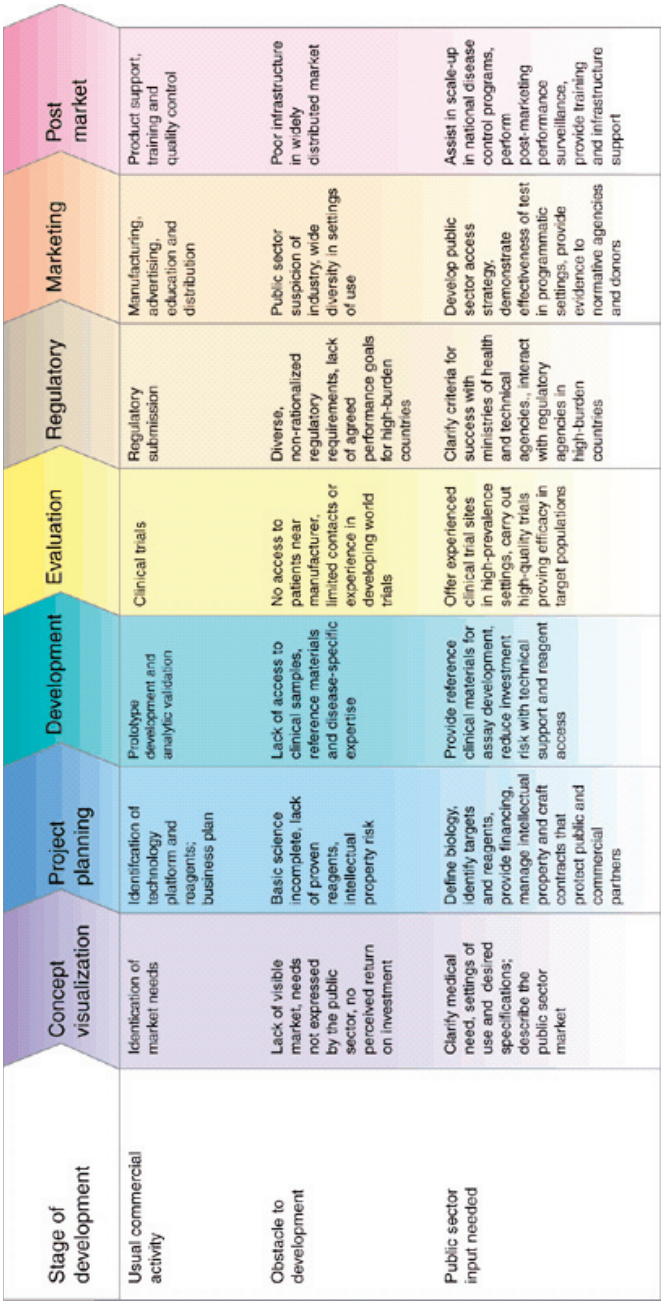

FIGURE 3-1 Product development path for microbial diagnostics.

creation of novel financing mechanisms and distribution strategies to increase industry confidence that a viable market will exist in resource-limited settings.

There are many examples of innovative public–private partnership for the development of drugs and vaccines. Few are, however, focused on diagnostics. The Foundation for Innovative New Diagnostics (FIND; Geneva, Switzerland; of which Mark D. Perkins is Chief Scientific Officer), is one such entity. Launched in 2003, FIND aims to develop a model for public sector action to drive the development of diagnostic products for diseases of the developing world, using the search for new diagnostics as the test case for the model's development. FIND seeks to identify the most promising product candidates and accelerate the process of development, testing, approval, distribution and incorporation into routine public health policy. Although motivated by the desire to create new public goods, FIND has many of the attributes of a private company, pursuing a clear business plan and using rigorous scientific criteria to identify priority product candidates.

RAPID INFECTIOUS DISEASE DIAGNOSTIC ASSAYS[4]

Mark J. Wolcott, Ph.D.[5]
U.S. Army Medical Research Institute of Infectious Diseases

Randal J. Schoepp, Ph.D.[5]
U.S. Army Medical Research Institute of Infectious Diseases

David A. Norwood, Ph.D.[5]
U.S. Army Medical Research Institute of Infectious Diseases

David R. Shoemaker, Ph.D.[5]
U.S. Army Medical Research Institute of Infectious Diseases

Rapid disease diagnostics ("serving to identify a particular disease or pathogen") for many infectious agents are not as well developed as other laboratory technologies. Laboratory tests for many infectious agents still rely on decades-old technologies and techniques. Culture remains the gold standard for identifying organisms, but not all pathogens can be cultured, making alternative tests necessary.

When culture is difficult or not available (virus cultures in field laboratories), serological diagnosis of the antibody response to the organism is typically used.

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[5]Diagnostic Systems Division.

However, a problem with both traditional culture and immunodiagnostics is the time required to obtain results. Culture may take several days and immunodiagnosis is limited by the time required to mount an antibody response, often a week or more (Figure 3-2). Current efforts in rapid diagnostics are shifting the window of detection closer to the point at which clinical disease symptoms become evident. Ultimately, future rapid diagnostics will shift the window to a point soon after exposure, giving the clinician the greatest opportunity to intervene in the disease process.

Orthogonal diagnostic testing is the key to improving the reliability of rapid diagnostic technologies. Orthogonal testing refers to tests that are statistically independent or non-overlapping but, in combination, provide a higher degree of certainty of the final result. Although orthogonal testing is not a standard perspective in the clinical diagnostic industry, the concept and its application are paramount when investigating some infectious agents. Any single detection technology has a set of limits with regard to sensitivity and, most importantly, specificity. Orthogonal testing seeks to overcome the inherent limitations of individual test results with the strength of data combinations (Henchal et al., 2001). The application of orthogonal diagnostic testing uses an integrated testing strat-

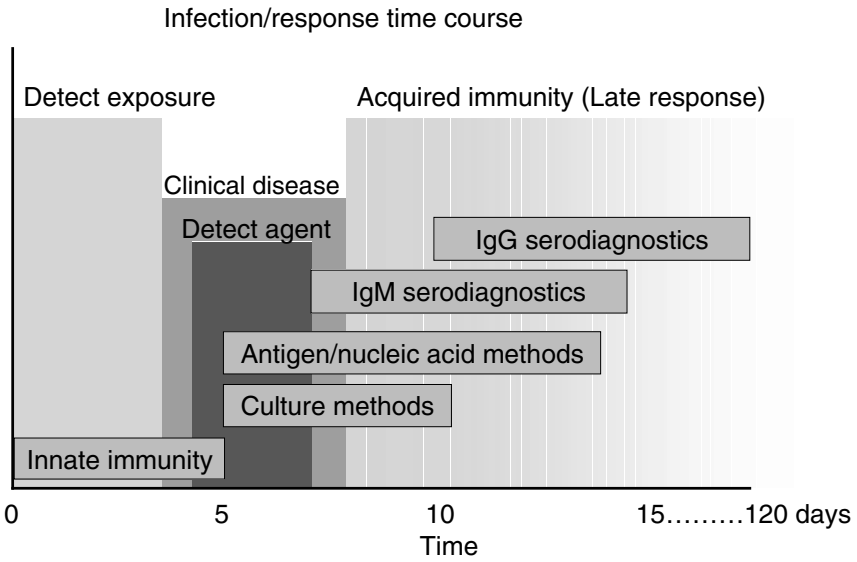

FIGURE 3-2 Infection and response time course. Various detection methodologies have highly different entry points in their use on human disease. As the time points extend out, the ability of medical interventions have less success. The earlier the time of medical intervention, the more successful the prognosis is for most diseases.
SOURCE: Wolcott (2006).

egy where more than one technology, technique, or biomarker is used to produce diagnostic results, which are then interpreted collectively (Figure 3-3).

The Department of Defense has an acquisition program to acquire quality diagnostic products that satisfy the needs of commanders with missions to support the warfighter. This acquisition program is designed to be timely with fair and reasonable associated costs. The acquisition program includes design, engineering, test and evaluation, production, and operations and support of defense systems (Table 3-1). To simplify and expedite the acquisition timeline for the fielding of a rapid diagnostic system, commercial off-the-shelf technology is evaluated and a formal selection process is used to select a system for further development and fielding. The Joint Biological Agent Identification and Diagnostic System (JBAIDS) acquisition program was formally launched in September 2003 with the award of the first phase, a molecular diagnostic system, in fall 2005 (Figure 3-4).

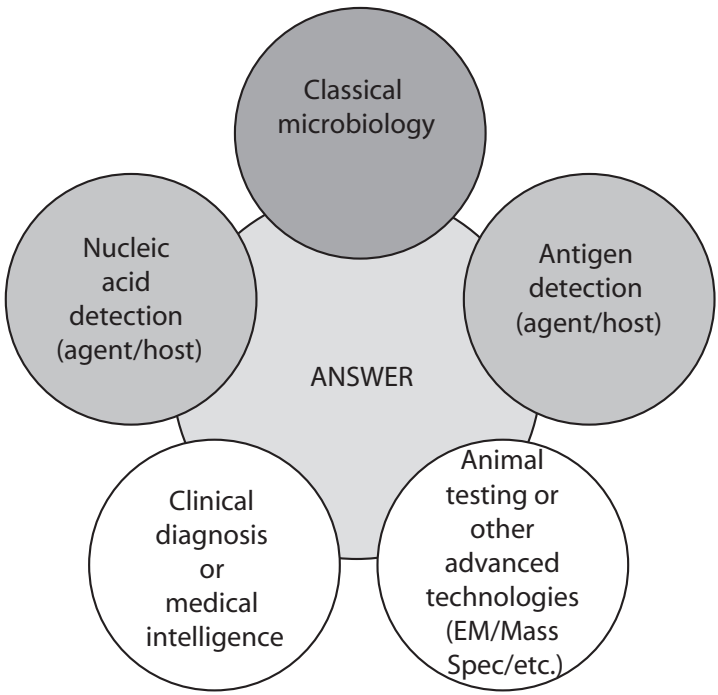

FIGURE 3-3 Orthogonal diagnostic testing. Although each method provides an independent assessment, together the power of the diagnostic becomes large. The failure of any one independent assessment does not fail the system.
SOURCE: Wolcott (2006).

TABLE 3-1 Department of Defense (DoD) Acquisition Program for Diagnostic Devices

Predevelopment		Advanced Development		Procurement Operations and Support	
Basic research	Technology evaluation	Demonstration and validation	Engineering and manufacturing development	Procurement and deployment	Operations and support
New technologies	Technology demonstrations	Prototypes	PMA/510K approval Initial operational testing	Final production	Follow-up evaluation

NOTE: The acquisition process moves from left to right through defined operational activities. Each activity is designed to provide a value-added service and ensure that DoD obtains the product needed at a reasonable cost investment for the country.
SOURCE: Wolcott (2006).

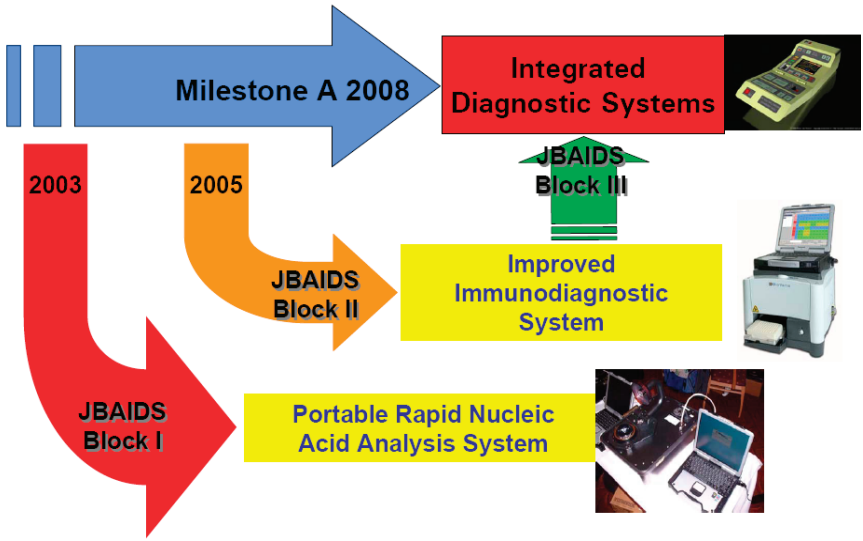

FIGURE 3-4 Acquisition program—evolutionary strategy. The acquisition process for developing and fielding a rapid infectious disease diagnostic assays system is designed around an evolutionary strategy. By leveraging commercial technologies that currently exist in the commercial market, and furthering development on those platforms, the final field-deployable system will be quicker and cheaper than trying to obtain the final product up front.
SOURCE: Wolcott (2006).

Current molecular diagnostic technologies are based on the amplification of specific DNA sequences from extracted nucleic acids, DNA or RNA. Amplification techniques take tiny amounts of nucleic acid material and replicate them many times through enzymatic reactions, some that occur through cycles of heating and cooling. These include methods that involve target amplification (e.g., polymerase chain reaction [PCR], reverse transcriptase–PCR [RT-PCR], strand displacement amplification, transcription amplification), signal amplification (e.g., branched DNA assays, hybrid capture), probe amplification (e.g., ligase chain reaction, cleavase-invader, cycling probes), or postamplification analysis (e.g., sequencing the amplified product or melting curve analysis as is done in real-time PCR).

Nucleic acid-based methods are generally specific and highly sensitive and can be used for all categories of microbes (Christensen et al., 2006; Emanuel et al., 2003a). Amplification methods can identify minute traces of the genetic material of an organism in a specimen, avoiding the need for culture. These techniques are particularly useful for organisms that are difficult to culture or identify using other methods (e.g., viruses, obligate intracellular pathogens), or are present in very low numbers. Results can be provided more rapidly than through most conventional methods, especially culture. However, because amplification methods are so sensitive, false positives from trace contamination of the specimen or equipment can easily occur. In addition, because these techniques depend on enzymatic activity, false-negatives also occur when a sample contains contaminants that inhibit enzyme activity (Hartman et al., 2005). Nucleic acid-based tests are also limited in that they do not provide information on the viability of the detected organism.

Immunodiagnostics is the standard against which many agent detection, identification, and diagnostic technologies are compared. Antibody-based assays continue to serve as preliminary and confirmatory diagnostic formats for many infectious and noninfectious diseases. These assays are typically rapid, sensitive, specific, reliable, and robust. Immunodiagnostic technologies are relatively unsophisticated, making them available to nearly any laboratory.

Hand-held assays (HHAs) are immunoassays that are based on immunochromatography or lateral flow assay format. Generally, a sample is applied to the testing unit and by flowing along a membrane, an indicator line forms where antibodies to the analyte of interest are bound. The presence of a line indicates the presence of the analyte, while the absence of a line denotes a negative result. Applying a sample solubilizes the tagged antibodies and initiates the first binding of the target by the tagged antibodies. As the sample continues migrating down the filter paper, the analyte of interest encounters a set of antibodies bound to the membrane and an antibody-analyte-antibody sandwich is formed. While early HHAs incorporated enzymes as labels to yield a visible signal, advances have done away with the multistep enzyme immunoassay format and have incorporated reporter molecules such as colloidal gold or colored latex spheres that yield

a direct signal. These physical signal generators rely on the aggregation of a large number of tags to enhance signal visualization by the naked eye. HHAs, like all analytic systems, have inherent limitations in their use and interpretation; they require a relatively large amount of sample, their sensitivity is limited, and they have a potential for false positives as a result of "dirty" environmental samples that form a confounding "dirt" line in the antibody capture zone. Although HHAs have limitations, their overall ease of use and quickness make them useful in certain situations.

Time-resolved fluorescence (TRF) is an immunoassay application that employs the basic immunoassay analyte sandwich capture format, but with detector antibodies that are directly labeled with a lanthanide chelate, such as europium, samarium, terbium, and dysprosium. The strengths of TRF are its increased sensitivity and the potential for multiplexing. TRF uses the differential fluorescence life span of lanthanide chelate labels compared to background fluorescence. The long-lived fluorescence signal and the difference in wavelength between absorbed and emitted light results in a very high signal-to-noise ratio and excellent sensitivity (Hemmila et al., 1984; Soini and Kojola, 1983). The long fluorescence decay time allows the measurement of immunoassay fluorescence after any background fluorescence has decayed. By pulsing the excitation light repeatedly, in 1 second the fluorescent material can be excited more than 100 times with an accumulation of the generated signal that improves both the overall signal and the reduction of background signals. TRF assays are particularly useful in clinical immunoassays, but have limitations with environmental samples where europium or other lanthanides naturally occur. The contaminating compounds behave much like labeled lanthanides, prolonging the background fluorescence and lowering TRF sensitivity.

Electrochemiluminescence (ECL) is immunoassay technology in which a detector antibody is tagged with a chemical that emits light (luminescence) when it is excited by an electrical stimulus. There are several electrochemiluminescent chemical moieties, but ruthenium is the most common. Ruthenium, in the form tris (2,2' - bipyridine) ruthenium (Ru), is relatively small, allowing easy conjugation to antibodies. The technology relies on two components: the ECL-label (Ru) coupled to an antibody and tripropylamine (TPA) present in the reaction buffer. When an electrical current is applied to an electrode, both components are activated by oxidation. The oxidized TPA is transferred into a highly reducing agent, which reacts with activated Ru to create an excited-state form of Ru. This form returns to its ground state with emission of a photon at 620 nm wavelength. An advantage of the Ru-TPA methodology is that the measurement of a single sample can be repeated multiple times because the electron-transfer photon-release reaction regenerates the Ru resulting in signal amplification. Although ECL assays are simple, rapid, and sensitive (Kijek et al., 2000; Smith et al., 2001), the sample matrix can affect the assay sensitivity. The sample matrix will influence the sensitivity by varying positive cut-off values; therefore, matrix-

specific positive and negative control samples are used to establish standard curves and cutoff values.

Several diagnostic systems are using a technology to analyze microsphere-based multiplex protein assays. The advantage of multiplex assays is that multiple results are available from one sample without individual testing. Up to 100 different biomolecules (proteins, peptides, or nucleic acids) can be analyzed in a single test. A microplate platform allows the automated analysis of a 96-well plate in 30 minutes yielding a throughput of 1,920 assays in a 20-plex system. Currently kits for simultaneous quantitative measurement of up to 25 to 30 proteins are available, including cytokines, phosphoproteins, growth factors, kinases, and transcription factors. Several investigators are using these systems to develop multiplexed assays for biological warfare agents. One system was evaluated by the U.S. Army with extremely good results, but the equipment is currently not rugged enough for use by the warfighters.

The key to future rapid diagnostic systems is the development of a completely and fully integrated system. Previous diagnostic research efforts were only concerned with the development of an assay technique and failed to address the full spectrum of an integrated system. To fully address an integrated system, protocols, sample processing, reagents, assays, platforms, and evaluations need to be completely explored. Protocols are equivalent to an intended-use statement. Without addressing how and why the assay or system is to be used, misapplication will result in incorrect and potentially serious testing reliability issues.

The single most important aspect of rapid testing is sample processing. The sample is the most important component in a system, and an inappropriate or improperly handled sample will jeopardize an otherwise robust assay. For example, detection of *Bacillus anthracis* is highly problematic. The spores of *Bacillus anthracis* are very refractile to easy and rapid sample preparation. Alternate methods are required to produce the highest quality sample, which include concentrating the sample (if possible) and methods to release either the nucleic acids or specific proteins from the spore. These include techniques such as germination, sonication, or mechanical disruption ("bead-beating"). Another consideration of sample preparation, especially for many molecular methods, is the removal or neutralization of inhibitors of amplification.

Systems consist of more than just assays (Figure 3-5). Developers need to be cognizant of all the details. While most commercial manufacturers have appropriate production systems and quality manufacturing practices in place for producing consistent, reliable, and appropriate reagents that are compliant with Food and Drug Administration (FDA) requirements, research-derived systems often fall short. In addition, integration of assays with various platforms is often overlooked in initial system development. While some assays perform well on multiple platforms, many assays suffer optimization issues when moved from one platform to another. Unless provisions are made for multi-platform development, and shown to be equally effective through validation, platform equivalency

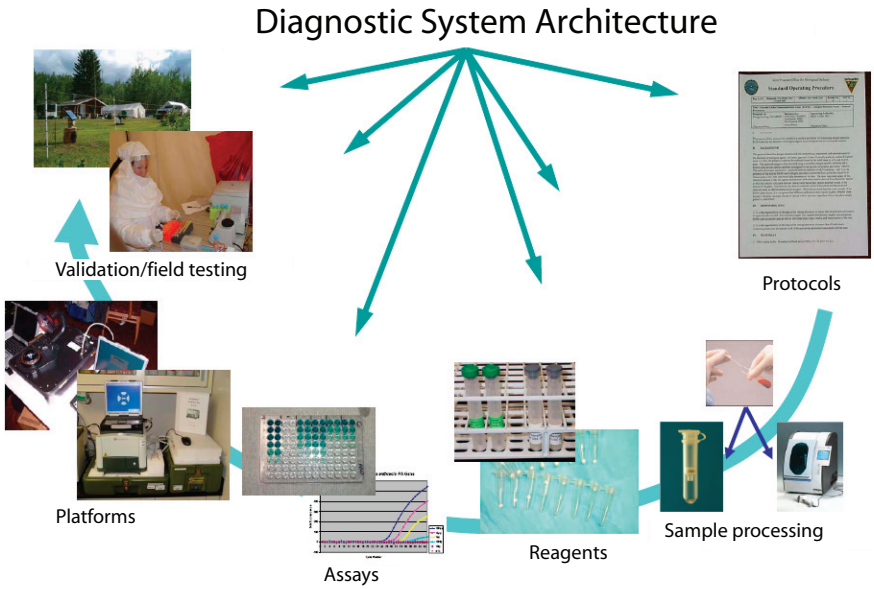

FIGURE 3-5 Diagnostic system architecture. Systems-based architecture needs to include the full gamut of functions from protocols through validation.
SOURCE: Wolcott (2006).

should not be assumed. Another consideration in system development for systems developed by professional scientists working in modern laboratory facilities is the inherent expectation that assays and systems will work in the hands of less trained personnel outside of the pristine laboratory facilities. Often, this is not the case. Field evaluation, under conditions of actual employment, is critical before assays and systems can be confidently deployed and used.

Validation of the appropriateness and effectiveness of assays and systems is paramount in the development process (Emanuel et al., 2003b). Development of assays and systems needs to include assay validation parameters such as linearity, limits of detection, inclusivity and exclusivity testing, ruggedness, robustness, and repeatability. Validation parameters are detailed in Box 3-1.

A critical and often overlooked issue is that diagnostic systems and tests intended to be used to test clinical samples must be approved by the U.S. Food and Drug Administration in order to legally be distributed and used in the United States. Many of the technologies discussed in this article are mature enough to produce clinically useful diagnostic products. However, companies that may have the capability to manufacture these diagnostic tests, and to gain FDA approval for them, typically are not interested in doing so for tests to diagnose tropical

BOX 3-1 Example of Diagnostic Systems Validation Parameters

1. Linearity (establish standard curve with single "type" strain). The concentrations will range from 100 pg to 1 fg of the target nucleic acid. When cloned material is required (i.e., Variola), the concentrations will range from 1 pg to 10 ag.
   a. There will be two replicates for each 10-fold dilution.
   b. Data will be used to estimate limit of detection (LOD).
   c. Slopes will be used to calculate amplification efficacy and efficiency using the formulas.
   d. All supporting data will be submitted in the data package.
   e. Real-time polymerase chain reaction (PCR) curves.
   f. Standard curve indicating slope and R2 values.
   g. PCR efficacy and efficiency calculations.
2. Limit of detection.
   a. LOD testing will be performed with the type strain.
   b. A minimum of 58 positive results is required to establish the LOD.
   c. 60 total replicates will be performed at the LOD of the assay consisting of:
      i. Three separate runs—two instruments—two operators—2 days.
      ii. A minimum of two positive and two negative controls.
   d. All supporting data will be submitted in the data package.
   e. Operators, instruments, and dates of performance should be documented.
3. Inclusivity/exclusivity.
   a. Inclusivity (testing the ability of the assay to pick up multiple strains of the same agent).
      i. Multiple strains of the target organism.
      ii. Duplicate samples.
   b. Exclusivity (test of whether assay cross-reacts with nucleic acids from other organisms).
      i. Panel will include near neighbor testing (genetic neighbors).
      ii. Panel will include broad cross-reactivity panel.
      iii. Duplicate on purified nucleic acids at a concentration at least 1,000x the established LOD of the assay.
   c. Environmental/matrix panel to include human DNA and cell culture extracts used to produce viral agents.

SOURCE: Wolcott (2006).

diseases or biological threat agents because the commercial demand is low. This is a chronic problem with no easy solution.

To help support the deployment of rapid agent identification systems, especially those that do not have enough commercial value to be fully supported by commercial manufacturers, the Department of Defense relies on the Joint Program Executive Office–Critical Reagents Program (CRP). The CRP is a national resource for the biological defense community, whose mission is production of

detection reagents, standardization of procedures and training, and optimization and transition of detection technologies. Their commodity areas include the production of antigenic and genomic materials for test and evaluation purposes, antibodies, to include the manufacturing of hand-held devices, molecular detection reagents, and sampling kits. Because of the confined nature of these materials and the lack of commercialization due to the limited customer base, CRP provides a vital link to the defense community to ensure harmonization of tests and evaluations and as an avenue for advanced development.

In the course of development of newer, faster, better, and cheaper rapid diagnostic devices, the Department of Defense program is looking at potential future platforms. Many characteristics of those future systems are discussed above, but one that is showing some promise is DNA microarrays. Microarrays or DNA chips are one of the latest methods for rapid infectious disease diagnostics. Microarrays are a recent adaptation of Northern blot technology (Grunstein and Hogness, 1975; Schena et al., 1995). The ability to label nucleotide sequences with fluorescent tags, much like fluorescent antibody technology, has increased their use in diagnostics. Microarrays are small, solid supports (typically glass slides) on which DNA sequences are attached, or spotted, at fixed, orderly, addressable locations. The DNA is composed of short, single-stranded fragments, typically 5 to 50 nucleotides long. Microarrays can have up to tens of thousands of spots, allowing for a large amount of data collected for each sample tested. Microarrays depend on the annealing of two nucleic acid strands to function. When sample DNA is prepared, usually through polymerase-based amplification, fluorescent dyes are incorporated into the amplicon so that hybridization can be detected. The kind of information required from microarrays drive how the arrays are developed and used. Microarrays can be spotted with known sequences of a variety of oligonucleotides for basic genomic investigation. Gaining wider acceptance is the use of microarrays to "resequence" organisms. Utilizing known sequences from already sequenced organisms and hybridizing genomic material from organisms not previously sequenced, sequence differences can be determined. With more than 10,000 sequences (and growing as automated systems improve) to interrogate on a single chip, variation in genomic sequences can provide accurate species and subspecies determination. Finally, one of the earliest applications of microarrays is their use in "transcriptomics" or gene expression studies. Gene expression-based measurements of mRNA levels, and the differences between these levels in various states of organism growth (i.e., aerobic versus anaerobic growth), has provided significant insights in gene regulation of various organism functions.

Although microarrays have the demonstrated potential for diagnostics, routine use is hampered by several considerations. The first hurdle for microarrays is the availability of high-quality, validated, and standardized arrays and processes. A key limitation to implementation of routine diagnostic microarrays is identification of appropriate targets. Although ribosomal RNA gene targets are widely

used, they are limited in their ability to resolve bacteria below the species level (Saliba et al., 1966). Other bacterial target genes, including housekeeping genes, are potentially useful, but data across the full breath of organisms are limited or nonexistent. Even with good targets, optimal hybridization conditions for all the probes on a single array are still challenging. Redundant variations in probes help compensate to a degree. Another challenge to microarray routine use is the sensitivity of most systems. To obtain appropriate sensitivity, polymerase amplification is necessary. In most systems, this requires a multitude of specific primers for the genes of interest. Because multiplexed PCR is limited to a dozen or so reactions, several hundred iterations of PCR could be required to completely cover all the potential probes on an array, which is not practical in routine use. Until a good on-chip amplification or signal detection method is developed, the use of diagnostic microarrays will be limited.

Ultimately, to meet the needs of users, rapid infectious disease diagnostic assays need a comprehensive integrated system. This includes automated sample processing and the use of multiple technologies to obtain results that can be interpreted against the clinical picture or medical intelligence. Currently, immunoassays and molecular assays are the most mature technologies. Immunoassays are a maturing technology that has improving sensitivity and specificity. With improvements in signal amplification and the use of monoclonal antibodies, immunoassays are fast, robust, and approaching the sensitivity of some molecular methods. Molecular methods are rapidly developing but are not at the full maturity level yet. Amplification methods achieve exquisite sensitivity, but at the risk of potential contamination events. Together, immunoassays and molecular techniques are very complementary and a powerful set of techniques for an integrated system (Henchal et al., 2001) (Figure 3-6).

The future for rapid infectious disease diagnostics is the lab-on-a-chip approach, where all sample processing, assay technologies, detection, and reporting are fully integrated into one unit. Miniaturized, disposable, and cost-effective units will evolve from our current systems. As technologies mature and new technologies are developed, rapid infectious disease diagnostics will become available and practical.

Ramping Up to Success

Although we believe that the products of strategic, adequately supported public–private partnerships to develop diagnostics could transform approaches to control infectious diseases in poor countries, progress inevitably will be incremental, especially in the near term. Because new tests are likely to be imperfect, we will need flexibility and creativity to ensure that these tools are used to maximum effect. For example, rather than discard a rapid tuberculosis test with high sensitivity but low specificity, we should consider incorporating it into a diagnostic algorithm to quickly rule out tuberculosis in most patients present-

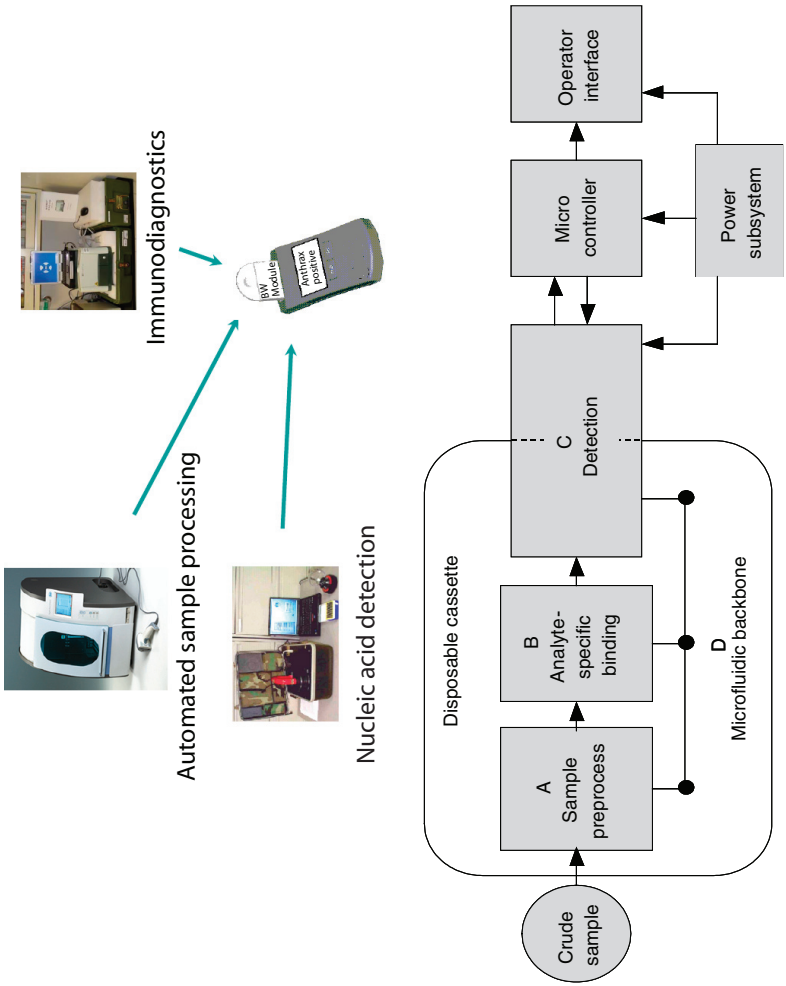

FIGURE 3-6 Comprehensive integrated diagnostic system. Integrated systems that employ more than one technology along with the sample handling component are being investigated for the next-generation diagnostic systems.

ing with chronic cough—a step that could dramatically decrease the workload of tuberculosis clinics. Rather than develop a single test to replace the sputum microscopy, we should embrace the concept of market segmentation and develop a range of new tools suitable for different diagnostic environments.

We must also accept that new technology may require changes to longstanding public health practices. For example, tuberculosis epidemiology has long been tracked by monitoring the number of smear-positive patients. If microscopy is replaced with a more sensitive test, tracking of tuberculosis trends could be disrupted. But this is a small price to pay for better serving patients and strengthening the world's ability to bring tuberculosis under control. Similarly, microscopy offers quantitative estimates of parasite burden, which is often used by clinicians to estimate the severity of illness or to monitor the effectiveness of treatment. Replacement with qualitative testing will force a change of practice, even as it brings the power of confirmatory diagnosis out of referral laboratories and into the community.

Finally, we emphasize that the impact of a new diagnostic test ultimately will be determined by the extent to which it is used. Expanding use of a new technology, as with any global health intervention, ultimately will depend on political will. Integration of improved diagnostics into national programs in the same structured fashion that has been used for standard and second-line tuberculosis drugs is possible, but only if leaders confront a range of issues that will make implementation possible—from lifting import taxes to improving laboratory capacity to modifying disease control guidelines. Is this too much to ask to give our health-care practitioners the tools they need to do their jobs?

EMERGING TOOLS FOR MICROBIAL DIAGNOSIS, SURVEILLANCE, AND DISCOVERY

W. Ian Lipkin, M.D.[6]
Columbia University

Thomas Briese, Ph.D.[6]
Columbia University

Introduction

Here we describe methods and perspectives for pathogen surveillance and discovery, and discuss challenges associated with proving causality. We provide examples from our own experience to illustrate the complexity of pursuing

[6]Jerome L. and Dawn Greene Infectious Disease Laboratory, Mailman School of Public Health.

research in this arena and to provide the reader with insights into the process that led to the implementation of particular strategies.

Proof of Causation

Discovery of an organism in association with disease is only the first step in understanding its role in pathogenesis. Many have wrestled with the challenge of codifying the process of proving causation. Based on the germ theory of disease formulated by Pasteur, Koch, and Loeffler proposed precise criteria that define a causative relationship between agent and disease: The agent should be present in every case of a disease, it should be specific for a disease (i.e., present in none other), and it should be propagated in culture and proven capable of causing the same disease upon inoculation into a naïve host. Known as Koch's postulates (Koch, 1891), these criteria were subsequently modified by Rivers for specific application to viruses (Rivers, 1937), and by Fredricks and Relman to reflect the advent of molecular methods (Fredricks and Relman, 1996) (Table 3-2). Nonetheless, Koch's postulates remain the ideal standard by which causality is considered to be proven. There are problems with holding to this standard. Some agents cannot be propagated in culture. Additionally, for many human viral pathogens, there may be no animal model. In many acute viral diseases, the responsible agent can be readily implicated because it replicates at high levels in the affected tissue at the time the disease is manifest, morphological changes consistent with infection are evident, the agent is readily identified with classical or molecular methods, and there is evidence of an adaptive immune response. However, implication of viruses in chronic diseases may be confounded because persistence requires restricted gene expression, classical hallmarks of infection are absent, and/or mechanisms of pathogenesis are indirect or subtle. In the final analysis, investigators are occasionally left with what amounts to an assessment of strength of epidemiological association based on the presence of the agent, its footprints (nucleic acid, and preferably, an immune response), and biological plausibility based on analogy to diseases with related organisms where linkage is persuasive.

Many Routes to Microbial Pathogenesis

Implication of an infectious agent is most straightforward in instances where it is present at the site of disease at the time the disease is manifest. Two classic examples where effects are readily appreciated at the infection site are poliomyelitis, where virus replicates in motor neurons of the brain and spinal cord, causing cell loss and paralysis, and cholera, where *Vibrio cholerae* replication and local elaboration of toxin in the intestine alters ion transport, resulting in diarrhea. A more complex example of intoxication is botulism where replication of *Clostridium botulinum* in the skin or the gastrointestinal tract leads to local

TABLE 3-2 Criteria for Proof of Causation

Robert Koch (1890)[a]	Thomas R. Rivers (1937)	Fredricks and Relman (1996)
A microbe must be: • Present in every case of a disease. • Specific for that disease. • Isolated, propagated, in culture, and shown to induce disease upon inoculation into the experimental host. • Reisolated from the experimental host wherein the original syndrome is replicated. NOTE: This fourth postulate though not required by Koch, logically follows his other conditions and so has been added by some reviewers.	• A specific virus must be found associated with a disease with a degree of regularity. NOTE: The possibility of a viral carrier state was recognized and Koch's requirements of propagation in media or cell culture was abandoned. • The virus must be shown to be the causative agent of disease in the sick individual. NOTE: The pathogen should be present at the proper time in specific regions and the disease should be produced with some regularity by serious inoculation of infected material into a susceptible host.	• Candidate sequences should be present in most cases of disease and at sites of disease. • Few or no sequences should be present in host or tissue without disease. • Sequences should diminish in frequency with resolution of disease and increase with relapse. • Sequences should be present prior to the onset of disease.

[a]Although Koch included basic points already in earlier papers, especially his 1884 paper on the etiology of tuberculosis, his most explicit presentation was given at the 1890 International Congress of Medicine; the proceedings of which were published in 1891.
SOURCE: Koch (1891); Rivers (1937); Fredricks and Relman (1996).

expression of a toxin that traffics to the neuromuscular junction to interfere with motor function. Host responses to infection may contribute to pathogenesis. Acute infection with influenza virus or severe acute respiratory syndrome (SARS) coronavirus elicits cytokines and chemokines that cause pulmonary dysfunction. Chronic inflammation in hepatitis B and hepatitis C infections can result in hepatic failure and hepatocellular carcinoma. Infection can also lead to inhibition of immune function. The capacity of viruses to enhance susceptibility to opportunistic agents is now best known in the context of HIV/AIDS; however, the observation of virus-induced immunosuppression dates back to the early 1900s when von Pirquet noted the loss of skin reactivity to tuberculin in association with measles infection. The effects of infection may depend on the age and maturation status of the host. Individuals at either extreme of life are at increased risk for acute morbidity and mortality with a wide variety of infections. Encephalitis

is far more common in individuals infected with West Nile virus after the age of 50 years than in other adults or children. Infection during organogenesis may have different consequences than at other times. Congenital rubella infection, for example, can be associated with characteristic cardiac and central nervous system defects. Persistent viral infections are described in animal models where subtle effects on cellular physiology result in alterations in the expression of neurotransmitters or hormones that have profound effects including cognitive impairment, hypothyroidism, or diabetes mellitus. Whether similar mechanisms can be implicated in human disease remains to be determined; nonetheless, these preclinical studies indicate biological plausibility. Infection can break tolerance for "self," resulting in autoimmune disease. A classical example is molecular mimicry in group A beta-hemolytic streptococcus infection where cross-reactivity to heart and brain results in valvular disease and chorea, respectively. The capacity for infections to cause disease via myriad mechanisms, direct and indirect, short and long term, pose challenges for pathogen discovery.

Molecular Strategies for Pathogen Discovery

Methods for cloning nucleic acids of microbial pathogens directly from clinical specimens offer new opportunities to investigate microbial associations in chronic diseases (Relman, 1999). The power of these methods is that they can succeed where methods for pathogen identification through serology or cultivation may fail due to absence of specific reagents or fastidious requirements for agent replication. Over the past decade, the application of molecular pathogen discovery methods resulted in identification of novel agents associated with both acute and chronic diseases, including Borna disease virus, hepatitis C virus, Sin Nombre virus, HHV-6, HHV-8, *Bartonella henselae*, *Tropheryma whippelii*, West Nile virus, and SARS coronavirus (Challoner et al., 1995; Chang et al., 1994; Choo et al., 1989; Lipkin et al., 1990; Nichol et al., 1993; Relman et al., 1990, 1992; VandeWoude et al., 1990).

Various methods are employed or proposed for cultivation-independent characterization of infectious agents. These can be broadly segregated into methods based on direct analysis of microbial nucleic acid sequences (e.g., complementary DNA [cDNA] microarrays, consensus polymerase chain reaction [cPCR], representational difference analysis [RDA], differential display [DD]), direct analysis of microbial protein sequences (e.g., mass spectrometry), immunological systems for microbe detection (e.g., expression libraries, phage display), and host response profiling.

The decision to employ a specific method is guided by the clinical features, epidemiology, and spectrum of potential pathogens to be implicated. Expression libraries, composed of cDNAs or synthetic peptides, may be useful tools in the event that large quantities of acute and convalescent sera are available for screening purposes; however, the approach is cumbersome and labor-intensive,

and success depends on the presence of a specific, high-affinity humoral immune response. Mass spectrometry is an intriguing approach to pathogen discovery (Dalluge, 2000; van Baar, 2000); however, potential confounds include mutations in flora that alter spectra without clinical correlation; the requirement for establishment of large libraries of spectra representing flora of thousands of organisms propagated *in vitro* and isolated *in vivo*; and the difficulties associated with extending this technology to viruses, where disease may occur without robust protein expression, and pathogenicity may be correlated with single base substitutions. The utility of host response messenger RNA (mRNA) profile analysis has been demonstrated in several *in vitro* paradigms and some inbred animal models (Diehn and Relman, 2001; Taylor et al., 2000; Zhu et al., 1998); nonetheless, a variety of organisms may activate similar cascades of chemokines, cytokines, and other soluble factors that influence host gene expression to produce what are likely to be convergent gene expression profiles. RDA is an important tool for pathogen identification and discovery. However, RDA is a subtractive cloning method for binary comparisons of nucleic acid populations (Hubank and Schatz, 1994; Lisitsyn et al., 1993). Thus, although ideal for analysis of cloned cells or tissue samples that differ only in a single variable of interest, RDA is less well suited to investigation of syndromes wherein infection with any of several different pathogens results in similar clinical manifestations, or infection is not invariably associated with disease. An additional caveat is that because the method depends on the presence of a limited number of restriction sites, RDA is most likely to succeed for agents with large genomes. Indeed, in this context, it is noteworthy that the two viruses detected by RDA were herpesviruses (Challoner et al., 1995; Chang et al., 1994).

Consensus PCR also has been a remarkably productive tool for biology. In addition to identifying pathogens, this method has facilitated identification of a wide variety of host molecules, including cytokines, ion channels, and receptors. One difficulty in applying cPCR to pathogen discovery in virology has been that it is difficult to identify conserved viral sequences of sufficient length to allow cross-hybridization, amplification, and discrimination in a traditional PCR format. Although this may not be problematic when one is targeting only a single virus family, the number of assays required becomes infeasible when preliminary data are insufficient to permit a more directed, efficient analysis. To address this problem, we adapted cPCR to differential display, a PCR-based method for simultaneously displaying the genetic composition of multiple sample populations in acrylamide gels (Liang and Pardee, 1992). This hybrid method, known as domain-specific differential display (DSDD), employs short, degenerate primer sets designed to hybridize to viral genes that represent larger taxonomic categories than can be resolved in cPCR. Although this modification allowed us to identify West Nile virus as the causative agent of the 1999 New York City encephalitis outbreak (Briese et al., 1999), it did not resolve issues of low throughput with cPCR due to limitations in multiplexing.

To address the need for sensitive, facile, highly multiplexed pathogen surveillance, we established two new platforms for viral detection, MassTag PCR and the GreeneChip. MassTag PCR is a multiplex PCR method that can accommodate in excess of 20 genetic targets with sensitivity in the range of 10 to 1,000 RNA copies (variability is a function of primer degeneracy). The GreeneChip is a comprehensive viral microarray that addresses all vertebrate viruses in the International Committee on Taxonomy of Viruses (ICTV) database. Both methods rely on the presence of an agent related to one already known. In instances where agents are novel or sufficiently distant in sequence to related agents to confound hybridization it may be necessary to resort to subtractive cloning or high-throughput unbiased sequencing. Our algorithm for characterization of clinical materials is illustrated in Figure 3-7. Where the list of candidates to be considered can be addressed using MassTag PCR this is our method of choice due to low cost, speed, and sensitivity. Where MassTag PCR fails or the list of candidates exceeds 30 targets, we move to GreeneChips (viral or panmicrobial). In the event that GreeneChips fail we shift to unbiased high-throughput sequencing or subtractive cloning.

MassTag PCR

Although singleplex PCR assays are well established in clinical microbiology and have proved indispensable in management of HIV and hepatitis C virus (HCV), and in control of outbreaks where an agent is identified, multiplex assay applications have lagged behind. Fluorescence reporter systems in real-time PCR achieve quantitative detection with sensitivity similar to nested amplification; however, their capacity to simultaneously query multiple targets is limited to the number of fluorescent emission peaks that can be unequivocally separated. At present up to four fluorescent reporter dyes are detected simultaneously. To address the need for highly multiplexed assays, we created MassTag PCR, a platform wherein digital mass tags rather than fluorescent dyes serve as reporters (Figure 3-8). The first description of this method was published in the context of a panel that distinguishes 22 different viral and bacterial respiratory pathogens (Briese et al., 2005). It allowed us to identify viral and bacterial sequences in respiratory samples as well as cultured materials, and to recognize instances of coinfection not appreciated in reference laboratories using established diagnostics assays. We later expanded the repertoire to include causative agents of hemorrhagic fever, and to subtype influenza viruses. Between October and December 2004, an increased incidence of influenza-like illness (ILI) was recorded by the New York State Department of Health that tested negative for influenza virus by molecular testing, and negative for other respiratory viruses by culture. Concern that a novel agent might be implicated led us to investigate clinical materials (Lamson et al., 2006). MassTag PCR resolved 26 of 79 previously negative samples, revealing the presence of rhinoviruses in a large proportion of samples,

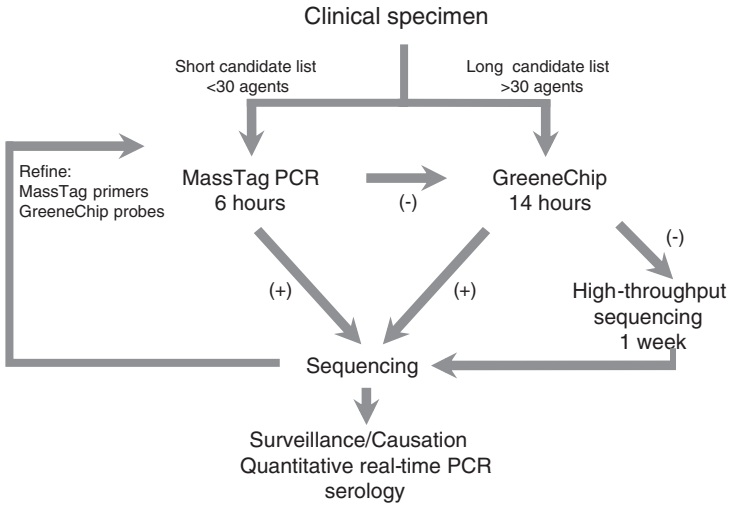

FIGURE 3-7 A staged strategy for pathogen detection and discovery.
SOURCE: Lipkin (2006).

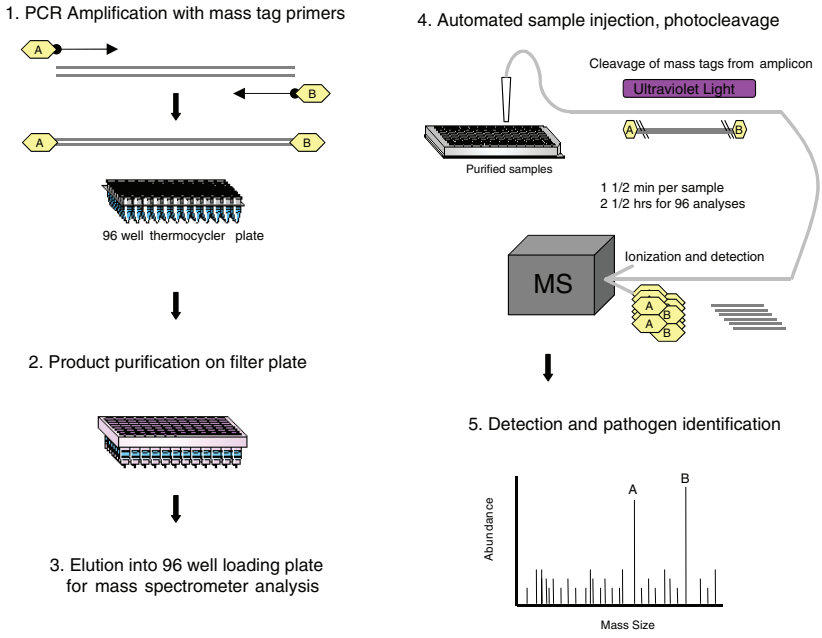

FIGURE 3-8 Schematic representation of MassTag PCR procedure.
SOURCE: Briese et al. (2005).

about half of which belonged to a previously uncharacterized genetic clade. The 2004 New York ILI study confirmed the utility of MassTag PCR for surveillance, outbreak detection, and epidemiology by demonstrating its potential to rapidly query samples for the presence of a wide range of candidate viral and bacterial pathogens that may act alone or in concert.

MassTag PCR may not suffice in instances where either larger numbers of known pathogens must be considered or sequence divergence may impair binding of PCR primers. The limitations of MassTag PCR (and other PCR platforms) were poignantly demonstrated during analysis of samples from Marburg hemorrhagic fever outbreaks in the Democratic Republic of Congo during 1998–1999 wherein two of five subjects were negative. The explanation for failure became clear after cPCR amplification and sequencing revealed three mismatches in the forward and one in the reverse primer (Palacios et al., 2006). If we had enjoyed our current access to unpublished, proprietary filovirus sequences at the time primers were designed, we would have averted difficulty in this instance. Nonetheless, despite access to sequences in World Health Organization (WHO) network laboratories, this experience reinforced the need for a complementary tool with higher tolerance for sequence divergence, and led us to develop the GreeneChip, a DNA microarray system.

Establishment of the Greene Microbial Database

A critical early step in the development of the MassTag PCR and microarray tools was the establishment of a viral sequence database. This effort was facilitated in 2002 by the move of the ICTVdB (International Committee on Taxonomy of Viruses Database)[7] and its director, Cornelia Büchen-Osmond, from Biosphere 2 (Earth Institute) in Oracle, Arizona, to the Greene Laboratory; and the establishment of a Northeast Biodefense Center Biomedical Informatics Core. Because vertebrate viruses are highest priority for human disease, we focused on them first, with a plan to extend the database to viruses of invertebrates, plants, and prokaryotes as resources permitted. To ensure comprehensive coverage, we included every vertebrate virus listed in the ICTVdB, a taxonomic database that describes viruses at the levels of order, family, genus, and species. Efforts to identify cognate sequences for members of each of these taxa in the National Center for Biotechnology Information (NCBI) sequence database proved to be more difficult than anticipated. The NCBI database is not exhaustively curated; thus, it contains many entries where annotation is missing, outdated, or inaccurate. An additional confound is that only incomplete sequence is available for many viruses, bacteria, and parasites, particularly some relevant to this project, where genomic sequencing efforts are less advanced. To circumvent limitations in curation and nomenclature in the NCBI database, and to minimize computa-

[7]See http://phene.cpmc.columbia.edu.

tional costs in establishment of multiple alignments at the nucleotide (nt) level, we began construction of the Greene Viral Database (GreeneVrdB) by using the Protein Families database of alignments (Pfam)[8] and Hidden Markov Models (HMM). Sequences for the design of oligonucleotide probes and MassTag PCR primers were selected based on biological parameters, including the degree of conservation of proteins or domains, their expression level during infection, and the amount of data available for the respective region.

The GreeneVrdB was established by integrating the taxonomy database of ICTV and the sequence database of NCBI (Figure 3-9).[9] The majority of viral protein coding sequences in the NCBI database (84 percent) were represented in the Pfam database; the remainder were mapped using pair-wise Basic Local Alignment Search Tool (BLAST) alignments. A panmicrobial database (GreenePmdB) was established by supplementing the GreeneVrdB with ribosomal RNA (rRNA) sequences of fungi, bacteria, and parasites obtained from the Ribosomal Database Project (RDP)[10] or the NCBI database. At the time of this writing the GreenePmdB comprises the 382,512 viral sequences of the GreeneVrdB, representing both complete and partial viral genomes; 41,790 bacterial 16S rRNAs; 4,109 fungal 18S rRNAs; and 2,626 18S parasitic rRNAs. These sequences represent all 2,011 vertebrate virus species and 135 bacterial, 73 fungal, and 63 parasite genera.

GreeneChips

DNA microarrays have potential to provide a platform for highly multiplexed differential diagnosis of infectious diseases. The number of potential features far exceeds that with any other known technology. Furthermore, probes of up to 70 nt are not uncommon. Thus, unlike PCR where short primer sequences demand precise complementarity between probe and target, DNA arrays are less likely to be confounded by minor sequence mismatches. Lastly, one can incorporate both microbial and host gene targets. This affords an opportunity to both detect microbes and assess host responses for signatures consistent with various classes of infectious agents. Despite these advantages, DNA arrays have not been widely employed because of limited sensitivity. Although a viral array was helpful in identifying the causative agent of SARS in 2003, critical to its success was the discovery that the agent could be propagated to high titer and had cytopathic effect in Vero cells (Ksiazek et al., 2003). Once this advance was shared, several investigators rapidly and independently identified the agent by electron microscopy, differential display, cDNA cloning, microarray, and cPCR. The challenge of array sensitivity has now been addressed with improved methods for sample

[8]See http://pfam.wustl.edu.
[9]See http://www.ncbi.nih.gov.
[10]See http://rdp.cme.msu.edu.

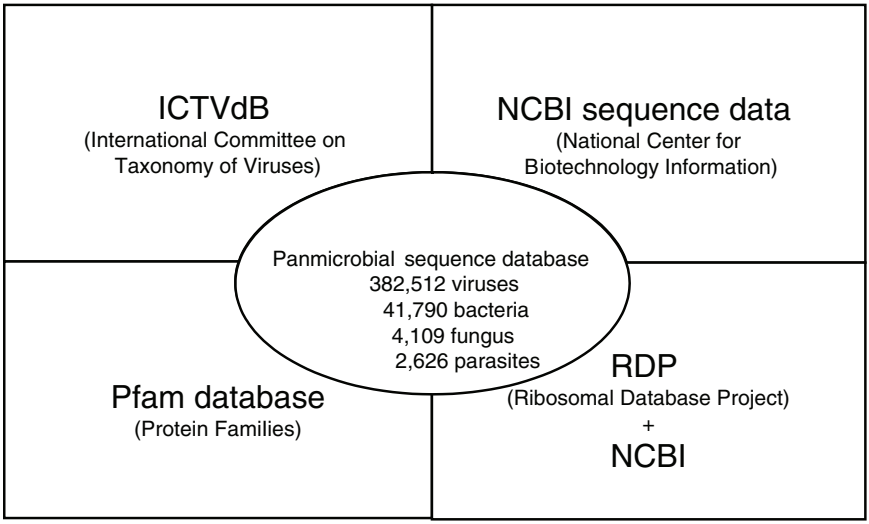

FIGURE 3-9 Greene pathogen database.
SOURCE: Lipkin (2006).

preparation, amplification, labeling, and printing. Together with Agilent Technologies, we created a DNA array platform suited to analysis of clinical materials without amplification in culture. Investigation by MassTag PCR and viral DNA microarray of blood collected during the 2005 Angola Marburg virus outbreak from an individual who died of hemorrhagic fever failed to yield a pathogen; however, implementation of a panmicrobial DNA array, GreeneChipPm, implicated *Plasmodium falciparum* infection (Palacios et al., 2007).

Microbial Probes

Viral probes were designed to represent a minimum of three distinct genomic target regions for every family or genus of vertebrate virus in the ICTVdB. Where possible, we chose highly conserved regions within coding sequence for an enzyme such as a polymerase, and two other regions corresponding to more variable structural proteins. Our reasoning was that RNAs encoding structural proteins may be present at higher levels than those encoding proteins needed only in catalytic amounts, and that use of probes representing noncontiguous sites along the genome might allow detection of naturally occurring or intentionally created chimeric viruses. The viral array has been through several iterations as the database evolved and technology allowed increases in probe density. The first release, GreeneChipVr1.0, comprised a total of 9,477 viral probes. The second release, GreeneChipVr1.1, added 6,271 more typing probes for influenza virus A hemagglutinin and neuraminidase genes. Recent releases,

GreeneChipVr1.5 (15,700 probes) and GreeneChipVr2.0 (86,300 probes), are the result of higher printing density on the Agilent array platform and a new generation of probe design algorithms. The process for identifying bacterial, fungal, and parasitic probes was similar, although restricted to 16S and 18S rRNA sequences. GreeneChipPm1.0 contained a total of 29,495 probes, including the probes comprising GreeneChipVr1.1 as well as 11,479 16S rRNA bacterial, 1,120 18S rRNA fungal, and 848 18S rRNA parasite probes.

Host Gene Markers

Identification of signal(s) representing a microbe in samples from affected subjects is a primary objective in pathogen discovery. Nonetheless, evidence of infection is bolstered by coterminous evidence of gene expression consistent with an activated host immune response. Furthermore, gene expression profiles may be helpful in implicating specific strains or serotypes (e.g., Th1 cytokine responses are more robust with H5N1 than H1N1 influenza infection) (Cheung et al., 2002). Finally, in cases where we fail to find clear evidence of a known pathogen, a profile consistent with immune activation may be helpful in determining whether to pursue additional studies focused on pathogen discovery. Thus, GreeneChips include probes for genes associated with cytokines, chemokines, and their receptors; components of the interferon-inducible signaling pathways; immunoglobulins (Igs) and Ig receptors; toll-like receptors and their downstream signaling pathways; complement components; major histocompatibility complex (MHC) molecules; and heat shock proteins from a set of validated oligonucleotides (Wright and Church, 2002).

GreeneLAMP Analysis Software and GreeneChip Validation

GreeneLAMP (Log-transformed Analysis of Microarrays using P-values) version 1.0 software was created to assess results of GreeneChip hybridizations. Common analysis software focuses on the differential two-color analysis used in gene expression arrays, which is not applicable to the GreeneChip. GreeneLAMP has a robust and generalized framework for microarray data analysis, including: flexible data loading, filtering, and control experiment subtraction. Probe intensities are background corrected, $\log_2$-transformed, and converted to Z-scores (and their corresponding p-values). Where available, control matched experiments from uninfected samples are used and spots >2 standard deviations (SD) from the mean are subtracted. In instances where matched control samples are not available, the background distribution of signal fluorescence is calculated using fluorescence associated with 1,000 random 60-mers (Null probes). In both scenarios, positive events are selected by applying a false-positive rate of 0.01 (the rate at which Null probes are scored as significant) and a minimum p-value per probe of 0.1 (in cases with a matching control) and 0.023 (2 SD; in cases without

a matching control). A map, built from a Basic Local Alignment Search Tool for nucleotides (BLASTN) alignment of probes to the Greene Pathogen Database, is used to connect probe sequences to the respective entries in the Greene Pathogen Database. Each of those sequences corresponds to an NCBI Taxonomy ID (TaxID). The individual TaxIDs are mapped to nodes in a taxonomic tree built based on ICTV virus taxonomy or NCBI taxonomic classification for other organisms. The program output is a ranked list of candidate TaxIDs. Candidate TaxIDs are ranked by combining the p-values for the positive targets for that TaxID using the QFAST method of Bailey and Gribskov (Bailey and Gribskov, 1998).

The specificity of the viral GreeneChip was assessed using extracts of cultured cells infected with adeno-, alpha-, arena-, corona-, entero-, filo-, flavi-, herpes-, orthomyxo-, paramyxo-, pox-, reo-, and rhabdoviruses (a total of 49 viruses). All were accurately identified by GreeneLAMP analysis. To assess sensitivity, viral RNA extracted from infected cell supernatants (adeno-, West Nile, St. Louis encephalitis, respiratory syncytial, entero-, SARS corona-, and influenza viruses) was quantitated by real-time PCR, serially diluted, and subjected to GreeneChip analyses. The threshold of detection for adenovirus was 10,000 RNA copies; the threshold of detection for the other reference viruses was 1,000 RNA copies per reverse transcription (RT)-reaction. The respiratory GreeneChip was tested for detection and typing with 31 influenza virus A and B reference strains of human and animal origin and, because reference strains represent only a limited fraction of the genetic variability, with numerous circulating human influenza virus strains isolated worldwide since 1999. In summary, a total of 69 viruses comprising 54 influenza virus A and B isolates of human, avian, and porcine origin and 15 non-influenza human respiratory viruses were tested, identified, and subtyped.

GreeneChips were also validated with clinical samples from patients with respiratory disease, hemorrhagic fever, tuberculosis, and urinary tract infections, and were demonstrated to identify human enterovirus A, human respiratory syncytial virus A, influenza A virus, Lake Victoria marburgvirus, SARS coronavirus, lactobacillus, mycobacteria, and gammaproteobacteria in various specimen types, including cerebrospinal fluid, nasopharyngeal swabs, sera/plasma, stools, and urine.

Recovery of Hybridized Sequences from GreeneChips

Arrays can facilitate cloning and sequence analysis as well as pathogen identification. Hybridized products typically range from 200 nt to >1,000 nt. Because GreeneChips display three or more probes representing different genomic regions for each virus, one can rapidly recover sequence not only for hybridized products but also for sequences between those products through use of PCR.

Unbiased High-Throughput Sequencing

The advent of high-throughput sequencing technology affords unique opportunities for pathogen discovery. Unlike consensus PCR or array methods where investigators are limited by known sequence information and must make choices regarding the range of pathogens to consider in a given experiment, high-throughput sequencing is unbiased. Several systems are in development. We have experience with the pyrosequencing system of 454 Life Sciences; however, the principles for sample preparation and data analysis are broadly applicable across platforms. Because all nucleic acid in a sample (whether host or pathogen) is amplified and sequenced, elimination of host nucleic acid can be critical to boosting pathogen signal toward the threshold for detection. Our approach is to apply a similar sample preparation and random PCR amplification protocol as developed for the GreeneChip including extensive DNase I treatment of the RNA template to remove host chromosomal DNA. This process obviates the potential for detecting DNA genomes of pathogens; however, our reasoning is that an active infection should be associated with transcription. After amplification and sequencing reads typically range in size from 40 to 400 base pairs. Raw sequence reads are trimmed to remove sequences derived from the amplification primer and filtered to eliminate highly repetitive sequences. After trimming and eliminating repeats, sequences are clustered into nonredundant sequence sets. Unique sequence reads are assembled into contiguous sequences, which are then compared to the nonredundant sequence databases using programs that examine homology at the nucleotide and amino acid levels (using all six potential reading frames with adjustments for sequence gaps). Specific PCR tests are then designed to examine association with disease, measuring burden, and obtaining additional sequence for phylogenetic characterization.

Vignettes in Pathogen Discovery

Borna Disease Virus and Neuropsychiatric Disease

In 1985, Rott and Koprowski reported that serum from patients with bipolar disorder reacted with cells infected with Borna disease virus (BDV), an unclassified infectious agent named after a town in Saxony (eastern Germany) that had large outbreaks of equine encephalitis in the late 1800s. Intrigued both by the concept that infection might be implicated in a neuropsychiatric disease, and that established methods for virus isolation had failed, we and others began to pursue characterization of this elusive neurotropic virus using molecular tools. BDV nucleic acids were isolated by subtractive hybridization in 1989, the first successful application of subtractive cloning in pathogen discovery (Lipkin et al., 1990). This effort relied on cDNA cloning with home brew kits as it preceded the advent of polymerase chain reaction and ready access to sequencing technologies.

The correlation between cloned materials and disease was achieved by demonstrating that (1) candidate cDNAs competed with RNA template from brains of infected rats for transcription and translation of a protein biomarker present in brain (hybrid arrest experiments), (2) the distribution of candidate nucleic acid correlated with pathology in brains of experimentally infected rats and naturally infected horses (*in situ* hybridization), and (3) no signal was obtained in Southern hybridization experiments, wherein normal brain was probed with candidate clones. Based on northern hybridization experiments the genome was variously reported as a 8.5 kb negative polarity RNA or an 11 kb positive polarity RNA. Over the next 5 years, the genome was cloned, and the virus was visualized and classified as the prototype of a new family of nonsegmented negative-strand (NNS) RNA virus with unusual properties: nuclear replication/transcription, posttranscriptional modification of selected mRNA species by splicing, low-level productivity, broad host range, neurotropism, and capacity for persistence (Briese et al., 1992, 1994; Cubitt et al., 1994; de la Torre, 1994; Schneemann et al., 1995; Schneider et al., 1994). It was widely held that the introduction of specific reagents such as recombinant proteins and nucleic acid probes would allow rapid assessment of the role of BDV in human disease. However, in a classic example of the pitfalls of PCR diagnostics, particularly using nesting methods, BDV was implicated in a wide variety of disorders that included unipolar depression, bipolar disorder, schizophrenia, chronic fatigue syndrome, AIDS encephalopathy, multiple sclerosis, motor neuron disease, and brain tumors (glioblastoma multiforme) (Lipkin et al., 2001; Schwemmle et al., 1999). At the time of this writing, there is no conclusive evidence that BDV infects humans. BDV is nonetheless a fascinating virus, and its discovery has yielded intriguing models of viral pathogenesis, and provided guidance regarding methods for rigorously investigating the role of infection in chronic disease with sensitive molecular tools. It is worth noting that the two years of molecular gymnastics required to identify BDV could be collapsed into a few weeks with current art. However, even with the explosion in viral sequence data over the past decade, BDV is sufficiently different that it could not be identified by consensus PCR or microarrays based on sequences other than those representing *Bornaviridae*. To our knowledge it is unique in this respect.

West Nile Virus Encephalitis

In late August 1999, health officials reported an outbreak of encephalitis accompanied by profound weakness in Queens, New York. There was neither an apparent increase in the frequency of encephalitis in New York, nor an automatic reporting event that resulted in detection of the outbreak. Thus, the recognition of the syndrome was due to the clinical acumen of Deborah Asnis, an infectious diseases physician at Flushing Hospital Medical Center, and Marcelle Layton, Assis-

tant commissioner, Communicable Disease Program, New York City Department of Health, and their associates.

On September 3, serology for the presence of antibodies to North American arboviruses yielded results consistent with infection with St. Louis encephalitis virus (SLEV) (Asnis et al., 2000). St. Louis encephalitis (SLE) had not been reported previously in New York although mosquito vectors competent for transmission of SLE were present. Investigation of the outbreak epicenter revealed sites of active mosquito breeding and early victims of the outbreak had histories consistent with mosquito exposure. Thus, on September 3, a mosquito eradication program was adopted by the state and by the city of New York. Concurrently, wildlife observers independently noted increased mortality of avian species, including free-ranging crows and exotic birds housed in the Bronx Zoo. Tracy McNamara, a veterinary pathologist at the Wildlife Conservation Society, performed histologic analysis of birds and found meningoencephalitis, gross hemorrhage of the brain, splenomegaly, and myocarditis (Steele et al., 2000). Although 70 percent of emerging infectious diseases are zoonoses and the coincidence between the human and nonhuman outbreaks was striking, McNamara was unable to persuade her colleagues in human infectious disease surveillance to review materials. She forwarded tissue samples from diseased birds to the U.S. Department of Agriculture (USDA) National Veterinary Service Laboratory in Ames, Iowa, where virus was cultured and electron micrographs reported to be consistent with the presence of either a togavirus or a flavivirus. Thereafter the avian virus was forwarded from USDA to the Centers for Disease Control and Prevention (CDC) in Fort Collins, Colorado, for molecular analysis (Lanciotti et al., 1999).

On September 13–15, the CDC Encephalitis Project (composed of centers in California, New York, and Tennessee) held its annual meeting in Albany, New York. Data emerging from both California and New York over an 18-month survey period indicated that an etiological agent was never identified in 70 percent of cases of encephalitis despite culture, serology, and molecular analyses. In this context, our group was invited to discuss methods for identification of unknown pathogens and to consider application to project samples of a new method for amplifying viral nucleic acids, domain-specific differential display (DSDD). Sherif Zaki at CDC Atlanta had demonstrated the presence of flavivirus protein in brains of human victims of the New York City outbreak; however, efforts to amplify SLEV or other flaviviral sequences by conventional reverse transcription PCR (RT-PCR) had been unsuccessful. Employing several degenerate primer sets designed to target in DSDD highly conserved domains in the NS3, NS5, and 3'-untranslated regions of flaviviruses, we obtained positive results for four of the five New York patients in only a few hours. Sequence analysis confirmed the presence of a lineage one West Nile virus (Briese et al., 1999; Jia et al., 1999). Concurrently, our colleagues at CDC in Fort Collins reported West Nile-like

sequences in cell lines infected with homogenates from New York birds. In concert these findings confirmed that the outbreak in New York City was a zoonosis due to West Nile virus (WNV).

Subsequently, we established quantitative real-time PCR assays for sensitive high-throughput detection of virus in clinical materials and mosquito pools. Analysis of blood samples from infected humans revealed the presence of WNV sequences in late 1999 (Briese et al., 2000); however, the significance of human-human transmission was not appreciated until 2002, when transmission through organ transplants and blood transfusion led to implementation of blood screening by nucleic acid amplification tests (CDC, 2003, 2004). This outbreak illustrates the power of molecular methods for addressing the challenges of emerging infectious diseases. As an example of an emerging zoonosis it also underscores the significance of enhancing communication between the human and veterinary medicine communities.

Enteroviruses and Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a disorder characterized by progressive loss of motor neurons and muscle atrophy. An inherited form caused by mutations in the superoxide dismutase gene has been described; however, the majority of cases are idiopathic. In 2000 Berger and colleagues, using nested PCR, sequencing, and *in situ* hybridization methods, reported the striking finding that 15 of 17 French subjects with ALS, and only 1 of 29 subjects with other neurologic diseases had sequences of a novel echovirus in the spinal cord (Berger et al., 2000). Although other enteroviruses such as poliovirus and human enterovirus 71 have been unequivocally implicated in acute motor neuron disease, this publication was the first to provide compelling evidence that enteroviruses could cause slowly progressive chronic neurologic disease. Given the potential utility of antiviral treatment of this devastating neurodegenerative disorder we were encouraged by the National Institute of Neurological Disorders and Stroke (NINDS) to try to independently replicate the echovirus data. Our experience in the BDV field, where problems with PCR hygiene had led to spurious links to disease, was invaluable in directing experimental design. Whereas the Berger group had used RNA template extracted from sections cut on cryostats and analyzed by nested PCR in the same laboratory, we collected frozen tissues from two tissue banks, extracted RNA in a laboratory with no history of virus research, and performed blinded real-time PCR analyses in yet another laboratory. Real-time PCR is similar in sensitivity to nested PCR but is less sensitive to false-positive results because assays are performed in a closed system wherein signal is read as fluorescent signal. Analysis of spinal cord and motor cortex from 20 subjects with ALS and 14 controls revealed no echovirus sequences (Walker et al., 2001). These results were well received by colleagues but elicited less positive correspondence from some individuals who noted that

our publication was foreclosing a promising research lead and clinical trials with antiviral drugs.

Future Perspectives

Technologies will continue to evolve, allowing faster, more sensitive, and less expensive methods for pathogen surveillance and discovery. Although multiplex PCR is relatively mature, microarray technology is still in its infancy; near-term modifications already in development include microfluidic sample processing and direct measurement of conductance changes associated with hybridization. We have only touched the surface of proteomics and host response profiling. It is conceivable that biomarkers will be found that are specific for classes of infectious agents and/or provide insights that can guide clinical management. In chronic diseases the most substantive advances are likely to come not from technical improvements, but from investments in prospective serial sample collections and an appreciation that many diseases reflect intersections of genes and environment in a temporal context.

Acknowledgments

We thank our colleagues at the Scripps Research Institute, the University of California–Irvine, and Columbia University who have enabled our work in pathogen discovery over a period of more than 20 years. Current efforts are supported by National Institutes of Health awards AI062705, AI070411, HL083850-01, AI51292, AI056118, AI55466, AI57158 (Northeast Biodefense Center-Lipkin), NS047537, and EY017404.

THE POTENTIAL IMPORTANCE OF PRESYMPTOMATIC, HOST-BASED DIAGNOSIS IN BIODEFENSE AND STANDARD HEALTH CARE

Stephen Albert Johnston, Ph.D.[11]
Arizona State University

Abstract

Through programs such as BioShield, BioWatch, and BioSense we have created a first line of defense against traditional biothreats—our *Bio-Maginot Line*. However, the biotechnology revolution is driving the potential to create engineered pathogens that could circumvent these barriers. The increased risk inherent in this revolution is unstoppable, and efforts to control the risk through

[11]Professor, Life Sciences; director, Center for Innovations in Medicine, The Biodesign Institute.

regulation are probably unwise. Fortunately, for historical and technical reasons we may have a window of opportunity to get ahead of this threat curve. Key to this opportunity is the development of a diagnostic capability that could detect infections before symptoms appeared. This host-based detection system would be capable of detecting any type of threat agent—engineered or natural. Key aspects of this diagnostic system are that it would be capable of reading hundreds to thousands of blood, sputum, or urine components; rely on self-normalization by regular testing of individuals; and be widely distributed in homes. Evidence to date indicates that it may be possible to develop such a system. Obviously, its cost could not be justified by the unpredictable probability of a biothreat attack. Fortunately, the need for such a capability for biodefense is exactly in line with the need for the same capability to transform traditional medicine, most obviously for detecting natural outbreaks. The current health-care system is economically unsustainable. One solution to this crisis is to convert standard health practice from one that treats symptoms to one that detects disease very early—even presymptomatically. The convergence of the need for presymptomatic diagnosis capability, both for biodefense and standard medical practice, justifies an Apollo-like effort to create this technology.

Particularly since 9/11 there has been increasing concern about biological attacks. In the area of detection of attacks, we are relying on two basic strategies. One strategy, BioWatch, would have enough detectors distributed throughout the country to pick up airborne releases of pathogens. The hope is that a biothreat release would be detected before people develop symptoms. The problems with this strategy have been widely debated, but largely come down to the cost–benefit ratio of sustaining a system that would be effective. There is also the concern that engineered organisms would not be detected. The second major strategy is based on sufficient, organized surveillance of health-related data to detect early evidence of symptomatic people. The BioSense program is one example of this effort. Unlike BioWatch, this type of approach has a clear crossover advantage to standard medical practice. However, in the specific application to biothreat detection, it is dependent on detecting sick people.

Programs such as BioWatch (defined on page 4), BioShield,[12] and BioSense[13] have created a certain level of defense, largely against pathogens and scenarios based on analysis from the past century. This Bio-Maginot Line would provide a measure of defense against the obvious attack. As with the real Maginot Line, the concern is that the attack would go around the fortifications (Figure 3-10). Although no one can predict the risk of a future attack, let alone one that would

[12]On July 21, 2004, President Bush signed into law Project BioShield, which provides new tools to improve medical countermeasures protecting Americans against a chemical, biological, radiological, or nuclear (CBRN) attack (White House, 2004).

[13]BioSense is a national program intended to improve the nation's capabilities for conducting near real-time biosurveillance, enabling health situational awareness through access to existing data from health-care organizations across the country (CDC, 2007).

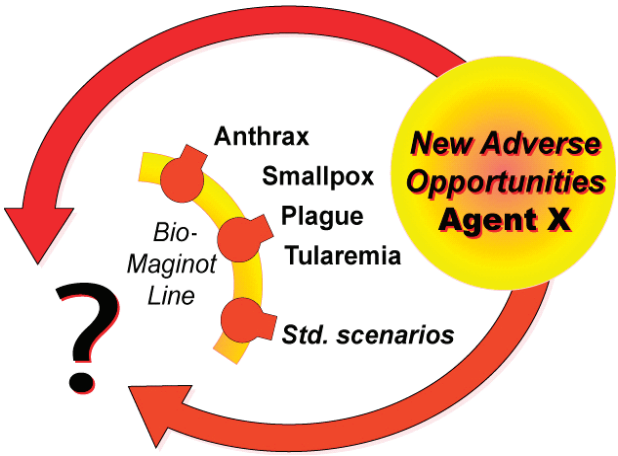

FIGURE 3-10 The Bio-Maginot Line.
SOURCE: Johnston (2006).

involve an engineered organism, there is little doubt that the threat will increase over time. As cartooned in Figure 3-11, this increase is largely due to the biotechnology revolution. The ability to both understand and manipulate life is increasing exponentially. Most measures of technological capability in biotechnology, like microchips, are obeying Moore's Law.[14] Whether it be growth in sequence deposits to GenBank (Figure 3-12), ability to sequence DNA, or facility at synthesizing genes, the revolution is amazing.

This revolution will drive remarkable change, but with it will come new opportunities for ill application. For example, the science of interfering RNAs started with some strange observations in plants in the 1990s. It progressed quickly to study in animal systems and now is standard technique for manipulating gene expression. The technology is offered as kits, and several biotechnology companies are pursuing its medical applications. A Nobel Prize was given for its discovery in 2006, a record time from discovery to prize. Yet it takes relatively little imagination to see how the incorporation of RNA interference (RNAi) constructs into viruses might augment their virulence. Almost every new technology in biotechnology and almost every new understanding of immunology and host–pathogen interactions could be configured to ill ends.

The same revolution that will drive dramatic new opportunities for contributions from biotechnology will increase the prospects for bad applications,

[14]Moore's Law states that computing power will double every 1.5 years. This prediction has largely held.

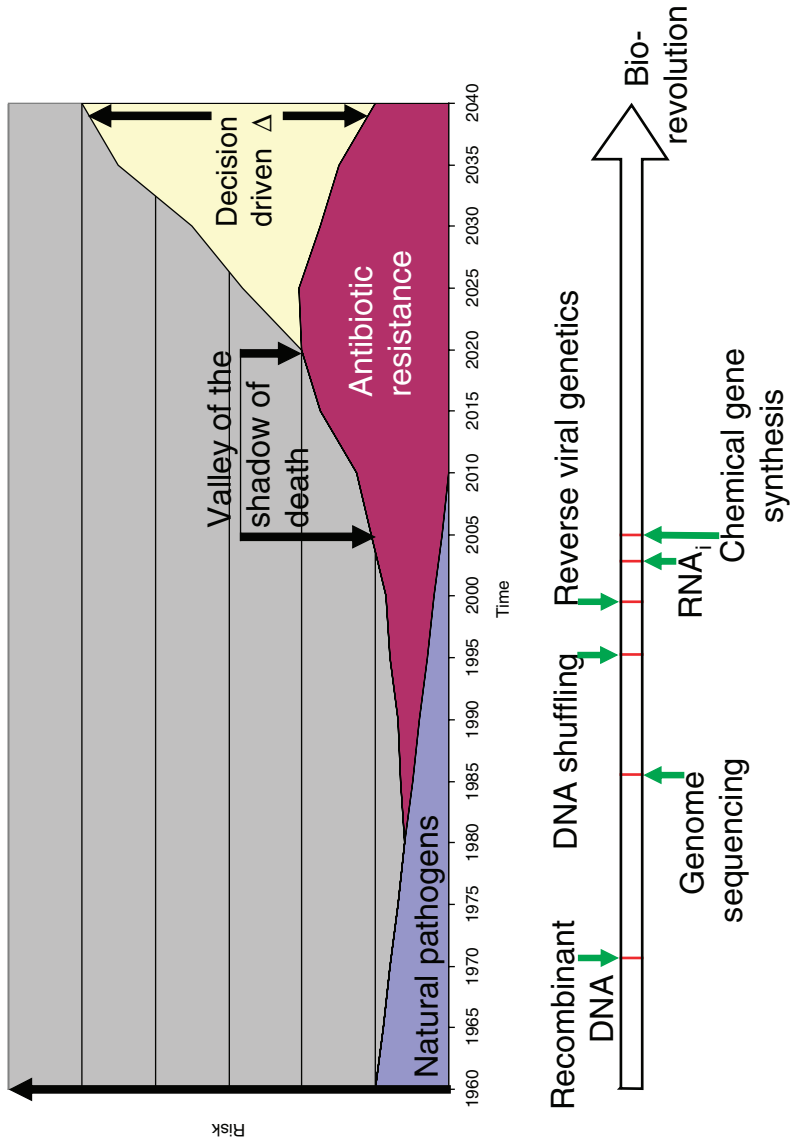

FIGURE 3-11 Changing spectrum of biothreat risk.
SOURCE: Johnston (2006).

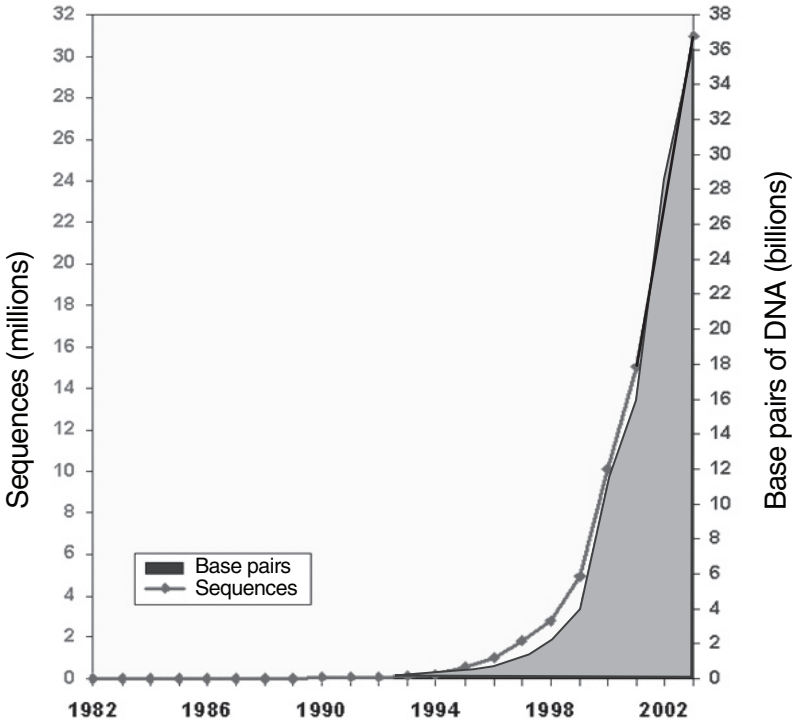

FIGURE 3-12 Growth of GenBank, 1982–2005.
SOURCE: NCBI (2007).

or even accidental events. The opportunities are dynamic. The sequence of any pathogen can be determined in one day. We are rapidly increasing our knowledge of host–pathogen interactions and the human immune response to infection. As stated above new technologies are being developed at a rapid pace. In addition, the ability to set up high-throughput screens is becoming more common. The combination of these trends will create the potential to create new pathogens (Figure 3-13).

The impact of these trends is clear. We are moving from a relatively simple threat space involving a list of potential pathogens and likely scenarios to one that has much higher dimensionality (Figure 3-14). The implications are that in the future, lists of relative importance of pathogens (e.g., Select Agent lists) and likely scenarios of attack are going to become, if they are not already, less useful.

That is the bad news. There is good news. For all the foreboding, a bioattack has not occurred since October 11, 2001. Why not if the risk is increasing? There are probably many explanations. One is that the Soviet biothreat program was

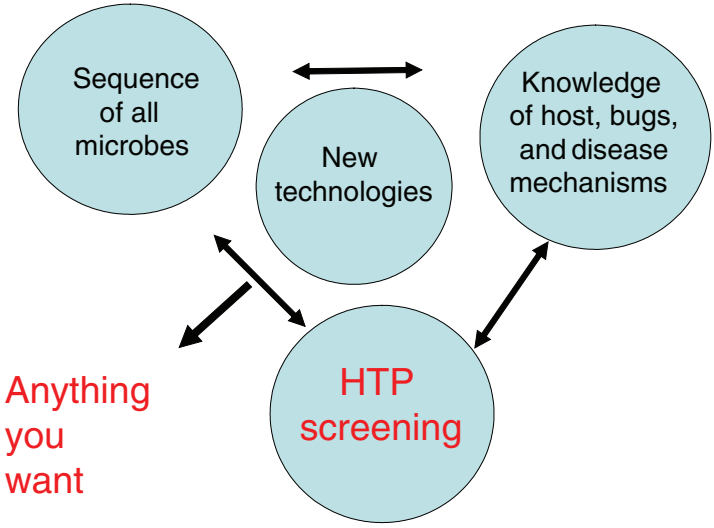

FIGURE 3-13 The combination of rapid knowledge and technological growth will create the potential to make new pathogens.
SOURCE: Johnston (2006).

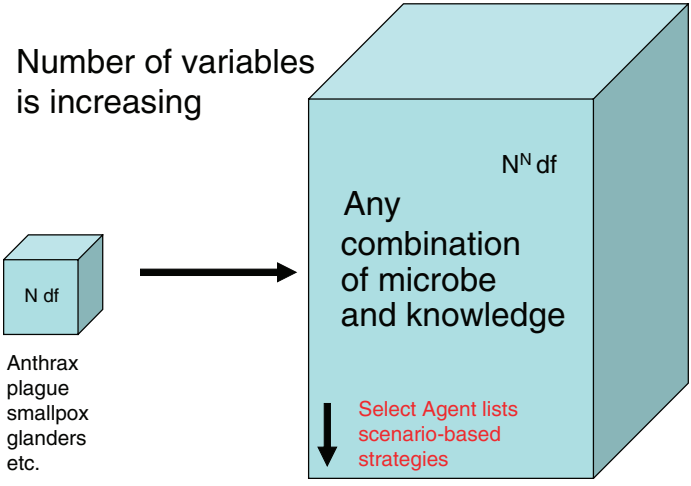

FIGURE 3-14 The threat space is becoming increasingly complex.
SOURCE: Johnston (2006).

decommissioned before the real revolution in biotechnology had penetrated their operation. Second, Islam has placed biology as a low science. This was reflected in the number of graduate students in biology versus engineering, though this trend may be changing. Finally, making biothreat agents is still not easy. It would involve multiple steps and specific reagents. Anything of this nature can easily have one step go wrong. Of course if enough attempts are made, one will likely succeed—but the odds are now in our favor.

We may now be in a grace period relative to preparing for a biological attack—the valley of the shadow of death (Figure 3-11). If we continue to base our preparedness on protection against specific pathogens or scenarios, we may be in trouble. An alternative is to invest in developing platform technologies and strategies that offer broad-based defense. Examples include developing systems to generate and validate vaccines rapidly, and creating strategies to quickly produce new therapeutics to new pathogens from preexisting modules. However, I think the most important shift in emphasis would be to host-based diagnosis to allow presymptomatic detection of infections. The ability to detect infections before they are symptomatic has obvious value to strategies from quarantine to antibiotic treatment. It also addresses the problem of detecting the release of a new pathogen as the sensing is the host itself. Detection is not dependent on knowing what pathogens might be used.

The premise for this concept is presented in Figure 3-15. All of the factors that determine a person's health status could be monitored in near-real time by

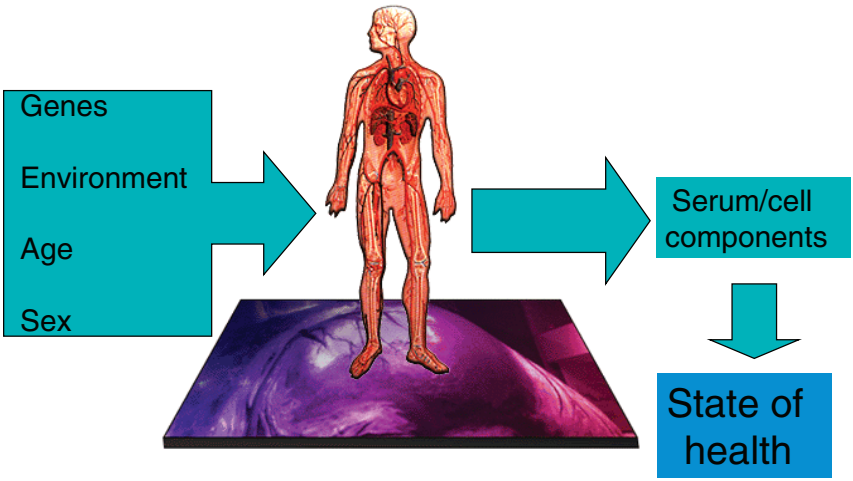

FIGURE 3-15 Biosignature pattern recognition in human diseases. Host-based presymptomatic detection of events.
SOURCE: Johnston (2006).

profiling all the components of blood. Blood chemistry, or that of sputum or urine, reflects changes in health, specifically early effects of infection. Continuous monitoring of blood components of healthy individuals would create their own biosignatures of health and disease (Figure 3-16), the ultimate in personalized diagnostics. Devices capable of generating such biosignatures are already in development. These units are aimed at a clinical setting largely for application to early detection or characterization of a specific illness, such as cancer. A DocInBox diagnostic device relevant to biodefense would have to be capable of detecting the early events of infection against the background of all other causes of change in health status.

This type of biosignature diagnosis has two distinctive features. Approximately 45 biomarkers are FDA approved. In contrast, biosignatures would involve measuring hundreds or possibly thousands of blood components. If the basis of disease could be anything, one has to sample broadly. Second, real-time and frequent monitoring of individuals would allow normalizing each person's bio-

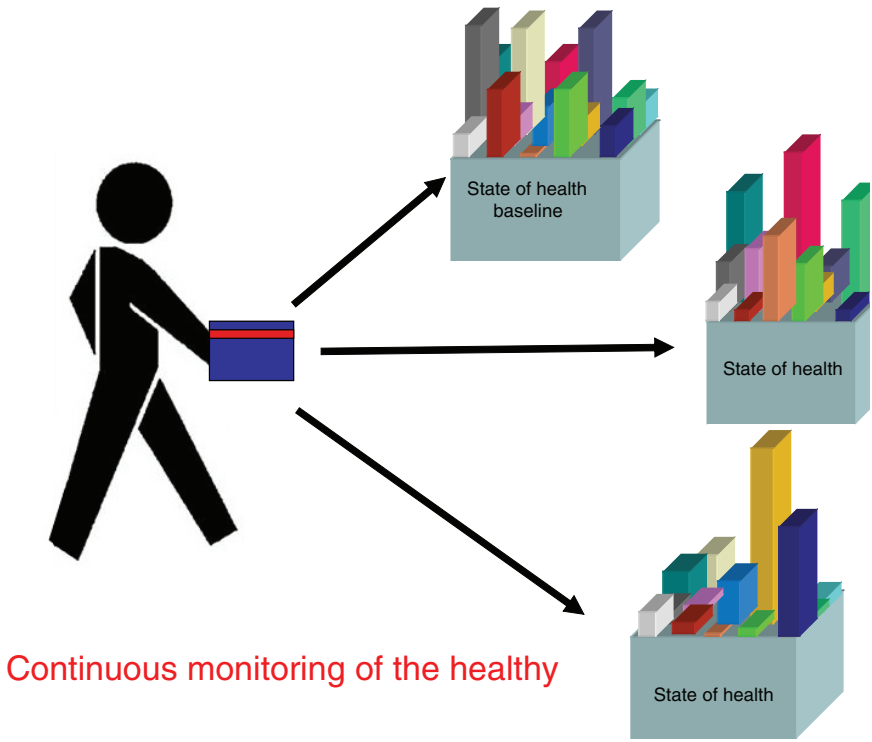

FIGURE 3-16 Personalized medicine based on biosignatures.
SOURCE: Johnston (2006).

signature to himself or herself. This is in contrast to traditional biomarkers where diagnosis is made based on values established in the population (Figure 3-17).

To meet these expectations the basic specifications for such a DocInBox are clear. To detect a pathogen release, the unit must work in near-real time. Most respiratory infections have a presymptomatic period of a few days at most (Figure 3-18). An assay system that takes a week to process has little value relative to infections, but would for other chronic ailments. If the goal is presymptomatic diagnosis obviously well people need to be monitored. Particularly for infectious disease, it follows that the diagnostic devices should be in the homes or places of work. Having these units in the physician's office or emergency room will do little good in detecting a biothreat release. If the units are to be dispersed in homes, their operation must be rugged and inexpensive.

There are two issues relative to the possibility of attaining this goal. First, is presymptomatic diagnosis of infections biologically feasible? The evidence is scant in this regard. This topic will be the focus of a more extensive review, but there are some positive indications. *In vitro* studies have shown that the transcription pattern of dendritic cells changes on exposure to pathogens and that different pathogens elicit different patterns (Huang et al., 2001). This is important as dendritic cells are in the first line of exposure to pathogens. Microarray analysis of human blood cells has shown that individual patterns can be monitored over time (Whitney et al., 2003). Finally, it appears that microarrays of gene expres-

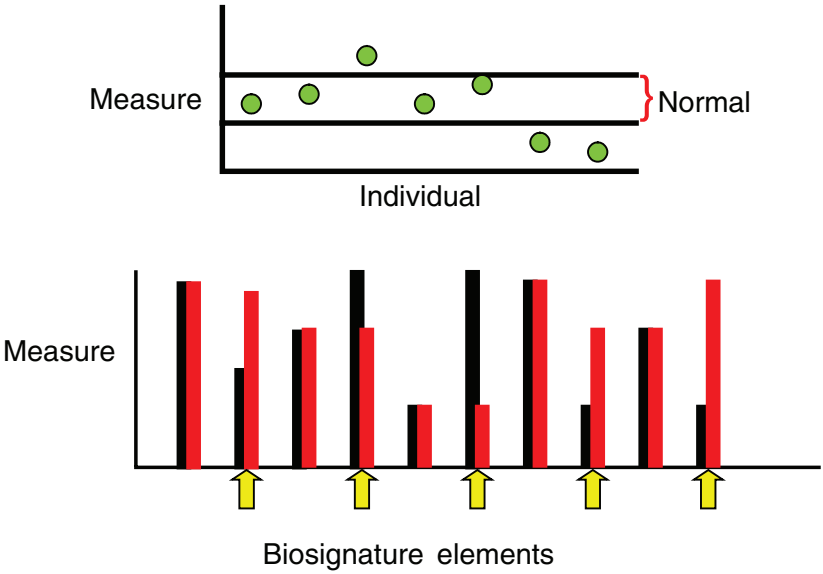

FIGURE 3-17 Biosignatures versus biomarkers.
SOURCE: Johnston (2006).

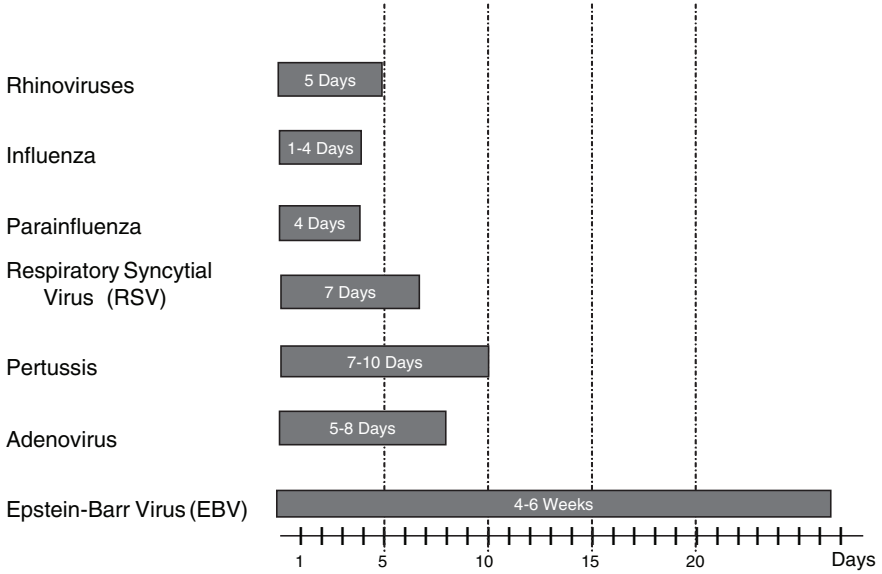

FIGURE 3-18 Upper respiratory disease incubation periods.
SOURCES: Adapted from Meneghetti (2006); Basu (1998); Smith et al. (2006).

sion can also detect presymptomatic responses in primates (Rubins et al., 2004). We have preliminary evidence (Johnston and Magee, unpublished) from a model of cowpox infection in mice that the infected mice can be distinguished from mock-infected mice three hours after infection, also by microarray analysis of blood cells. Clearly, more definitive studies of the limitations of presymptomatic diagnosis are needed.

The other issue is the technological challenge of creating the diagnostic system. This will be a formidable challenge. It will involve a coordinated, highly interdisciplinary effort that will include new instrumentation, modeling/algorithm development, data handling and transmission as well as judicious use of animal models and clinical testing (Figure 3-19). One challenge we have been addressing is how to develop the binding agents to measure thousands of blood components.

Though the technological challenges are great, such a diagnostic system is probably feasible. If developed it would be a major factor in preventing large-scale loss from a biothreat attack and may serve as a serious deterrent. However, the effort and cost to put such a system in place could not be justified based solely on the probability of a biothreat attack. Though its application to detection of natural outbreaks could be more easily supported, even this use would probably not drive an economic imperative to initiate this development program.

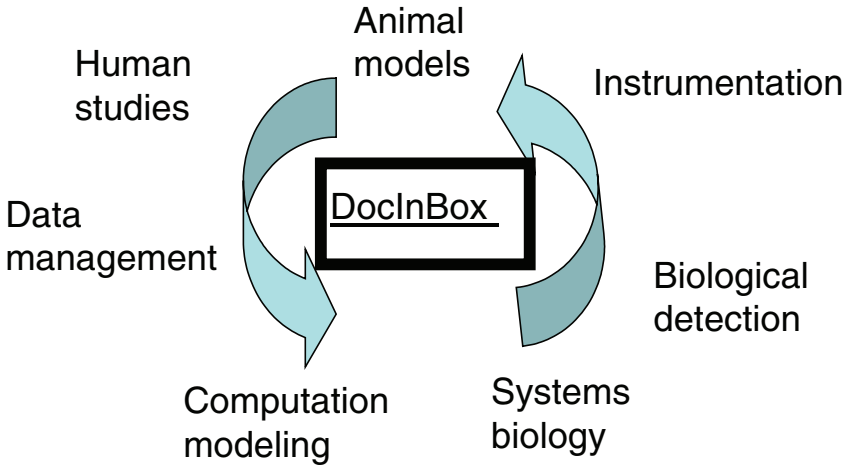

FIGURE 3-19 Program to create DocInBox diagnosis.
SOURCE: Johnston (2006).

Fortunately, a presymptomatic diagnostic system is also needed for another more easily justifiable application—the impending crisis in standard health care.

The cost of U.S. health care was approximately $2.2 trillion in 2006. This cost is estimated to be approximately $4 trillion by 2015 (Figure 3-20). Currently this cost accounts for approximately 19 percent of our Gross Domestic Product (GDP), rising to 25 percent or more by 2015 (Figure 3-21). By comparison, health-care costs have outpaced energy costs since the 1980s (Figure 3-22). Because most health costs are in the later years of life, with an aging population these trends are expected to continue (Figure 3-23). Clearly, we spend an enormous amount of our wealth on health care. If this investment contributes substantially to the productivity and creative output of the population it is money well spent. However, approximately 85 percent of this expenditure is on taking care of sick people and only about 15 percent on drugs and diagnostics. Our health-care system costs so much because it is largely postsymptomatic focused, and therefore centered on taking care of sick people. This system is clearly unsustainable economically. It will require either reducing care or revolutionizing medicine. If we opt for the latter, the key aspect will be converting medicine to a focus on presymptomatic diagnosis. A corollary of this transition will be improvement in quality of life. This will afford a "squaring" of the life curve (Figure 3-24) such that we not only live longer, but better.

We are fortunate that a key technology required for being prepared for the biothreats of the future is also the exact capability we have basically no choice but to develop for standard health care of the future, as well as for more prob-

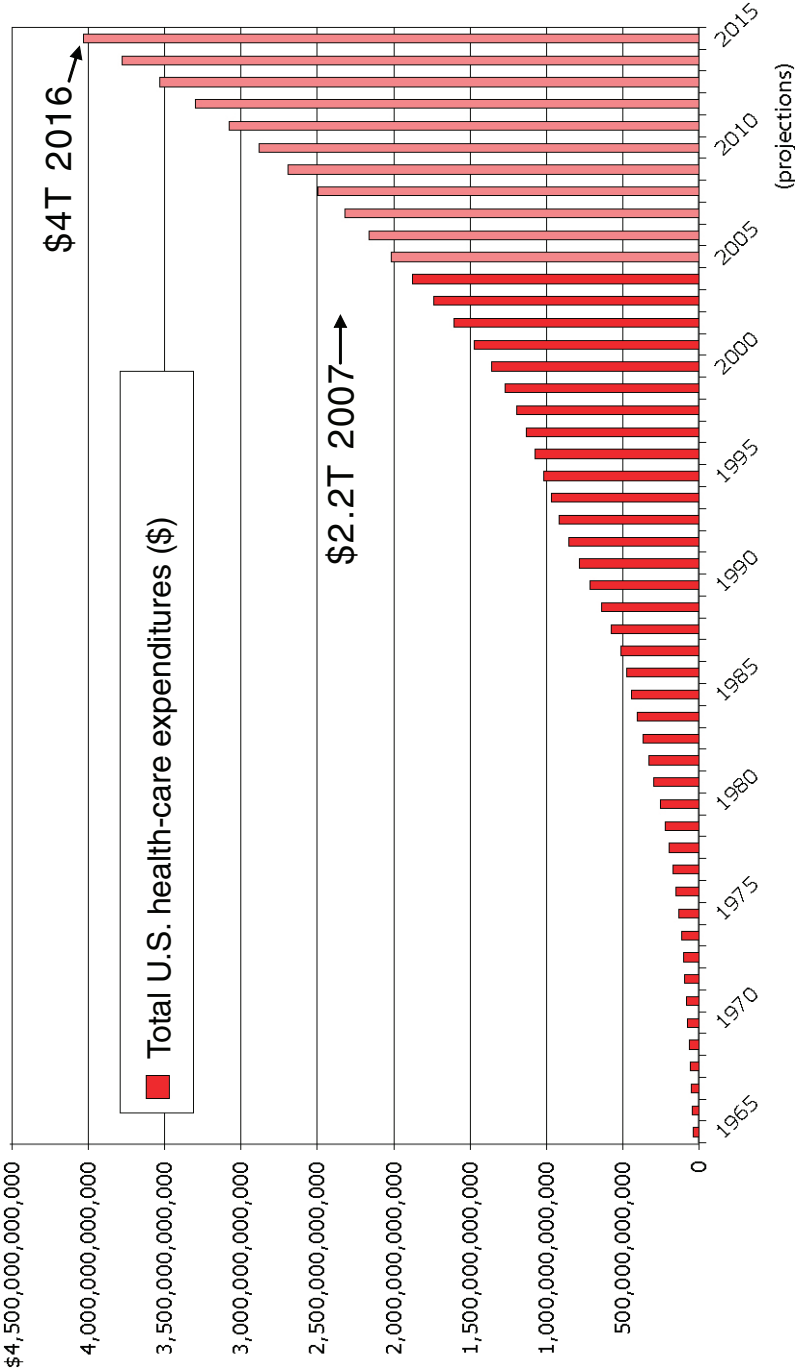

FIGURE 3-20 Health-care spending projections.
SOURCE: Adapted from HHS (2007).

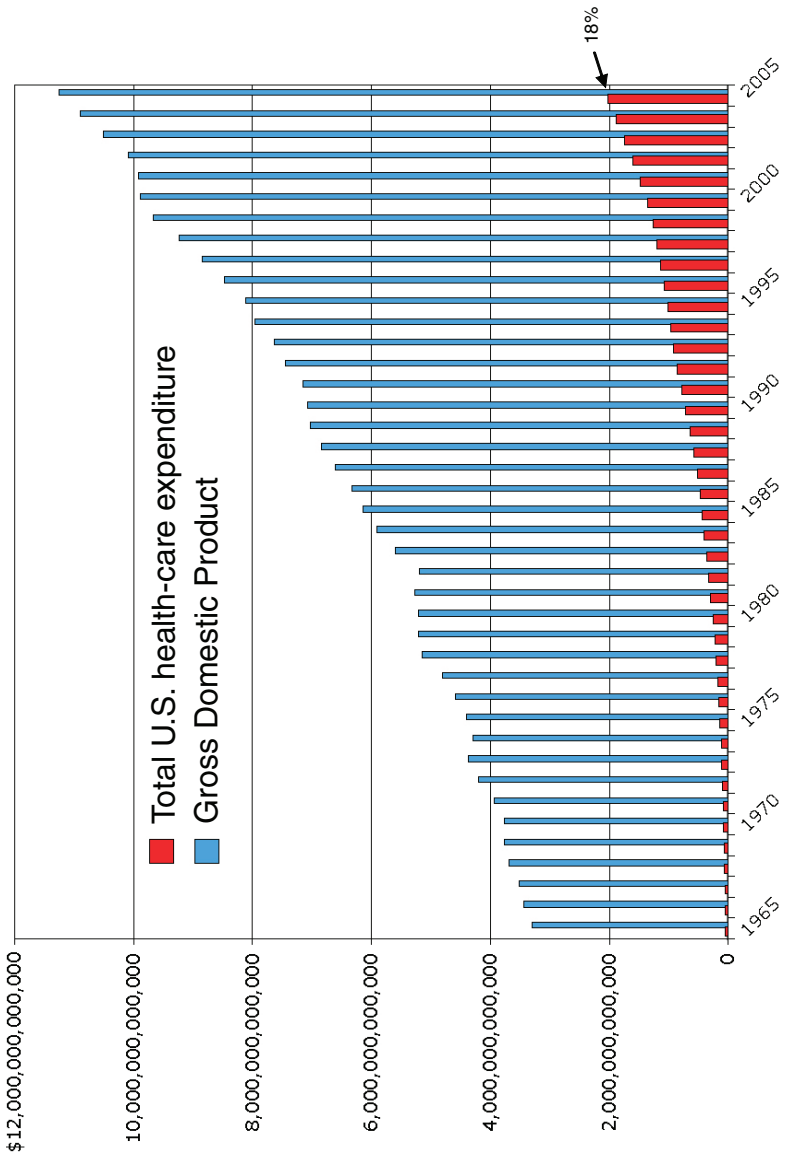

FIGURE 3-21 In 2005, 18 percent of GDP was spent on health care. By 2015, it is projected to be 25 to 30 percent.
SOURCE: Adapted from HHS (2007).

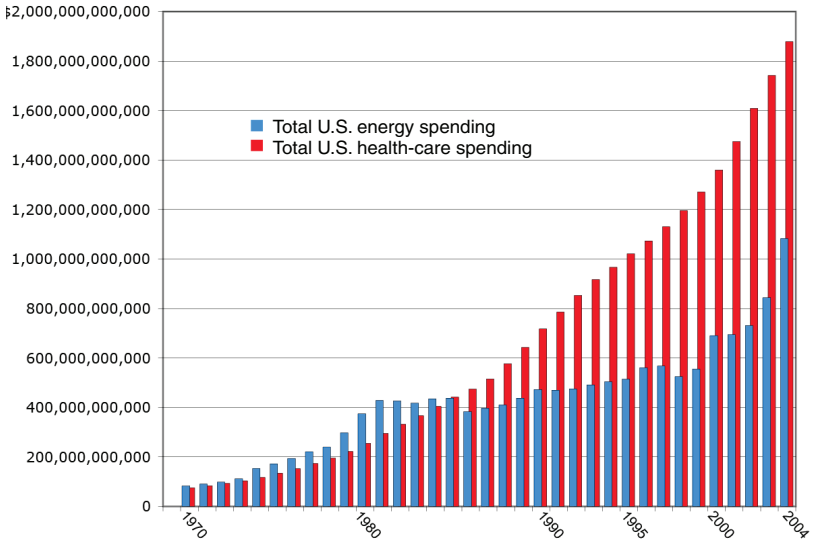

FIGURE 3-22 Comparison of U.S. spending on energy and health care, 1970–2004.
NOTE: The 2001 to 2004 numbers were projected based on oil prices. Total energy costs 2002–2004: Numbers are estimates based on extrapolation of energy price increase based on increases in petroleum prices, applied to Department of Defense known energy use figures. OPEC basket price averaged $50.71 per barrel in 2005, $36.05 per barrel in 2004, $28.10 per barrel in 2003, $24.36 per barrel in 2002, $23.12 per barrel in 2001, and $27.60 per barrel in 2000 (DoE, 2006).
SOURCES: EIA (2005); HHS (2007).

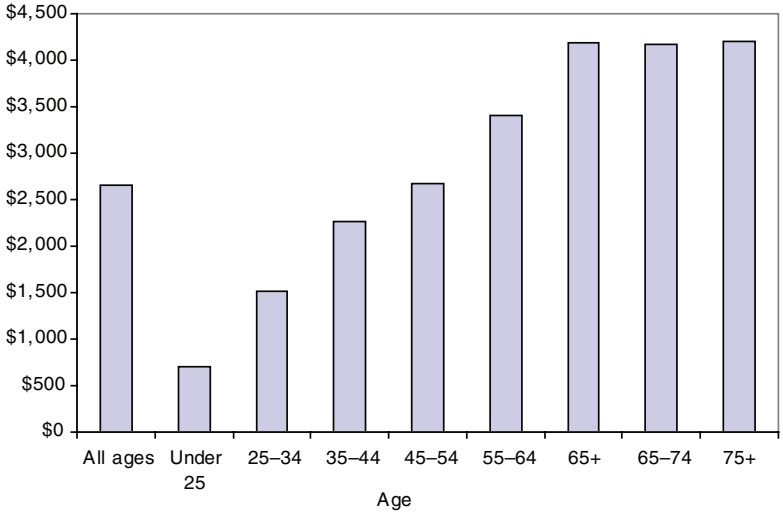

FIGURE 3-23 Average annual health-care expenditures by age, 2005.
SOURCE: DoL (2007).

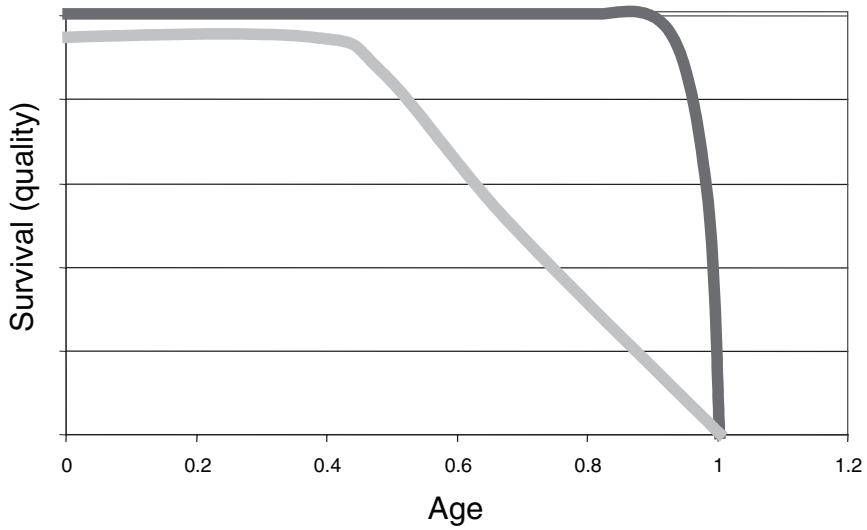

FIGURE 3-24 Human species needs to square life's curve: Higher quality = less cost. SOURCE: Johnston (2007).

able threats from natural infections. From the perspective of being prepared for engineered biothreats, we should take advantage of the valley of the shadow of death (Figure 3-11) to get ahead of the threat curve. Presymptomatic diagnosis should be a key element in this preparedness. From the perspective of standard of care, this same technology could be key to revolutionizing us as a species. Such potential merits an Apollo-like effort to complete.

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4

Resource Needs and Opportunities

OVERVIEW

Following workshop sessions that emphasized technical considerations for infectious disease surveillance, detection, diagnosis, and reporting, the final session focused on relevant issues in public health policy, many of which had been raised in prior discussions.

Global Coordination

The opening presentation, by Will Hueston, of the School of Public Health and College of Veterinary Medicine of the University of Minnesota, describes challenges in coordinating these vital public health activities. In his contribution to this chapter, Hueston adopts a business perspective to analyze key technical and social impediments to coordination. He explores how surveillance might be repurposed as part of a system of disease detection, reporting, and outbreak investigation; then he outlines political, technical, and educational measures that would support such reform. By way of conclusion, Hueston employs business strategic planning analysis to identify strengths, weaknesses, opportunities, and threats inherent in current approaches to addressing infectious diseases.

Following Hueston's presentation, a panel discussion explored diverse perspectives on resource needs and opportunities for infectious disease surveillance, detection, diagnosis, and reporting. William Karesh, who spoke in a previous session about infectious disease surveillance in animals (see Summary and Assessment and Chapter 1), concurred with Hueston's position that surveillance should be designed to answer questions of long-term importance, rather than of present-

day urgency. Noting that "society is healthier because more people understand health," Karesh advocated greater information sharing by public health officials as a way to reduce, rather than increase, panic in response to disease threats, and also to increase popular support for funding public health. He envisioned a two-way exchange of surveillance information, with the global public both supplying essential data and receiving the benefits of its meaningful interpretation.

Panelist James LeDuc, Director for Global Health in the Institute of Human Infections and Immunity at University of Texas Medical Branch, offered a concrete example of the potential for such "grassroots" surveillance: In Cambodia, a network of "semitrained" villagers with cell phones and Mopeds swab sick chickens and ducks to check for avian influenza and alert the health community to suspected human cases. Multinational companies represent another newly tapped source of global surveillance information; LeDuc noted that the Centers for Disease Control and Prevention (CDC) has established collaborations with a number of major companies operating in China, encouraging them to share signs of unusual disease activity. He also identified two recent developments at the World Health Organization (WHO) as significant opportunities for global coordination in addressing infectious disease: the appointment to Director-General of Margaret Chan, who has extensive experience in this area, and the ratification of the revised International Health Regulations (IHRs; see Summary and Assessment).

On Location and in the Lab

In contrast to the global perspective taken by LeDuc, panelists Marci Layton, Fernando Guerra, and Frances Downes offered local viewpoints on infectious disease surveillance and detection. Layton, who had previously discussed local public health surveillance as conducted by the New York City Department of Health and Mental Hygiene (DOHMH; see Summary and Assessment and Chapter 1 overview), reemphasized that public health is an essentially local pursuit, and that its most important asset is its infrastructure, particularly its workforce. While acknowledging advantages in disease detection conferred by the increasing volume of surveillance information available at the local level, she stressed the importance of passing this inevitably noisy data through a "public health filter," embodied in "an epidemiologist looking at the data, a physician interviewing other physicians to find out more deeply about a case, or field staff going out and investigating the case." This process converts raw surveillance data into "trustable" intelligence that avoids being premature or panic inducing, Layton said.

Guerra, Director of Health for San Antonio and Bexar County, Texas, works with a population much smaller than that of New York City, but one that is similarly diverse and changeable. His experiences in building and using surveillance systems, such as an immunization registry and tracking program, reveal the profound influence of social circumstances on public health and their potential contribution to "situational awareness" of disease threats, as discussed in prior

sessions (see Summary and Assessment). The terms of reference for syndromic surveillance need to be broadened, Guerra argued, and in particular should encompass psychosocial and environmental circumstances.

Downes, Laboratory Director for the Michigan Department of Community Health, discussed opportunities for improving infectious disease surveillance from the perspective of the public health laboratory. Her contribution to this chapter, which summarizes her presentation, describes the creation and strengthening of laboratory networks, the removal of barriers to disease reporting by laboratories, the role of information technologies, and the incorporation of syndromic surveillance and disease diagnosis in the field. Given its unique position as "the point at which laboratory science and public health surveillance intersect," the public health laboratory should lead the integration of nontraditional laboratory surveillance sources into public health surveillance, Downes observed.

Funding

Nearly every panel member discussed some aspect of funding, beginning with LeDuc's blunt assessment that support for government and academic research on public health is severely constrained, and will remain so for the foreseeable future. As a result, he said, investments in disease surveillance and detection must deliver the greatest value for money, and existing systems must be subject to ongoing evaluation. LeDuc advocated a "transparent independent investigation" of the federal BioSense (syndromic surveillance) and BioWatch (aerosol detection) programs to determine whether they are truly answering important questions. This would include considering the potential value of other questions and/or systems and their applicability to standard clinical practice, as well as for the detection of extraordinary disease threats. A similar argument was taken up by panelist and speaker Ian Lipkin, director of Columbia University's Greene Infectious Disease Laboratory (see Summary and Assessment and Chapter 3), who noted that thoughtful investments in the surveillance and detection of acute infectious disease may ultimately pay off in addressing chronic disease, in which infections and immunity appear to play a role. Recognizing that funding for surveillance tends to be tied to specific disease threats, LeDuc encouraged the development of systems that can be adapted to a broad range of conditions (e.g., from avian influenza to any infectious respiratory disease).

Layton identified investment in infrastructure as key to improved disease surveillance by DOHMH. "That means people," she explained. "It means field surveillance staff. It means public health nurses. It is physicians, laboratory support, environmental health scientists, veterinarians, and . . . information technology experts to allow us to process information and respond to it. Syndromic surveillance allows me to know what is going on in the city," she continued, "but the ability to do that [results from a] tremendous investment in staff infrastructure." Similarly, Downes noted that "the collection and analysis of surveillance data

is only one part of the challenge of responding to emerging infectious diseases. Epidemiologic and laboratory resources are needed to investigate early warning signals and take actions to interrupt continued disease transmission."

Workforce Issues

Several panelists identified a shrinking public health workforce as a challenge to infectious disease surveillance and detection, due in part to the relatively low salaries of public health professionals. To encourage the kind of interest and commitment necessary to produce the next generation of public health practitioners, Lipkin suggested engaging the media. "The number of kids who are interested in forensics as a result of CSI has gone up dramatically," he noted. "Why not do something similar in public health?" Karesh argued for rewarding researchers who pursue the public good as their primary goal; for example, those who release key information prior to publication, and those whose negative results are difficult to publish, despite their epidemiological value.

COORDINATION OF DISEASE SURVEILLANCE, DETECTION, DIAGNOSTICS, AND REPORTING

William D. Hueston, D.V.M., Ph.D.[1]
University of Minnesota

Most of the presentations at this forum have focused on the technical aspects of surveillance, diagnostics, and detection. My presentation will focus primarily on the challenges of coordination as a leadership responsibility and management imperative, with coordination defined from a business perspective: "Synchronization and integration of activities, responsibilities, and command and control structures to ensure that the resources are used most efficiently in pursuit of the specified objectives" (BusinessDictionary, 2007). Before I address these broad issues, however, I would like to introduce five technical impediments to the coordination of infectious disease surveillance across animal and public health.

Technical Impediments to Coordination

First, there is the challenge of incorporating surveillance into the information architecture of medical and veterinary medical business systems. Medical and veterinary facilities decide to implement information systems when the benefits outweigh the cost of installation and support. Most medical records systems are designed to collect and compile records to enhance business efficiency, an obvious benefit that reduces the volume of paper records and the personnel needed to

[1]College of Veterinary Medicine and School of Public Health.

compile the records. Generating bills and tracking cost center performance present different information management challenges than analyzing agent, host, and environment data to support surveillance systems and epidemiological analyses. Although the benefits of having a national or global surveillance system may be readily apparent on a societal level, there may not be a visible return on the investment required for an individual business to participate. Surveillance and epidemiology generally are viewed as public goods, that is, the benefits accrue to the whole society. Hence individual institutions and businesses often are reluctant to participate in national surveillance programs without some inducement such as government grants or preferred insurance rates, or some penalty, like a legal requirement for involvement. Understanding the "value proposition" is critical to forming productive collaborations.

A second challenge involves the lack of a common lexicon, so that certain terms have different meanings in different disciplines. Various ontologies exist to annotate biological terms such as the International Classification of Diseases (ICD) and Standardized Nomenclature for Medicine (SNOMED) for human medicine, and the Standardized Nomenclature for Veterinary Diagnoses and Operations (SNVDO) and Standardized Nomenclature for Veterinary Medicine (SNOVET) for veterinary medicine. The challenges of defining an integrated human/veterinary system are myriad, such as rectifying hand versus paw versus hoof naming conventions and adding population data—a cow is a member of a herd and a chicken a member of a flock, where the population data represent one element of the diagnosis. Although substantial progress has been made, no global standard has emerged for an ideal medical vocabulary for use in both human and veterinary medicine.

A third issue is the need for standardized communication protocols that enable surveillance, detection, and response systems to share data and results in real time. In this age of high-tech communications and increasing international travel, a classic example of the lack of standardization exists with the differences in cell phone or videotaping protocols between the United States and Europe. Agreeing on a standardized approach can be a monumental undertaking, such as establishing an animal identification system in the United States. The U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) worked for years with a variety of stakeholders to reach a decision to move ahead with a 15-character animal identification number, a 13-character group/lot identification number, and a 7-character premises identification number (USDA, 2006).

A fourth concern is how to secure the resources to support surveillance, particularly global surveillance. Despite widespread recognition of the importance of global surveillance for the public good, health-care systems are nationally based and, in a number of countries, funded largely by third-party payers and user fees. The development of the Global Early Warning Systems (GLEWS) in 2006 represents the first joint early warning and response system combining

and coordinating the separate surveillance activities of the World Organization for Animal Health (OIE[2]), the Food and Agricultural Organization of the United Nations (FAO), and the World Health Organization (WHO) (WHO, 2006). However, the GLEWS coverage is variable, reflecting huge differences in the capacity of individual countries in terms of their laboratory resources, trained personnel, internal surveillance systems, and reporting capabilities.

Confidentiality provides a final example of the technical challenges for coordination. Even when secure communications can be guaranteed, protecting individual privacy, proprietary business information, and sensitive national security data are topics of intense debate. Strategies like summarizing individual data to produce group statistics may obscure the very trends that are of public health interest. Differing objectives may bring those who provide the data and those who compile and report the data into conflict. Examples include "shunning" of individuals who test positive for a disease despite a low risk of transmission during casual social contact; regulatory action on voluntarily participating farms after detection of an agent of concern; changes in consumer purchasing patterns of finished products based on comparison of contamination rates on raw ingredients before processing; and imposition of trade restrictions following the voluntary reporting of an animal disease agent detection considered to pose only a limited risk to production agriculture, such as detection of a low-pathology strain of avian influenza in wild birds.

Paradigm Impediments to Coordination

Our collective approach to surveillance is framed by the prevailing paradigms of our society. Currently, coordination of disease surveillance, detection, diagnostics, and reporting is stymied by an overriding philosophical framework comprising our public health focus, our definition of health, our perspective on risk, our fascination with disease agents, our propensity to glorify emergency response, and our preoccupation with technology. A series of examples will help to illustrate these challenges:

- Despite the fact that public health surveillance is all about populations, we tend to think in terms of the individual. Individual stories galvanize public action as they personalize stories of illness, pain, and death. Betty Ford's breast cancer and Rock Hudson's AIDS diagnosis are often cited as turning points for U.S. public health policy for these diseases. Furthermore, our focus tends to be parochial, evaluating public health priorities from our personal and local perspectives rather than considering the world at large.
- We tend to define health as absence of disease; success as complete cure or eradication of an infectious disease scourge; the primary public health function

[2]Office International des Epizooties.

as rapid response to crises; and our compelling public health vision as zero risk. In stark contrast, physicians explain that we can achieve a high quality of life despite a number of illnesses and afflictions; economists argue that the focus on eradication of disease is not optimal use of our health-care dollars; decreasing prevention budgets contribute to the occurrence of crises needing rapid response; and scientists point out that zero risk is unachievable.

- All too often we focus our infectious disease resources on the agent, ignoring the web of causation, including genetics, host immunity, and social and environmental factors. By focusing disproportionately on the agent, we fail to adequately track host and environmental risk factors that contribute to the emergence and reemergence of infectious diseases and we are lulled into the erroneous conclusion that successful risk management depends on identification of the specific agent. However, agent identification was not a prerequisite for the public health heroes who made important contributions prior to the formulation of the germ theory of disease, such as Ignaz Semmelweis (whose advocacy of hand washing drastically reduced mortality due to puerperal fever) and John Snow (a father of epidemiology, who gathered evidence that linked the spread of cholera with water contaminated by waste from infected people).
- We are strongly influenced by what I call the "John Wayne mentality," which dictates that when something goes wrong, someone is to blame and that party must be hunted down and punished and thereby, the problem is solved (often this mindset results in a case of shooting the messenger). We wholeheartedly embrace the war metaphor, wherein public health wages battles against infectious diseases. Such conflicts have winners and losers, and it is our job to win; indeed, victory over infectious disease was prematurely declared by U.S. Surgeon General William H. Stewart in 1967 (IOM, 2006, particularly pp. 1-2).
- We are fascinated by technology. Even though few of us use even a fraction of the power of our computers or cell phones, we rush to upgrade to the latest and greatest improvement of speed, graphics, communications, and games software. While partially inured to the exaggerated claims of biotechnology, genomes, and pharmaceuticals, we still cling to the hope that technology will provide the silver bullet. When we complete careful reviews of our public health program failures, technology is rarely the culprit. The lack of people skills—including leadership and teamwork—is far more commonly cited as a major contributor to public health program underperformance than a shortage of technology. Disciplinary silos and professional egos are more damaging than absence of the latest "techno-solution" or "miracle-mycin."

Coordination as a Leadership and Management Imperative

The overall high health status of people and animals in the United States contributes to the prevailing attitude of "if it ain't broke, don't fix it." Our comparative good health also leads us to focus on the "disease du jour" or the crisis

of the moment rather than prioritizing our investments by the potential impact they can make on measures of population health such as infant mortality, risk factor avoidance, or adolescent pregnancy. In the absence of a headline-grabbing outbreak or the untimely demise of a celebrity, we are loath to fund surveillance systems that could anticipate such threats and trigger proactive prevention campaigns. Success in a disease control program often is met with reduced funding or elimination of the surveillance and disease detection programs on which the success was based. As an example, the successful U.S. campaigns against the zoonoses bovine brucellosis (undulant fever in humans) and bovine tuberculosis (one form of tuberculosis in humans) depended on a traceability system that allowed affected cattle detected at slaughter to be traced back to their herd of origin. Given the eradication successes, however, funding was dropped for the identification systems and the United States has slipped backward in its ability to trace cattle back to the farm of origin. While the most highly trained fire-fighting unit in most communities—that of its local airport—is rarely used, our tendency is to decommission surveillance, detection, diagnostic, and reporting infrastructures when the disease of concern becomes rare.

An Alternative World View

Coordinating surveillance requires that we "begin with the end in mind," as Stephen Covey memorialized (Covey, 1989). What is the surveillance intended to accomplish? Why is coordination important? How will the surveillance results be used? What benefits will the surveillance yield for those who are expected to participate? Presumably the overarching goal of coordinated surveillance is improvement of public health, that is, the health of the community. Public health involves identifying problems, setting priorities, formulating policies to address these priorities, promoting health and preventing illness, and providing access to health care.

Achieving these lofty public health goals requires a very different paradigm characterized by a global perspective, a focus on health, an ecosystem approach (agent, host, environment), a risk management goal, prioritization based on importance rather than urgency, and a commitment to working with people to manage the dilemmas rather than seeking a technology quick fix (Table 4-1).

We increasingly recognize that we live in a complex world of microbial ecology, a world in which microbes are ubiquitous and adaptive and in which disease and emergent disease is the norm rather than the exception. If we think of surveillance only in terms of agent detection, we will not be able to effectively manage these new risks. For example, initial responses to recent foodborne disease outbreaks in leafy greens demonstrated a lack of understanding of complex food production and distribution systems. These complex systems must incorporate multiple critical control points including the application of best practices and targeted monitoring and feedback loops.

TABLE 4-1 Current Public Health Paradigm and Alternative World View

Current Paradigm	Alternative World View
Health is absence of disease	Health is well-being (in mind, body, spirit)
Infectious disease is all about the agent	Infectious disease emerges at the convergence of agent, host, environment
Zero risk is achievable	Zero risk is unachievable; risk management is the goal
Success is eradication/cure	Success is homeostasis with microbes that are ubiquitous, constantly evolving and adapting
Public health function is to react	Public health function is health promotion
Reaction requires agent detection	Risk management can be successful whether or not microbe is identified
Urgency dictates priority	Surveillance informs policy and guides action on basis of importance
Answers lie solely in technology	Answers involve people, politics, partners

SOURCE: Hueston (2006).

Real-time surveillance of food products and their raw materials must be combined with quality control and food safety systems in processing and distribution, sensitive public health disease detection, prompt reporting, and rapid outbreak investigation. The entire food system must retain the flexibility to adjust its risk management strategies to changing risk factors (hosts, agents, and the environment) without waiting for outbreaks to occur. Without a dynamic and adaptive food safety system, significant resources will be squandered on useless activities such as large recalls announced after most of the product has already been consumed.

The Politics of Coordination

Coordination is all about politics, which I define as the interpersonal dynamics that occur whenever two or more people are gathered together. Politics of societies are influenced by culture, and the organizational culture of the various public health agencies and the regulated industries is as germane to the practice of public health as is ethnicity, gender, religion, and other factors. To coordinate—to harmonize in common action and effort—requires effective political processes over the long term. "People skills" are needed to build coordination and collaboration, yet the social sciences are rarely emphasized—or even mentioned—in the

programs that train doctors, public health professionals, veterinarians, and plant pathologists. Interpersonal and teamwork skills are described as "non-technical" or "soft skills" and omitted from the curriculum. As has been demonstrated time and time again, university faculties assume that students "ought to know all that stuff before they get into graduate school or professional school."

Toward Optimal Surveillance

The optimal surveillance system is integrated and dynamic, with ongoing data collection. Real-time analysis would generate information relevant to risk management that would in turn drive policy and action. This ideal surveillance system incorporates feedback processes, permitting continuous, evolutionary change. It would integrate information on infectious disease in humans, domestic animals, wildlife, and plants collected and maintained through cross-disciplinary collaboration such as plant pathologists working in public health or psychiatrists working in veterinary medicine.

What is the way forward toward such a "system of systems?" Beginning with the end in mind, we need to prioritize public health goals. We need to complement agent surveillance with host and environmental monitoring. We need to recognize that societal stability and economic security are critical for maintaining a functional public health infrastructure, and find ways to make "doing the right thing" both beneficial to society and profitable for the private sector. We need multiple functional models that will work in the developing world as well as in industrialized countries. The information systems we need to develop would support global public health. Finally, because we can anticipate many future challenges, we must incorporate capacity for adaptation into the design of integrated surveillance systems.

Changing the Prevailing Paradigms

There is no magic formula for changing paradigms. However, change can occur incrementally, by rewarding progress no matter how slow, and then identifying, documenting, and celebrating successes, large and small. Fostering paradigm change is difficult, requiring a number of simultaneous activities, including:

- We must nurture a new generation of public health professionals who adopt a holistic, global perspective of health, and who look for creative ways to manage risks. We need to imbue these emerging public health professionals with a commitment to transdisciplinary approaches. We also need to encourage them to embrace change and be adaptable in a world that will never be risk free.
- Combining experiential learning opportunities with more didactic educational approaches will enable our new public health professionals to be more

effective, to be more adaptive, to understand complex challenges and opportunities, and to manage the complex dilemmas of the future.

- We must establish a robust, global public health infrastructure that incorporates interoperable high- and low-tech solutions, such as the cell phone surveillance system described in this report (see Johnson and Blazes in Chapter 2). Like Voxiva, we need to bring cultural anthropologists into health delivery teams to examine motivators for promoting public health in different cultures.
- We must examine the ethics of surveillance, and in particular the question as to whether effectively contained disease outbreaks need be reported to the public. I found the HealthMap presentation (see Brownstein in Chapter 2) both exciting and frightening, because it labels countries as to whether or not they have a given infectious disease within their borders. Although that knowledge may help us to detect global disease patterns and target intervention resources, it also has the potential to set back international development, given that reports of infectious disease can lead to trade embargoes and reductions in tourism and investment. This, in turn, will decrease infectious disease reporting. Futhermore, labeling an entire country in terms of disease presence or absence acts against the recognizing potential to safely establish free zones or even agricultural enterprises within a country where a specific disease is widespread.
- Finally, we must build public–private partnerships for global health. While public funding will always be constrained by other societal demands, we can identify potential benefits of improving public health in ways that make sense to corporations. The private sector can move much faster and contribute a wider array of resources toward those shared public health goals than the public sector can.

Strengths, Weaknesses, Opportunities, and Threats

SWOT analysis emerged in the 1960s and 1970s as a strategic planning tool used to evaluate the ***S***trengths, ***W***eaknesses, ***O***pportunities, and ***T***hreats of a project or initiative. Looking at current disease surveillance, detection, diagnostics, and reporting systems, we can draw several conclusions from a brief SWOT analysis.

The public health dilemmas of infectious diseases are global, not local. While our local strengths include the vast array of technology and data at our disposal, our principal weakness is the disparate global environment in which we must operate, where countries vary greatly in terms of infrastructure capacity, human and fiscal resources, and commitment to public health. We are also plagued by the disconnect between surveillance and action, which is exacerbated by the misconception of surveillance as a goal, rather than as a means to an end.

Progress toward integrated, global surveillance is threatened by the potential for unintended consequences. The potential for surveillance to deepen the first-world/third-world divide is a huge threat to global coordination and collaboration. Thus we need to discuss the possible consequences—both intended and

unintended—with our stakeholders and the beneficiaries we serve, both domestically and globally.

A key opportunity lies in the possibility of developing an overarching, integrated, global surveillance plan that will take us out of our disciplinary silos—a plan that sets priorities based on global considerations of public health impacts and identifies the resources necessary for coordination. These priorities necessarily must balance the potential impact on and the degree of buy-in from the community that they are meant to serve. Experience has taught me that ideal solutions lacking community support will fail, while popular, partial solutions will succeed. We must be willing to address today's complex public health dilemmas one small step at a time. After all, as I am frequently reminded by a mentor, "slow progress is progress."

Finally, we have a tremendous opportunity to foster a new generation of global public health leaders who will catalyze coordination through very different paradigms than those held today. Progress toward coordinated surveillance will be accelerated by active transdisciplinary leadership development programs in global public health.

Defining Success

How can we measure our progress toward global coordination of infectious disease surveillance, detection, diagnostics, and reporting? A successful system will allow us to more effectively anticipate new threats and will adapt fluidly to manage risk under novel conditions. It will encourage the formation of public–private partnerships to support surveillance. New leaders will step forward to promote international collaboration toward shared goals. Finally, we will know we have succeeded when we can document incremental improvement in global public health.

IMPROVING INFECTIOUS DISEASE SURVEILLANCE AND DETECTION: A PUBLIC HEALTH LABORATORY PERSPECTIVE

Frances Pouch Downes, Dr.P.H.[3]
Michigan Department of Community Health

The practice of infectious disease surveillance has co-evolved with the public health laboratory to address important health concerns with ever-advancing technologies. This ongoing partnership is essential to the continued improvement of surveillance systems. Public health laboratories in the United States are major contributors of infectious disease reports. In Michigan, for example, 60 percent of all laboratory results in the Michigan Disease Surveillance System are received

[3]Laboratory Director.

from the state's public health laboratory. Nationally, public health laboratories perform more than 40 million tests annually and are responsible for generating 35 to 65 percent of all positive laboratory findings for reportable diseases (APHL, 2002).

This essay examines key opportunities for improving infectious disease surveillance from the perspective of the public health laboratory. These include the creation and strengthening of laboratory networks; the acknowledgment and removal of barriers to disease reporting by laboratories; the adoption and adaptation of information technologies by and for laboratory use; and the extension of the laboratory–surveillance partnership to refine and validate syndromic surveillance and rapid field diagnosis of reportable diseases.

Establishing Laboratory Networks

Surveillance benefits from the collection of comprehensive data from diverse sources, and public health laboratories can play an instrumental role in facilitating and garnering support for this process. The public health laboratory community increasingly has embraced the concept of laboratory networks that enable a wide variety of laboratories to contribute their testing results to surveillance and disease control databases. Examples of current and potential laboratory networks are described in the following paragraphs.

The National Laboratory System

In 2001, the Centers for Disease Control and Prevention (CDC) launched pilot programs in four states (Michigan, Minnesota, Nebraska, and Washington) to implement a National Laboratory System (NLS) of statewide laboratory networks (CDC, 2004). Since the initiation of the NLS, many public health laboratories have undertaken network development programs within their states that improve public health response and surveillance through partnerships with traditional and nontraditional partners, including clinical and hospital laboratories, health advocacy organizations, agriculture and veterinary laboratories, and commercial laboratories.

Integrated Surveillance Networks

The public health laboratory is the juncture at which medical laboratory science and public health surveillance intersect. Due to this unique position, the public health laboratory must provide the leadership to forge relationships that eventually will lead to the integration of nontraditional laboratory surveillance data sources into public health surveillance.

Recent infectious disease emergence and foodborne disease outbreaks demonstrate the need for public health surveillance to integrate nontraditional sources

of data. Peanut butter, fresh spinach, and tomatoes recently have been identified as vehicles of enteric bacterial infections. In these examples, improved access to, and monitoring of, agriculture and food processor laboratory results by public health practitioners may have enabled earlier identification of disease activity and outbreaks. Because most emerging infectious diseases are zoonotic, animal diagnostic testing is clearly another rich source of data to collect for improved surveillance of emerging, reemerging, or novel infections.

Technical and Professional Networks

Although network-building activities rarely involve increased screening or testing for public health laboratories themselves, public health laboratories undertaking these efforts frequently provide technical training (e.g., in rapid screening for bioterrorism agents), consultation (e.g., on antimicrobial resistance testing), and feedback (e.g., the use of laboratory reports for surveillance and outbreak response). Network development also encourages the development of best practice guidelines for tests of public health importance (e.g., rapid HIV testing, estimated glomerular filtration rate, cholesterol screening). Even simple efforts such as the development of educational materials or tools and presentations to remind laboratorians about the importance of their role in disease reporting, or the participation of public health laboratories in state and regional clinical laboratory professional organizations, can ultimately improve the completeness and timeliness of disease reporting. Equally important, technical and professional networks develop relationships among organizations that can work together to refine surveillance systems through the use of mechanisms such as electronic medical record exchanges and electronic laboratory reporting.

Addressing Barriers to Reporting

To improve the timeliness and completeness of reporting by laboratories, and thereby the quality of surveillance, the following critical barriers must be addressed.

Reporting Costs

The cost of preparing and shipping isolates and specimens to public health laboratories for reference and molecular epidemiology testing are not reimbursed by third-party insurance providers or public health agencies. Recent changes to the U.S. Postal Service (USPS) regulations prohibiting the use of the USPS for shipping infectious agents have only exacerbated this problem. For example, some states require that clinical laboratories submit their public health laboratory isolates of *Mycobacterium tuberculosis* and other microbes. These isolates must now be shipped to public health laboratories by commercial courier services that

attach a $50 surcharge to each infectious agent shipment. The burden of this cost is borne by the clinical or other originating laboratory and is not reimbursable by public or third-party insurers.

Shrinking Workforce

The medical laboratory is beginning to see the first signs of a looming shortage of trained professionals. Between 1980 and 2003, the number of medical technology programs declined from nearly 800 to 240, and the annual number of graduates of accredited programs declined from 6,184 to 1,668 (Personal communication, S. Anderson at the 2004 Clinical Laboratory Education Conference). The laboratory professional workforce will be exacerbated as the majority of the workforce reach retirement age in the next two decades. Less than 10 percent of the laboratory professional workforce is eligible for retirement now, but in the next 10 years, approximately 40 percent of the current workforce will be eligible, and in 15 years 62 percent will be eligible (Personal communication, S. Anderson at the 2004 Clinical Laboratory Education Conference). Vacancies due to an inadequate pool of qualified candidates translate into less time available to prepare and ship isolates and specimens to public health laboratories, prepare and submit reports of reportable diseases to public health agencies, and participate in training on emerging health issues and disease reporting.

Labor-Intensive Methods

Antigen detection and other simple point-of-care tests, among other emerging testing technologies, may be more rapid and require less equipment and labor. However, public health reference and molecular testing used to detect and investigate disease outbreaks often requires a microbial isolate. For example, isolates of suspect *Mycobacterium tuberculosis* must be available for public health testing using currently practiced methods for the public health testing of reference level identification (Metchock et al., 1999), antimicrobial susceptibility testing (NCCLS, 2003; Plikaytis, 1992), and genotyping (Cowan et al., 2002). Public health laboratories may need to perform more preliminary testing to obtain isolates from rapid test specimens and work with front-line practitioners to assure quality of point-of-care tests and collection of additional specimens for confirmatory and molecular epidemiology testing. Eventually, alternative public health laboratory confirmatory and typing methods that do not require microbial isolates will need to be developed.

Standardized Reporting

Laboratory testing to identify potential cases of reportable disease is increasingly performed for multiple states by commercial clinical laboratories. Com-

municable disease reporting requirements, however, vary from state to state. Reporting and isolate submission compliance by multistate laboratories will only improve when states standardize reporting and isolate submission lists and formats.

Adoption and Adaptation of Information Technology

Information technology that can improve current surveillance systems is available, but it has not been universally adopted. CDC's Public Health Information Network (PHIN)[4] standards make adopting this technology nationally feasible. As with the establishment of laboratory networks, trust and resources are needed to achieve data exchange between the clinical laboratory and public health surveillance systems in the following critical areas.

Electronic Laboratory Information System Reporting

As noted in the contribution by Joseph Lombardo (see Chapter 1), many hospitals use the Health Level Seven (HL-7) format, which can create a message from the originating laboratory information system and transfer it to a surveillance information system that captures and stores disease surveillance data for case investigation and data analysis. Widespread adoption of electronic laboratory reporting would eliminate the current slow, labor-intensive practice of transcription of results from a laboratory information system to a paper form and submission by mail or reentering results to a web-based interface with the surveillance system. Broader adoption of this faster and more complete method of laboratory reporting may require additional linkage to hospital information systems that contain patient-specific information not available in the laboratory information system. Also, resource commitment is required from both the clinical laboratory and the surveillance system to initiate and maintain electronic laboratory reporting.

Electronic Health Records

Regional initiatives are underway to develop electronic health record exchanges throughout the United States. While economics and quality of care are often the motivating forces in the development of the health information exchange networks, these networks can and should be designed and used for public health surveillance (and registry) reporting. Public health entities are able to

[4]The PHIN is CDC's vision for advancing fully capable and interoperable information systems in the many organizations that participate in public health. PHIN is a national initiative to implement a multiorganizational business and technical architecture for public health information systems (CDC, 2007).

receive patient-specific health information while still complying with the Health Insurance Portability and Accountability Act (HIPAA).[5]

The Role of the Laboratory in Syndromic Surveillance and Field Diagnosis

Syndromic Surveillance

Novel surveillance systems are being piloted and used in a variety of settings for a variety of uses. Laboratory-based reporting is highly specific but not sensitive; conversely, syndromic surveillance is very sensitive, but not specific. Syndromic surveillance systems are designed to detect large-scale events clustered in time and space. They will not detect low-frequency events like the first cases of disease outbreak.

Syndromic surveillance systems can complement, but cannot replace, traditional case and laboratory-based reporting systems. Syndromic surveillance system data should be validated periodically with traditional case confirmation and laboratory testing methods. It is also important to evaluate programmatic investments in syndromic surveillance early warning systems, such as BioSense and BioWatch, to determine if they have been used as intended and if the investment is warranted (GAO, 2005).

Field Diagnosis

Global public health surveillance and clinical patient care may benefit from easily performed microbe-specific rugged tests. The "gold standard" tests are essentially unavailable in many parts of the world and are often so time consuming that they stymie disease control efforts. Exciting advances in the development of field-ready diagnostics are resulting from public–private partnerships. However, investment in such technology should not supersede investments or precede efforts in total quality systems.

A comprehensive laboratory quality system approach is relevant for any test, whether it is complex or simple to perform, and in any testing setting, whether it is the traditional laboratory, the clinic, or the field (CLSI, 2004). Inaccurate results generated from unmonitored testing can lead to misdirected patient care, inaccurate disease reporting to surveillance systems, and wasted resources. When rugged, simple field tests are used, traditional microbiology also should be accessible to provide reference-level testing to detect emerging infectious diseases (i.e., microbes that will not be recognized by disease-specific tests) and to validate field tests on an ongoing basis.

[5]Enacted in 1996, HIPAA required the Department of Health and Human Services to establish national standards for electronic health-care transactions and national identifiers for providers, health plans, and employers. It also addressed the security and privacy of health data (HHS, 2005).

Conclusion

As investments are made in surveillance systems, it is also critical to commit adequate resources to analyzing and responding to the increased volume of surveillance data. For example, PulseNet[6]—a much-heralded early warning system for foodborne diseases—does not live up to its full potential due to inadequate resources for laboratory studies and epidemiology. Moreover, the collection and analysis of surveillance data is only one part of the challenge of responding to emerging infectious diseases. Epidemiologic and laboratory resources are needed to investigate early warning signals and to take effective actions to break the cycle of disease transmission.

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[6]PulseNet is a national network of public health and food regulatory agency laboratories coordinated by the CDC. The network consists of state health departments, local health departments, and federal agencies (CDC, U.S. Department of Agriculture/Food Safety and Inspection Service, Food and Drug Administration). PulseNet participants perform standardized molecular subtyping (or "fingerprinting") of foodborne disease-causing bacteria by pulsed-field gel electrophoresis (PFGE) in order to distinguish strains at the DNA level. DNA "fingerprints," or patterns, are submitted electronically to a dynamic database at CDC, allowing for rapid comparison of the patterns (CDC, 2006).

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Appendix A

Agenda

Global Infectious Disease Surveillance and Detection:
Assessing the Challenges—Finding Solutions
The National Academies
500 Fifth Street, NW – Room 100
Washington, DC
December 12–13, 2006

Tuesday, December 12, 2006

8:00 a.m.	Continental Breakfast
8:30 a.m.	Welcome and Opening Remarks P. Fred Sparling, M.D., Vice Chair Forum on Microbial Threats
8:45–9:15 a.m.	Keynote Address: "Syndromic Surveillance: Moving from Theory to Practice" Patrick W. Kelley, M.D., Dr.P.H. The National Academies
9:15–9:45 a.m.	Discussion

Session I:
Surveillance for Emerging, Reemerging, and Novel Infectious Diseases

Moderator: Col. Ralph Erickson, M.D., Department of Defense Global Emerging Infectious Surveillance and Response System

9:45–10:15 a.m.	Public Health Infectious Disease Surveillance Michael Stoto, Ph.D. Georgetown University
10:15–10:45 a.m.	Infectious Disease Surveillance: The "Local" Perspective Marci Layton, M.D. New York City Department of Health and Mental Hygiene
10:45–11:00 a.m.	Break
11:00–11:30 a.m.	Animal Disease Surveillance William Karesh, D.V.M. Wildlife Conservation Society
11:30 a.m.–12:00 p.m.	Plant Disease Surveillance and Detection Jacque Fletcher, Ph.D. Oklahoma State University Jim Stack, Ph.D. Kansas State University
12:00–12:30 p.m.	Open Discussion of Session I
12:30–1:15 p.m.	Lunch

Session II:
Infectious Disease Detection and Diagnostics

Moderator: David Relman, M.D., Stanford University

1:15–1:45 p.m.	Mark D. Perkins, M.D. Foundation for Innovative New Diagnostics (FIND)
1:45–2:15 p.m.	Stephen Johnston, Ph.D. Arizona State University

2:15–2:45 p.m.	Animal Disease Detection: Diagnostic Laboratory Perspective Alex Ardans, D.V.M. California Animal Health & Food Safety Laboratory System
2:45–3:00 p.m.	Break
3:00–3:30 p.m.	Rapid Infectious Disease Diagnostic Assays Mark Wolcott, Ph.D. U.S. Army Medical Research Institute of Infectious Diseases
3:30–4:00 p.m.	Discussion of the GreeneChip: A Panmicrobial Oligonucleotide Array for the Diagnosis of Infectious Diseases W. Ian Lipkin, M.D. Columbia University
4:00–5:00 p.m.	Open Discussion of Session II
5:00–5:45 p.m.	Open Discussion of Day 1
6:00–7:00 p.m.	Open Reception

Wednesday, December 13, 2006

8:00 a.m.	Continental Breakfast
8:30 a.m.	Opening Remarks/Summary of Day 1 Peggy Hamburg, Vice Chair Forum on Microbial Threats

Session III:
Current and Future Methods for Infectious Disease Surveillance, Reporting, and Communication

Moderator: Stephen S. Morse, Ph.D., Columbia University

8:40–9:10 a.m.	Discussion of ProMED-mail Stephen S. Morse, Ph.D. Columbia University

9:10–9:40 a.m.	Discussion of the Global Public Health Intelligence Network Abla Mawudeku, M.P.H. Global Public Health Intelligence Network
9:40–10:10 a.m.	Implications of "Real Time" and "Batch Reporting" for Surveillance Joseph Lombardo, Ph.D. The Johns Hopkins University Applied Physics Laboratory
10:10–10:30 a.m.	Break
10:30–11:00 a.m.	Using Cell Phone Technology for Infectious Disease Surveillance Pamela Johnson, Ph.D. Voxiva David Blazes, M.D., M.P.H. Naval Medical Research Unit, Peru
11:00–11:30 a.m.	HealthMap: A Global Disease Alert Mapping System John Brownstein, Ph.D. Harvard Medical School
11:30 a.m.–12:15 p.m.	Open Discussion of Session III
12:15–1:00 p.m.	Lunch

Session IV:
Infectious Disease Detection, Surveillance, and Reporting—Resource Needs and Opportunities

Moderator: Fred Sparling, M.D., University of North Carolina

1:00–1:30 p.m.	Coordination of Disease Surveillance, Detection, Diagnostics, and Reporting Will Hueston, D.V.M., Ph.D. University of Minnesota
1:30–3:30 p.m.	Discussion Panel • Marci Layton, M.D. New York City Department of Health and Mental Hygiene

- Fernando Guerra, M.D., M.P.H.
  San Antonio Department of Health
- Frances P. Downes, Dr.P.H.
  Michigan Public Health Laboratory
- W. Ian Lipkin, M.D.
  Columbia University
- James LeDuc, Ph.D.
  University of Texas Medical Branch

3:30–4:15 p.m.	Open Discussion of Session IV
4:15–4:30 p.m.	Closing Remarks/Adjourn

Appendix B

Acronyms

ALS	amyotrophic lateral sclerosis
APHIS	Animal and Plant Health Inspection Service
ARIMA	autoregressive moving average
ARS	Agricultural Research Service
BDV	Borna disease virus
BLAST	Basic Local Alignment Search Tool
BSN	Basic Surveillance Network
CBP	Customs and Border Protection
CDC	Centers for Disease Control and Prevention
cDNA	complementary DNA
CGIAR	Consultative Group on International Agriculture Research
cPCR	consensus polymerase chain reaction
CRP	Critical Reagents Program
CSREES	Cooperative State Research, Education, and Extension Service
DD	differential display
DHS	Department of Homeland Security
DoD	Department of Defense
DOHMH	Department of Health and Mental Hygiene (New York City)
DoI	Department of the Interior
DoS	Department of State
DOTS	directly observed therapy shortcourse

DSDD	domain-specific differential display
DSN	disease surveillance network
ECDC	European Center for Disease Control
ECL	electrochemiluminescence
ED	emergency department
EDR	Emerging Disease Reports
EFSA	European Food and Safety Authority
EISS	European Influenza Surveillance Scheme
EMEA	European Agency for the Evaluation of Medicinal Products
END	exotic Newcastle disease
ER	emergency room
ESSENCE	Electronic Surveillance System for the Early Notification of Community-Based Epidemics
EU	European Union
EWGLI	European Working Group for Legionella Infections
EWRS	Early Warning Response System
FAO	Food and Agriculture Organization of the United Nations
FAS	Federation of American Scientists
FDA	Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
FMD	foot-and-mouth disease
FTP	File Transfer Protocol
GAINS	Global Avian Influenza Network for Surveillance
GAO	Government Accountability Office
GEIS	Global Emerging Infections Surveillance and Response System
GIS	Geographic Information System
GLEWS	Global Early Warning and Response System
GOARN	Global Outbreak Alert and Response Network
GPHIN	Global Public Health Intelligence Network
GreenVrdB	Greene Viral Database
HCV	hepatitis C virus
HHA	hand-held assay
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL-7	Health Level Seven
HMM	Hidden Markov Models
HSPD	Homeland Security Presidential Directive

ICD	International Classification of Diseases
ICTV	International Committee on Taxonomy of Viruses
ICTVdB	International Committee on Taxonomy of Viruses Database
ICU	intensive care unit
IEEE	Institute of Electrical and Electronics Engineers
IHR	International Health Regulation
ILI	influenza-like illness
INSTEDD	International System for Total Early Disease Detection
IOM	Institute of Medicine
IPM	Integrated Pest Management
ISID	International Society for Infectious Diseases
IT	information technology
ITU	International Telecommunications Union
JBAIDS	Joint Biological Agent Identification and Diagnostic System
LEADERS	Lightweight Epidemiological Advanced Detection Emergency Response System
LOD	limit of detection
MedISys	Medical Intelligence System
MHC	major histocompatibility complex
MoH	Ministry of Health
mRNA	messenger RNA
MS	messaging system
NATO	North Atlantic Treaty Organization
NCBI	National Center for Biotechnology Information
NGO	nongovernmental organization
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NLS	National Laboratory System
NMRCD	Naval Medical Research Center Detachment
NPDN	National Plant Diagnostic Network
NPDRS	National Plant Disease Recovery System
NRC	National Research Council
NRDM	National Retail Data Monitor
OIE	World Organization for Animal Health
OIG	Office of the Inspector General

PCR	polymerase chain reaction
PDA	personal digital assistant
Pfam	Protein families database of alignments
PHIN	Public Health Information Network
PMM	ProMED-mail
ProMED	Program for Monitoring Emerging Diseases
RDA	representational difference analysis
RDP	Ribosomal Database Project
RDT	rapid diagnostic test
RFI	request for information
RODS	Real-Time Outbreak and Disease Surveillance System
RSS	Really Simple Syndication
RSVP	Rapid Syndrome Validation Project
RT-PCR	reverse transcriptase–PCR
SARS	severe acute respiratory syndrome
SD	standard deviation
SLEV	St. Louis encephalitis virus
SMS	short message service
SNOMED	Standardized Nomenclature for Medicine
SNOVET	Standardized Nomenclature for Veterinary Medicine
SNVDO	Standardized Nomenclature for Veterinary Diagnoses and Operations
SPC	statistical process control
SWOT	Strengths, Weaknesses, Opportunities, and Threats
SYRIS	Syndromic Reporting Information System
TaxID	Taxonomy identification
TB	tuberculosis
TED	Technology, Entertainment, and Design
TPA	tripropylamine
TRF	time-resolved fluorescence
USAID	U.S. Agency for International Development
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USDA	U.S. Department of Agriculture
USGS	U.S. Geological Survey
USPS	U.S. Postal Service
VPN	virtual private network

WCS	Wildlife Conservation Society
WHO	World Health Organization
WHO-OVL	Outbreak Verification List
Wildlife GAINS	Wildlife Global Animal Information Network for Surveillance
WNV	West Nile virus

Appendix C

Forum Member Biographies

Stanley M. Lemon, M.D. (*Chair*), is the John Sealy Distinguished University Chair and director of the Institute for Human Infections and Immunity at the University of Texas Medical Branch (UTMB) at Galveston. He received his undergraduate A.B. degree in biochemical sciences from Princeton University summa cum laude and his M.D. with honors from the University of Rochester. He completed postgraduate training in internal medicine and infectious diseases at the University of North Carolina at Chapel Hill and is board certified in both. From 1977 to 1983 he served with the U.S. Army Medical Research and Development Command, followed by a 14-year period on the faculty of the University of North Carolina School of Medicine. He moved to UTMB in 1997, serving first as chair of the Department of Microbiology and Immunology, then as dean of the School of Medicine from 1999 to 2004. Dr. Lemon's research interests relate to the molecular virology and pathogenesis of the positive-stranded RNA viruses responsible for hepatitis. He has had a long-standing interest in antiviral and vaccine development and has served previously as chair of the Anti-Infective Drugs Advisory Committee of the U.S. Food and Drug Administration (FDA). He is the past chair of the Steering Committee on Hepatitis and Poliomyelitis of the World Health Organization (WHO) Programme on Vaccine Development. He currently serves as a member of the U.S. Delegation of the U.S.–Japan Cooperative Medical Sciences Program, and he chairs the Board of Scientific Councilors of the National Center for Infectious Diseases (NCID) of the Centers for Disease Control and Prevention (CDC). He was co-chair of the Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats for the National Academy of Sciences (NAS), and he recently chaired an Institute of Medicine (IOM) study committee related to vaccines

for the protection of the military against naturally occurring infectious disease threats.

Margaret A. Hamburg, M.D. (*Vice-chair*), is vice president for Biological Programs at the Nuclear Threat Initiative, a charitable organization working to reduce the global threat from nuclear, biological, and chemical weapons. She is in charge of the biological program area. She completed her internship and residency in internal medicine at the New York Hospital/Cornell University Medical Center and is certified by the American Board of Internal Medicine. Dr. Hamburg is a graduate of Harvard College and Harvard Medical School. Before taking on her current position, she was the assistant secretary for planning and evaluation, U.S. Department of Health and Human Services (HHS), serving as a principal policy advisor to the secretary of health and human services with responsibilities including policy formulation and analysis, the development and review of regulations and legislation, budget analysis, strategic planning, and the conduct and coordination of policy research and program evaluation. Prior to this, she served for nearly six years as the commissioner of health for the city of New York. As chief health officer in the nation's largest city, her many accomplishments included the design and implementation of an internationally recognized tuberculosis control program that produced dramatic declines in tuberculosis cases, the development of initiatives that raised childhood immunization rates to record levels, and the creation of the first public health bioterrorism preparedness program in the nation. She currently serves on the Harvard University Board of Overseers. She has been elected to membership in the IOM, the New York Academy of Medicine, and the Council on Foreign Relations and is a fellow of the American Association for the Advancement of Science (AAAS) and the American College of Physicians.

P. Frederick Sparling, M.D. (*Vice-chair*), is the J. Herbert Bate Professor Emeritus of Medicine, Microbiology, and Immunology at the University of North Carolina (UNC) at Chapel Hill and is director of the North Carolina Sexually Transmitted Infections Research Center. Previously he served as chair of the Department of Medicine and chair of the Department of Microbiology and Immunology at UNC. He was president of the Infectious Diseases Society of America (IDSA) from 1996 to 1997. He was also a member of the IOM's Committee on Microbial Threats to Health (1991–1992). Dr. Sparling's laboratory research is in the molecular biology of bacterial outer membrane proteins involved in pathogenesis, with a major emphasis on *gonococci* and *meningococci*. His current studies focus on the biochemistry and genetics of iron-scavenging mechanisms used by *gonococci* and *meningococci* and the structure and function of the *gonococcal porin* proteins. He is pursuing the goal of a vaccine for gonorrhea.

David W. K. Acheson, M.D., is chief medical officer at the FDA's Center for Food Safety and Applied Nutrition. He received his medical degree at the Uni-

versity of London. After completing internships in general surgery and medicine, he continued his postdoctoral training in Manchester, England, as a Wellcome Trust research fellow. He subsequently was a Wellcome Trust training fellow in Infectious Diseases at the New England Medical Center and at the Wellcome Research Unit in Vellore, India. He was associate professor of medicine, Division of Geographic Medicine and Infectious Diseases, New England Medical Center, until 2001. He then joined the faculties of the Department of Epidemiology and Preventive Medicine and Department of Microbiology and Immunology at the University of Maryland Medical School. Currently at FDA, Dr. Acheson's research concentration is on foodborne pathogens and encompasses a mixture of molecular pathogenesis, cell biology, and epidemiology. Specifically, his research focuses on Shiga toxin-producing *E. coli* and understanding toxin interaction with intestinal epithelial cells using tissue culture models. His laboratory has also undertaken a study to examine Shiga toxin-producing *E. coli* in food animals in relation to virulence factors and antimicrobial resistance patterns. More recently, Dr. Acheson initiated a project to understand the molecular pathogenesis of *Campylobacter jejuni*. Other studies have undertaken surveillance of diarrheal disease in the community to determine causes, outcomes, and risk factors of unexplained diarrhea. Dr. Acheson has authored or coauthored more than 72 journal articles and 42 book chapters and reviews, and he is coauthor of the book *Safe Eating* (Dell Health, 1998). He serves as a reviewer for more than 10 journals and is on the editorial boards of *Infection and Immunity* and *Clinical Infectious Diseases*. He is a fellow of the Royal College of Physicians and a fellow of the Infectious Diseases Society of America, and he holds several patents.

Ruth L. Berkelman, M.D., is the Rollins Professor and director of the Center for Public Health Preparedness and Research at the Rollins School of Public Health, Emory University in Atlanta. She received her A.B. from Princeton University and her M.D. from Harvard Medical School. Board certified in pediatrics and internal medicine, she began her career at CDC in 1980 and later became deputy director of NCID. She also served as a senior advisor to the director, CDC, and as assistant surgeon general in the U.S. Public Health Service. In 2001 she came to her current position at Emory University, directing a center focused on emerging infectious disease and other urgent threats to health, including terrorism. She has also consulted with the biologic program of the Nuclear Threat Initiative and is most recognized for her work in infectious diseases and disease surveillance. She was elected to the IOM in 2004. Currently a member of the Board on Life Sciences of The National Academies, she also chairs the Board of Public and Scientific Affairs at the American Society of Microbiology (ASM).

Enriqueta C. Bond, Ph.D., is president of the Burroughs Wellcome Fund. She received her undergraduate degree from Wellesley College, her M.A. from the University of Virginia, and her Ph.D. in molecular biology and biochemical

genetics from Georgetown University. She is a member of the IOM, the AAAS, the ASM, and the American Public Health Association. Dr. Bond serves on the council of the IOM as its vice chair; she chairs the Board of Scientific Counselors for NCID at CDC, and she chairs the IOM's Clinical Research Roundtable. She serves on the board and the executive committee of the Research Triangle Park Foundation and on the board of the Medicines for Malaria Venture. Prior to being named president of the Burroughs Wellcome Fund in 1994, she had served on the staff of the IOM since 1979, becoming the IOM's executive officer in 1989.

Roger G. Breeze, Ph.D., received his veterinary degree in 1968 and his Ph.D. in veterinary pathology in 1973, both from the University of Glasgow, Scotland. He was engaged in teaching, diagnostic pathology, and research on respiratory and cardiovascular diseases at the University of Glasgow Veterinary School from 1968 to 1977 and at Washington State University College of Veterinary Medicine from 1977 to 1987, where he was professor and chair of the Department of Microbiology and Pathology. From 1984 to 1987 he was deputy director of the Washington Technology Center, the state's high-technology sciences initiative, based in the College of Engineering at the University of Washington. In 1987, he was appointed director of the U.S. Department of Agriculture's (USDA's) Plum Island Animal Disease Center, a biosafety level 3 facility for research and diagnosis of the world's most dangerous livestock diseases. In that role he initiated research into the genomic and functional genomic basis of disease pathogenesis, diagnosis, and control of livestock RNA and DNA virus infections. This work became the basis of U.S. defense against natural and deliberate infection with these agents and led to his involvement in the early 1990s in biological weapons defense and proliferation prevention. From 1995 to 1998, he directed research programs in 20 laboratories in the Southeast for the USDA Agricultural Research Service before going to Washington, DC, to establish biological weapons defense research programs for USDA. He received the Distinguished Executive Award from President Clinton in 1998 for his work at Plum Island and in biodefense. Since 2004 he has been chief executive officer of Centaur Science Group, which provides consulting services in biodefense. His main commitment is to the Defense Threat Reduction Agency's Biological Weapons Proliferation Prevention program in Europe, the Caucasus, and Central Asia.

Steven J. Brickner, Ph.D., is research advisor, antibacterials chemistry, at Pfizer Global Research and Development. He received his Ph.D. in organic chemistry from Cornell University and was a National Institutes of Health (NIH) postdoctoral research fellow at the University of Wisconsin–Madison. He is a medicinal chemist with nearly 20 years of research experience in the pharmaceutical industry, all focused on the discovery and development of novel antibacterial agents. He is an inventor or coinventor on 21 U.S. patents and has published numerous scientific papers, primarily within the area of the oxazolidinones. Prior to join-

ing Pfizer in 1996, he led a team at Pharmacia and Upjohn that discovered and developed linezolid, the first member of a new class of antibiotics to be approved in the past 35 years.

Nancy Carter-Foster, M.S.T.M., is senior advisor for health affairs for the U.S. Department of State, assistant secretary for science and health, and the secretary's representative on HIV/AIDS. She is responsible for identifying emerging health issues and making policy recommendations for U.S. foreign policy concerns regarding international health, and she coordinates the department's interactions with the nongovernmental community. She is a member of the IDSA and the AAAS. She has helped bring focus to global health issues in U.S. foreign policy and has brought a national security focus to global health. In prior positions as director for congressional and legislative affairs for the Economic and Business Affairs Bureau of the U.S. Department of State, foreign policy advisory to the majority whip of the U.S. House of Representatives, trade specialist advisor to the House of Representatives Ways and Means Trade Subcommittee, and consultant to the World Bank, Asia Technical Environment Division, Ms. Carter-Foster has worked on a wide variety of health, trade, and environmental issues amassing in-depth knowledge and experience in policy development and program implementation.

Gail H. Cassell, Ph.D., is vice president of Scientific Affairs, Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly & Company. Previously she was the Charles H. McCauley Professor and, beginning in 1987, the chair of the Department of Microbiology, University of Alabama Schools of Medicine and Dentistry at Birmingham, a department which, under her leadership, ranked first in research funding from NIH since 1989. She is a member of the Director's Advisory Committee of CDC. Dr. Cassell is past president of the ASM and is serving her third 3-year term as chair of the Public and Scientific Affairs Board of the ASM. She is a former member of the NIH Director's Advisory Committee and a former member of the Advisory Council of the National Institute of Allergy and Infectious Diseases. She has also served as an advisor on infectious diseases and indirect costs of research to the White House Office on Science and Technology and was previously chair of the Board of Scientific Counselors of NCID at CDC. She served 8 years on the Bacteriology-Mycology-II Study Section and served as its chair for 3 years. She serves on the editorial boards of several prestigious scientific journals and has authored more than 275 articles and book chapters. She has been intimately involved in the establishment of science policy and legislation related to biomedical research and public health. Dr. Cassell has received several national and international awards and an honorary degree for her research on infectious diseases.

Bill Colston, Ph.D., is currently the division leader for the Chemical and Biological Countermeasures Division at Lawrence Livermore National Laboratory

(LLNL). This newly formed division consists of four programs whose missions include threat awareness, detection, response, and attribution. These programs are made up of approximately 190 researchers from a variety of disciplines. The mission of these programs is to provide science, technology, and deployed capabilities to defend the nation, its people, and warfighters against the threat of biological and chemical terrorism. The larger vision is to meet the challenges of an ever-changing threat by transforming our understanding of pathogenicity and host response and expanding our reach globally. Dr. Colston holds a Ph.D. in biomedical engineering and has published numerous publications and patents, largely in biological measurement sciences. Directly prior to this assignment, he founded the Department of Homeland Security's Biodefense Knowledge Center.

Col. Ralph (Loren) Erickson, M.D., Dr.P.H., M.P.H., is the director of the Department of Defense Global Emerging Infections Surveillance and Response System (DoD-GEIS) headquartered in Silver Spring, Maryland. He holds a B.S. degree in chemistry from the University of Washington, an M.D. from the Uniformed Services University of the Health Sciences, an M.P.H. from Harvard, and a Dr.P.H. from Johns Hopkins. Residency trained and board certified in preventive medicine, Dr. Erickson has held a number of leadership positions within the Army Medical Department, including: director of the General Preventive Medicine Residency Program, Walter Reed Army Institute of Research; director of Epidemiology and Disease Surveillance, U.S. Army Center for Health Promotion and Preventive Medicine; commander of the U.S. Army Center for Health Promotion and Preventive Medicine (Europe); and specialty leader for all U.S. Army preventive medicine physicians.

Mark B. Feinberg, M.D., Ph.D., is vice president for Policy, Public Health, and Medical Affairs in the Merck Vaccine Division of Merck & Co., Inc. He received his bachelor's degree magna cum laude from the University of Pennsylvania in 1978 and his M.D. and Ph.D. from Stanford University School of Medicine in 1987. From 1985 to 1986, Dr. Feinberg served as a project officer for the Committee on a National Strategy for AIDS of the IOM and the NAS. Following receipt of his M.D. and Ph.D., he pursued postgraduate residency training in internal medicine at the Brigham and Women's Hospital of Harvard Medical School and postdoctoral fellowship research in the laboratory of Dr. David Baltimore at the Whitehead Institute for Biomedical Research. From 1991 to 1995, Dr. Feinberg was an assistant professor of medicine, microbiology, and immunology at the University of California, San Francisco (UCSF), where he also served as an attending physician in the AIDS/Oncology Division and as director of the Virology Research Laboratory at San Francisco General Hospital. From 1995 to 1997, he was a medical officer in the Office of AIDS Research in the office of the director of NIH, and chair of the NIH Coordinating Committee on AIDS Etiology and Pathogenesis Research. During this period, he also served as executive secretary of the NIH

Panel to Define Principles of Therapy of HIV Infection. Prior to joining Merck in 2004, Dr. Feinberg served as professor of medicine and microbiology and immunology at the Emory University School of Medicine and as an investigator at the Emory Vaccine Center. He also founded and served as the medical director of the Hope Clinic—a clinical research facility devoted to the clinical evaluation of novel vaccines and to translational research studies of human immune system biology. At UCSF and Emory, Dr. Feinberg and colleagues were engaged in the preclinical development and evaluation of novel vaccines for HIV and other infectious diseases and in basic research studies focused on revealing fundamental aspects of host–virus relationships that underlie the pathogenesis of HIV and simian immunodeficiency virus infections. In addition to his other professional roles, he has also served as a consultant to, and member of, several committees of the IOM and the NAS.

J. Patrick Fitch, Ph.D., is laboratory director for the National Biodefense Analysis and Countermeasures Center (NBACC) and the president of Battelle National Biodefense Institute, LLC (BNBI). BNBI manages and operates the NBACC national laboratory for the Department of Homeland Security as a Federally Funded Research and Development Center established in 2006. The NBACC mission is to provide the nation with the scientific basis for awareness of biological threats and attribution of their use against the American public. Dr. Fitch joined Battelle in 2006 as vice president for Biodefense Programs after more than 20 years of experience leading multidisciplinary applied science teams at the University of California's Lawrence Livermore National Laboratory. From 2001 to 2006, he led the LLNL Chemical and Biological National Security Program (CBNP), with applied science programs from pathogen biology and material science to deployed systems. CBNP accomplishments include performing more than 1 million assays on national security samples; setting up and operating 24/7 reach-back capabilities; setting up a nationwide bioalert system; receiving three R&D 100 awards; designing signatures for validated assays in the CDC Laboratory Response Network and the National Animal Health Laboratory Network; and designing, demonstrating, and deploying the BASIS biodetection system, leading to the nationwide BioWatch system. He has authored several books and book chapters, including *An Engineering Introduction to Biotechnology*. He has chaired and served on several panels of The National Academies. His advisory board activities have included U.S. Animal Health Association, Texas A&M University DHS Center of Excellence, Central Florida University (College of Engineering), Colorado State University (College of Engineering), California State Breast Cancer Research Program, and *Biomolecular Engineering*. Dr. Fitch was a fellow of the American Society for Laser Medicine and Surgery and an associate editor of *Circuits, Systems and Signal Processing*. He has received two national awards for medical devices, a technical writing award for an article in *Science*, and an international best paper award from the Institute of Electrical

and Electronics Engineers (IEEE). He also coinvented the technology, developed the initial business plan, and successfully raised venture investments for a high-tech medical device start-up company. Dr. Fitch received his Ph.D. from Purdue University and B.S. from Loyola College of Maryland.

Capt. Darrell R. Galloway, M.S.C., Ph.D., is chief of the Medical Science and Technology Division for the Chemical and Biological Defense Directorate at the Defense Threat Reduction Agency. He received his baccalaureate degree in microbiology from California State University in Los Angeles in 1973. After completing military service in the U.S. Army as a medical corpsman from 1969 to 1972, Captain Galloway entered graduate school and completed a doctoral degree in biochemistry in 1978 from the University of California, followed by 2 years of postgraduate training in immunochemistry as a fellow of the National Cancer Institute at the Scripps Clinic and Research Foundation in La Jolla, California. Captain Galloway began his navy career at the Naval Medical Research Institute in Bethesda, Maryland, where from 1980 to 1984 he served as a research scientist working on vaccine development. In late 1984 Captain Galloway left active service to pursue an academic appointment at Ohio State University, where he is now a tenured faculty member in the Department of Microbiology. He also holds appointments at the University of Maryland Biotechnology Institute and the Uniformed Services University of Health Sciences. He has an international reputation in the area of bacterial toxin research and has published more than 50 research papers on various studies of bacterial toxins. In recent years Captain Galloway's research has concentrated on anthrax and the development of DNA-based vaccine technology. His laboratory has contributed substantially to the development of a new DNA-based vaccine against anthrax that has completed the first phase of clinical trials. Captain Galloway is a member of the ASM and has served as president of the Ohio branch of that organization. He received an NIH Research Career Development Award. In 2005 Captain Galloway was awarded the Joel M. Dalrymple Award for significant contributions to biodefense vaccine development.

S. Elizabeth George, Ph.D., is deputy director, Biological Countermeasures Portfolio Science and Technology Directorate, Department of Homeland Security (DHS). Until merging into the new department in 2003, she was program manager of the Chemical and Biological National Security Program in the Department of Energy's National Nuclear Security Administration's Office of Nonproliferation Research and Engineering. Significant accomplishments include the design and deployment of BioWatch, the nation's first civilian biological threat agent monitoring system, and PROTECT, the first civilian operational chemical detection and response capability deployed in the Washington, DC, area subway system. Previously, she spent 16 years at the U.S. Environmental Protection Agency (EPA), Office of Research and Development, National Health and Ecological

Effects Research Laboratory, Environmental Carcinogenesis Division, where she was branch chief of the Molecular and Cellular Toxicology Branch. She received her B.S. in biology in 1977 from Virginia Polytechnic Institute and State University and her M.S. and Ph.D. in microbiology in 1979 and 1984, respectively, from North Carolina State University. From 1984 to 1986, she was a National Research Council fellow in the laboratory of Dr. Larry Claxton at EPA. Dr. George is the 2005 chair of the Chemical and Biological Terrorism Defense Gordon Research Conference. She has served as councilor for the Environmental Mutagen Society and president and secretary of the Genotoxicity and Environmental Mutagen Society. She holds memberships in the ASM and the AAAS and is an adjunct faculty member in the School of Rural Public Health, Texas A&M University. She is a recipient of the EPA Bronze Medal and Scientific and Technological Achievement Awards and DHS Under Secretary's Award for Science and Technology. She is the author of numerous journal articles and has presented her research at national and international meetings.

Jesse L. Goodman, M.D., M.P.H., is director of FDA's Center for Biologics Evaluation and Research (CBER), which oversees medical, public health, and policy activities concerning the development and assessment of vaccines, blood products, tissues, and related devices and novel therapeutics, including cellular and gene therapies. He moved full-time to FDA in 2001 from the University of Minnesota, where he was professor of and director of the Division of Infectious Diseases. A graduate of Harvard College, he received his M.D. at the Albert Einstein College of Medicine, did residency and fellowship training at the Hospital of the University of Pennsylvania and at the University of California–Los Angeles (UCLA; where he was also chief medical resident), and is board certified in internal medicine, oncology, and infectious diseases. He trained in the virology laboratory of Jack Stevens at UCLA and has had an active laboratory program in the molecular pathogenesis of infectious diseases. In 1995 his laboratory isolated the etiologic agent of human granulocytic ehrlichiosis (HGE) and subsequently characterized fundamental events involved in infection of leukocytes, including their cellular receptors. He is editor of the book *Tick Borne Diseases of Humans* published by ASM Press in 2005 and is a staff physician and infectious diseases consultant at the NIH Clinical Center and the National Naval Medical Center/Walter Reed Army Medical Center, as well as adjunct professor of medicine at the University of Minnesota. He is active in a wide variety of clinical, public health, and product development issues, including pandemic and emerging infectious disease threats, bioterrorism preparedness and response, and blood, tissue, and vaccine safety and availability. In these activities, he has worked closely with CDC, NIH, and other HHS components, academia, and the private sector, and he has put into place an interactive team approach to emerging threats. This model was used in the collaborative development and rapid implementation of nationwide donor screening of the U.S. blood supply for West Nile virus. He has

been elected to the American Society for Clinical Investigation (ASCI) and to the IOM.

Eduardo Gotuzzo, M.D., is principal professor and director at the Instituto de Medicina Tropical "Alexander von Humbolt," Universidad Peruana Cayetan Heredia (UPCH) in Lima, Peru, as well as chief of the Department of Infectious and Tropical Diseases at the Cayetano Heredia Hospital. He is also an adjunct professor of medicine at the University of Alabama, Birmingham School of Medicine. Dr. Gotuzzo is an active member in numerous international societies and has been president of the Latin America Society of Tropical Disease (2000–2003), the IDSA Scientific Program (2000–2003), the International Organizing Committee of the International Congress of Infectious Diseases (1994–present), president-elect of the International Society for Infectious Diseases (1996–1998), and president of the Peruvian Society of Internal Medicine (1991–1992). He has published more than 230 articles and chapters as well as six manuals and one book. Recent honors and awards include being named an honorary member of the American Society of Tropical Medicine and Hygiene in 2002, associate member of the National Academy of Medicine in 2002, honorary member of the Society of Internal Medicine in 2000, and distinguished visitor at the Faculty of Medical Sciences, University of Cordoba, Argentina, in 1999. In 1988 he received the Golden Medal for Outstanding Contribution in the Field of Infectious Diseases awarded by Trnava University, Slovakia.

Jo Handelsman, Ph.D., received her Ph.D. in molecular biology from the University of Wisconsin–Madison (UW–M) in 1984 and joined the faculty of the UW–M Department of Plant Pathology in 1985, where she is currently a Howard Hughes Medical Institute (HHMI) professor. Her research focuses on the genetic and functional diversity of microorganisms in soil and insect gut communities. The Handelsman lab has concentrated on discovery and biological activity of novel antibiotics from cultured and uncultured bacteria and has contributed to the pioneering of a new technique called metagenomics that facilitates the genomic analysis of assemblages of uncultured microorganisms. Handelsman is studying the mid-gut of the gypsy moth to understand the basis for resistance and susceptibility of microbial communities to invasion, developing it as a model for the microbial community in the human gut. In addition to her passion for understanding the secret lives of bacteria, Dr. Handelsman is dedicated to improving science education and the advancement of women in research universities. She is director of the HHMI New Generation Program for Scientific Teaching, which is dedicated to teaching graduate and postdoctoral students the principles and practices of teaching and mentoring. She is codirector of The National Academies Summer Institute for Undergraduate Education in Biology, a collaborative venture between HHMI and The National Academies that aims to train a nationwide network of faculty who are outstanding teachers and mentors. Dr. Handelsman

is codirector of the Women in Science and Engineering Leadership Institute at UW–M, whose mission is to understand the impediments to the successful recruitment and advancement of women faculty in the sciences and to develop and study interventions intended to reduce those barriers.

Carole A. Heilman, Ph.D., is director of the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID). She received her bachelor's degree in biology from Boston University in 1972 and earned her master's degree and doctorate in microbiology from Rutgers University in 1976 and 1979, respectively. Dr. Heilman began her NIH career as a postdoctoral research associate with the National Cancer Institute, where she carried out research on the regulation of gene expression during cancer development. In 1986, she came to NIAID as the influenza and viral respiratory diseases program officer in DMID and, in 1988, she was appointed chief of the respiratory diseases branch, where she coordinated the development of acellular pertussis vaccines. She joined the Division of AIDS as deputy director in 1997 and was responsible for developing the Innovation Grant Program for Approaches in HIV Vaccine Research. She is the recipient of several notable awards for outstanding achievement. Throughout her extramural career, Dr. Heilman has contributed articles on vaccine design and development to many scientific journals and has served as a consultant to the World Bank and WHO. She is also a member of several professional societies, including the IDSA, the ASM, and the American Society of Virology.

David L. Heymann, M.D., is currently assistant director-general for communicable diseases and the representative of the director-general for polio eradication at the World Health Organization. Prior to that, from July 1998 until July 2003, Dr. Heymann was executive director of the WHO Communicable Diseases Cluster which includes WHO's programs on infectious and tropical diseases, and from which the public health response to SARS was mounted in 2003. From October 1995 to July 1998 Dr. Heymann was director of the WHO Program on Emerging and other Communicable Diseases, and prior to that was the chief of research activities in the WHO Global Program on AIDS. Before joining WHO, Dr. Heymann worked for 13 years as a medical epidemiologist in sub-Saharan Africa (Cameroon, Côte d'Ivoire, Malawi, and the Democratic Republic of Congo—formerly Zaire) on assignment from the CDC in CDC-supported activities. These activities aimed at strengthening capacity in surveillance of infectious diseases and their control, with special emphasis on the childhood immunizable diseases including measles and polio, African haemorrhagic fevers, poxviruses, and malaria. While based in Africa, Dr. Heymann participated in the investigation of the first outbreak of Ebola in Yambuku (former Zaire) in 1976, then again investigated the second outbreak of Ebola in 1977 in Tandala, and in 1995 directed the international response to the Ebola outbreak in Kikwit. Prior to these

13 years in Africa, Dr. Heymann worked two years in India as a medical epidemiologist in the WHO Smallpox Eradication Program. Dr. Heymann holds a B.A. from the Pennsylvania State University, an M.D. from Wake Forest University, a Diploma in Tropical Medicine and Hygiene from the London School of Hygiene and Tropical Medicine, and has completed practical epidemiology training in the two-year Epidemic Intelligence Service (EIS) of CDC. He is a recipient of the American Public Health Association Award for Excellence and the American Society of Tropical Medicine and Hygiene Donald MacKay medal, and is a member of the IOM. Dr. Heymann has published over 140 scientific articles on infectious diseases and related issues in medical and scientific journals, and authored several chapters on infectious diseases in medical textbooks. He is currently editor of the 18th edition of the *Control of Communicable Diseases Manual*, a joint publication of WHO and the American Public Health Association.

Phil Hosbach is vice president of New Products and Immunization Policy at Sanofi Pasteur. The departments under his supervision are new product marketing, state and federal government policy, business intelligence, bids and contracts, medical communications, public health sales, and public health marketing. His current responsibilities include oversight of immunization policy development. He acts as Sanofi Pasteur's principal liaison with CDC. Mr. Hosbach graduated from Lafayette College in 1984 with a degree in biology. He has 20 years of pharmaceutical industry experience, including the past 17 years focused solely on vaccines. He began his career at American Home Products in Clinical Research in 1984. He joined Aventis Pasteur (then Connaught Labs) in 1987 as clinical research coordinator and has held research and development positions of increasing responsibility, including clinical research manager and director of clinical operations. Mr. Hosbach also served as project manager for the development and licensure of Tripedia, the first diphtheria, tetanus, and acellular pertussis (DTaP) vaccine approved by FDA for use in U.S. infants. During his clinical research career at Aventis Pasteur, he contributed to the development and licensure of seven vaccines and has authored or coauthored several clinical research articles. From 2000 through 2002, Mr. Hosbach served on the board of directors for Pocono Medical Center in East Stroudsburg, Pennsylvania. Since 2003 he has served on the board of directors of Pocono Health Systems, which includes Pocono Medical Center.

James M. Hughes, M.D., received his B.A. in 1966 and M.D. in 1971 from Stanford University. He completed a residency in internal medicine at the University of Washington and a fellowship in infectious diseases at the University of Virginia. He is board certified in internal medicine, infectious diseases, and preventive medicine. He first joined CDC as an epidemic intelligence service officer in 1973. During his CDC career, he has worked primarily in the areas of foodborne disease and infection control in health-care settings. He became

director of NCID in 1992. The center is currently working to address domestic and global challenges posed by emerging infectious diseases and the threat of bioterrorism. He is a member of the IOM and a fellow of the American College of Physicians, the IDSA, and the AAAS. He is an assistant surgeon general in the Public Health Service.

Stephen A. Johnston, Ph.D., is currently director of the Center for Innovations in Medicine in the Biodesign Institute at Arizona State University. His center focuses on formulating and implementing disruptive technologies for basic problems in health care. The center has three divisions: Genomes to Vaccines, Cancer Eradication, and DocInBox. The Genomes to Vaccines group has developed high-throughput systems to screen for vaccine candidates and is applying them to predict and produce chemical vaccines. The Cancer Eradication group is working on formulating a universal prophylactic vaccine for cancer. The DocInBox group is developing technologies to facilitate presymptomatic diagnosis. Dr. Johnston founded the Center for Biomedical Inventions (a.k.a., Center for Translation Research) at the University of Texas–Southwestern, the first center of its kind in the medical arena. He and his colleagues have developed numerous inventions and innovations, including the gene gun, genetic immunization, TEV protease system, organelle transformation, digital optical chemistry arrays, expression library immunization, linear expression elements, and others. He also was involved in transcription research for years, first cloning Gal4, then later discovering functional domains in transcription factors and the connection of the proteasome to transcription. He has been professor at the University of Texas Southwestern Medical Center at Dallas and associate and assistant professor at Duke University. He has been involved in several capacities as an advisor on biosecurity since 1996 and is a member of the WRCE SAB and a founding member of BioChem 20/20.

Gerald T. Keusch, M.D., is provost and dean for Global Health at Boston University and Boston University School of Public Health. He is a graduate of Columbia College (1958) and Harvard Medical School (1963). After completing a residency in internal medicine, fellowship training in infectious diseases, and 2 years as an NIH research associate at the Southeast Asia Treaty Organization (SEATO) Medical Research Laboratory in Bangkok, Thailand, Dr. Keusch joined the faculty of Mt. Sinai School of Medicine in 1970, where he established a laboratory to study the pathogenesis of bacillary dysentery and the biology and biochemistry of Shiga toxin. In 1979 he moved to Tufts Medical School and New England Medical Center in Boston to found the Division of Geographic Medicine, which focused on the molecular and cellular biology of tropical infectious disease. In 1986 he integrated the clinical infectious diseases program into the Division of Geographic Medicine and Infectious Diseases, continuing as division chief until 1998. He has worked in the laboratory and in the field in Latin

America, Africa, and Asia on basic and clinical infectious diseases and HIV/AIDS research. From 1998 to 2003, he was associate director for international research and director of the Fogarty International Center at NIH. Dr. Keusch is a member of the American Society for Clinical Investigation (ASCI), the Association of American Physicians, the ASM, and the IDSA. He has received the Squibb (1981), Finland (1997), and Bristol (2002) awards of the IDSA. In 2002 he was elected to the IOM.

Rima F. Khabbaz, M.D., is director of NCID at CDC. She received her B.S. in 1975 and her M.D. in 1979 from the American University of Beirut in Lebanon. She trained in internal medicine and completed a fellowship in infectious diseases at the University of Maryland in Baltimore. She is board certified in internal medicine. She first joined CDC as an epidemic intelligence service officer in 1980. During her CDC career, she worked primarily in the areas of health care–associated infections and viral diseases. She is a fellow of the IDSA and an elected member of the American Epidemiologic Society. She served on FDA's Blood Product Advisory Committee, on FDA's Transmissible Spongiform Encephalopathy Advisory Committee and on the Annual Meeting Scientific Program Committee of the IDSA. She played a leading role in developing CDC's programs related to blood and food safety and in CDC's responses to outbreaks of new and reemerging diseases.

Lonnie J. King, D.V.M., is currently the director of CDC's new National Center for Zoonotic, Vector-Borne, and Enteric Diseases (NCZVED). Dr. King leads the center's activities for surveillance, diagnostics, disease investigations, epidemiology, research, public education, policy development, and disease prevention and control programs. NCZVED also focuses on waterborne, foodborne, vectorborne, and zoonotic diseases of public health concern, which also includes most of CDC's select and bioterrorism agents, neglected tropical diseases, and emerging zoonoses. Before serving as director, he was the first chief of the agency's Office of Strategy and Innovation. In 1996 Dr. King was appointed dean of the College of Veterinary Medicine, Michigan State University. He served for 10 years as dean of the college. As dean, he was the chief executive officer for academic programs, research, the teaching hospital, diagnostic center for population and animal health, basic and clinical science departments, and outreach and continuing education programs. As dean and professor of large animal clinical sciences, Dr. King was instrumental in obtaining funds for the construction of the $60 million Diagnostic Center for Population and Animal Health, initiated the Center for Emerging Infectious Diseases in the college, served as the campus leader in food safety, and had oversight for the National Food Safety and Toxicology Center. He brought the Center for Integrative Toxicology to the college and was the university's designated leader for counterbioterrorism activities for his college and was involved in reestablishing public health programs at Michigan State University. Prior to this, Dr. King was

administrator for USDA's Animal and Plant Health Inspection Service (APHIS). Dr. King served as the country's chief veterinary officer for 5 years and worked extensively in global trade agreements within the North American Free Trade Agreement and the World Trade Organization. Before beginning his government career in 1977, he was in private veterinary practice for 7 years in Ohio and Georgia. He received his B.S. and D.V.M. from Ohio State University in 1966 and 1970, respectively. He earned his M.S. in epidemiology from the University of Minnesota while on special assignment with USDA in 1980. He received his master's in public administration from The American University in Washington, DC, in 1991. Dr. King has a broad knowledge of animal agriculture and the veterinary profession through his work with other governmental agencies, universities, major livestock and poultry groups, and private practitioners. Dr. King is a board-certified member of the American College of Veterinary Preventive Medicine and has completed the senior executive fellowship program at Harvard University. He served as president of the Association of American Veterinary Medical Colleges from 1999 to 2000 and was vice chair for the National Commission on Veterinary Economic Issues from 2000 to 2004. Dr. King helped start the National Alliance for Food Safety, served on the Governor's Task Force on Chronic Wasting Disease for the state of Michigan, and was a member of four NAS committees; most recently he chaired The National Academies Committee on Assessing the Nation's Framework for Addressing Animal Diseases. Dr. King is one of the developers of the Science, Politics, and Animal Health Policy Fellowship Program, and he lectures extensively on the future of animal health and veterinary medicine. He served as a consultant and member of the Board of Scientific Counselors to CDC's National Center for Infectious Diseases and is a member of the IOM's Forum on Microbial Threats. Dr. King is an editor for the OIE Scientific Review on Emerging Zoonoses, is a current member of FDA's Board of Scientific Advisors, and is president of the American Veterinary Epidemiology Society. Dr. King was elected to the IOM in 2004.

Col. George W. Korch, Ph.D., is commander, U.S. Army Medical Research Institute for Infectious Diseases, Ft. Detrick, Maryland. Dr. Korch attended Boston University and earned a B.S. in biology in 1974, followed by postgraduate study in mammalian ecology at the University of Kansas from 1975 to 1978. He earned his Ph.D. from the Johns Hopkins School of Hygiene and Public Health in Immunology and Infectious Diseases in 1985, followed by postdoctoral experience at Johns Hopkins from 1985 to 1986. His areas of training and specialty are the epidemiology of zoonotic viral pathogens and medical entomology. For the past 15 years, he has also been engaged in research and program management for medical defense against biological pathogens used in terrorism or warfare.

Joshua Lederberg, Ph.D., is professor emeritus of molecular genetics and informatics and Sackler Foundation Scholar at the Rockefeller University in New York

City. His lifelong research, for which he received the Nobel Prize in 1958, has been in genetic structure and function in microorganisms. He has a keen interest in international health and from 1990 to 1992 was co-chair of a previous IOM Committee on Emerging Microbial Threats to Health. Currently he is co-chair of the Committee on Emerging Microbial Threats to Health in the Twenty-First Century. He has been a member of the NAS since 1957 and is a charter member of the IOM.

Lynn G. Marks, M.D., is board certified in internal medicine and infectious diseases. He was on the faculty at the University of South Alabama College of Medicine in the Infectious Diseases Department, focusing on patient care, teaching, and research, where his academic research interest was in the molecular genetics of bacterial pathogenicity. He subsequently joined the anti-infectives clinical group of SmithKline Beecham (now GlaxoSmithKline) and later advanced to be global head of the Consumer Healthcare Division Medical and Regulatory Group. He then returned to pharmaceutical research and development as global head of the Infectious Diseases Therapeutic Area Strategy Team for GlaxoSmithKline.

Edward McSweegan, Ph.D., is a program officer at NIAID. He graduated from Boston College with a B.S. in 1978. He has an M.S. in microbiology from the University of New Hampshire and a Ph.D. in microbiology from the University of Rhode Island. He was a National Research Council Associate from 1984 to 1986 and did postdoctoral research at the Naval Medical Research Institute in Bethesda, Maryland. Dr. McSweegan served as an AAAS diplomacy fellow in the U.S. State Department from 1986 to 1988 and negotiated science and technology agreements with Poland, Hungary, and the former Soviet Union. After moving to NIH, he continued to work on international health and science projects in Egypt, Israel, India, and Russia. Currently, he manages NIAID's bilateral program with India, the Indo–U.S. Vaccine Action Program, and represents NIAID in the HHS Biotechnology Engagement Program with Russia and related countries. He is a member of the AAAS, the ASM, and the DC Science Writers Association. He is the author of numerous journal and science articles.

Stephen S. Morse, Ph.D., is founding director of the Center for Public Health Preparedness at the Mailman School of Public Health of Columbia University and is an associate professor in the epidemiology department. He recently returned to Columbia after 4 years in government service as program manager at the Defense Advanced Research Projects Agency (DARPA), where he codirected the Pathogen Countermeasures Program and subsequently directed the Advanced Diagnostics Program. Before coming to Columbia, he was assistant professor of virology at Rockefeller University in New York, where he remains an adjunct faculty member. He is the editor of two books, *Emerging Viruses* (Oxford University Press, 1993; paperback, 1996), which was selected by *American Scientist* for its

list of 100 Top Science Books of the 20th Century, and *The Evolutionary Biology of Viruses* (Raven Press, 1994). He currently serves as a section editor of the CDC journal *Emerging Infectious Diseases* and was formerly an editor-in-chief of the Pasteur Institute's journal *Research in Virology*. Dr. Morse was chair and principal organizer of the 1989 NIAID/NIH Conference on Emerging Viruses, for which he originated the term and concept of *emerging viruses/infections*. He has served as a member of the IOM/NAS Committee on Emerging Microbial Threats to Health, chaired its Task Force on Viruses, and was a contributor to the resulting report, *Emerging Infections* (1992). He was a member of the IOM's Committee on Xenograft Transplantation and he currently serves on the Steering Committee of the IOM's Forum on Emerging Infections (now the Forum on Microbial Threats). Dr. Morse also served as an adviser to WHO, the Pan-American Health Organization, FDA, the Defense Threat Reduction Agency, and other agencies. He is a fellow of the New York Academy of Sciences and a past chair of its microbiology section, a fellow of the American Academy of Microbiology of the American College of Epidemiology, and an elected life member of the Council on Foreign Relations. He was the founding chair of ProMED, the nonprofit international Program to Monitor Emerging Diseases, and was one of the originators of ProMED-mail, an international network inaugurated by ProMED in 1994 for outbreak reporting and disease monitoring using the Internet. Dr. Morse received his Ph.D. from the University of Wisconsin–Madison.

Michael T. Osterholm, Ph.D., M.P.H., is director of the Center for Infectious Disease Research and Policy at the University of Minnesota, where he is also professor at the School of Public Health. Previously, Dr. Osterholm was the state epidemiologist and chief of the acute disease epidemiology section for the Minnesota Department of Health. He has received numerous research awards from NIAID and CDC. He served as principal investigator for the CDC-sponsored Emerging Infections Program in Minnesota. He has published more than 240 articles and abstracts on various emerging infectious disease problems and is the author of the best-selling book, *Living Terrors: What America Needs to Know to Survive the Coming Bioterrorist Catastrophe*. He is past president of the Council of State and Territorial Epidemiologists. He currently serves on the IOM Forum on Microbial Threats. He has also served on the IOM Committee to Ensure Safe Food from Production to Consumption, the IOM Committee on the Department of Defense Persian Gulf Syndrome Comprehensive Clinical Evaluation Program, and as a reviewer for the IOM report on chemical and biological terrorism.

George Poste, Ph.D., D.V.M., is director of the Arizona Biodesign Institute and Dell E. Webb Distinguished Professor of Biology at Arizona State University. From 1992 to 1999, he was chief science and technology officer and president, Research and Development of SmithKline Beecham (SB). During his tenure at SB, he was associated with the successful registration of 29 drug, vaccine, and

diagnostic products. He is chairman of diaDexus and Structural GenomiX in California and Orchid Biosciences in Princeton. He serves on the board of directors of AdvancePCS and Monsanto. He is an advisor on biotechnology to several venture capital funds and investment banks. In May 2003, he was appointed as director of the Arizona Biodesign Institute at Arizona State University. This is a major new initiative combining research groups in biotechnology, nanotechnology, materials science, advanced computing, and neuromorphic engineering. He is a fellow of Pembroke College in Cambridge and distinguished fellow at the Hoover Institution and Stanford University. He is a member of the Defense Science Board of the U.S. Department of Defense. In this capacity he chairs the Task Force on Bioterrorism. He is also a member of the NAS Working Group on Defense Against Bioweapons. Dr. Poste is a board-certified pathologist, a fellow of the Royal Society, and a fellow of the Academy of Medical Sciences. He was awarded the rank of Commander of the British Empire by Queen Elizabeth II in 1999 for services to medicine and for the advancement of biotechnology. He has published more than 350 scientific papers; has coedited 15 books on cancer, biotechnology, and infectious diseases; and serves on the editorial board of multiple technical journals. He is routinely invited to be the keynote speaker at a wide variety of academic, corporate, investment, and government meetings to discuss the impact of biotechnology and genetics on health care and the challenges posed by bioterrorism.

David A. Relman, M.D., is an associate professor of medicine (infectious diseases and geographic medicine) and of microbiology and immunology at Stanford University School of Medicine, and chief of the infectious disease section at the Veterans Affairs (VA) Palo Alto Health Care System. Dr. Relman received his B.S. in biology from the Massachusetts Institute of Technology and his M.D. from Harvard Medical School. He completed his residency in internal medicine and a clinical fellowship in infectious diseases at Massachusetts General Hospital, Boston, after which he moved to Stanford for a postdoctoral fellowship in 1986, and joined the faculty there in 1994. His research focus is on understanding the structure and role of the human indigenous microbial communities in health and disease. This work brings together approaches from ecology, population biology, environmental microbiology, genomics, and clinical medicine. A second area of investigation explores the classification structure of humans and nonhuman primates with systemic infectious diseases, based on patterns of genome-wide gene transcript abundance in blood and other tissues. The goals of this work are to understand mechanisms of host–pathogen interaction, as well as predict clinical outcome at early time points in the disease process. His scientific achievements include the description of a novel approach for identifying previously unknown pathogens, the characterization of a number of new human microbial pathogens, including the agent of Whipple's disease, and some of the most in-depth analyses to date of human indigenous microbial communities. Among his other activities,

Dr. Relman currently serves as chair of the Board of Scientific Counselors of the National Institute of Dental and Craniofacial Research (NIH), is a member of the National Science Advisory Board for Biosecurity, and advises a number of U.S. government departments and agencies on matters related to pathogen diversity, the future life sciences landscape, and the nature of present and future biological threats. He was co-chair of the Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats for the NAS. He received the Squibb Award from the IDSA in 2001, the Senior Scholar Award in Global Infectious Diseases from the Ellison Medical Foundation in 2002, an NIH Director's Pioneer Award in 2006, and a Doris Duke Distinguished Clinical Scientist Award in 2006. He is also a fellow of the American Academy of Microbiology.

Gary A. Roselle, M.D., received his M.D. from the Ohio State University School of Medicine in 1973. He served his residency at the Northwestern University School of Medicine and his infectious diseases fellowship at the University of Cincinnati School of Medicine. He is the program director for infectious diseases for the VA Central Office in Washington, DC, as well as the chief of the medical service at the Cincinnati VA Medical Center. He is a professor of medicine in the Department of Internal Medicine, Division of Infectious Diseases at the University of Cincinnati College of Medicine. Dr. Roselle serves on several national advisory committees. In addition, he is currently heading the Emerging Pathogens Initiative for the Department of Veterans Affairs. He has received commendations from the Cincinnati Medical Center director, the under secretary for health for the Department of Veterans Affairs, and the secretary of veterans affairs for his work in the infectious diseases program for the Department of Veterans Affairs. He has been an invited speaker at several national and international meetings and has published more than 80 papers and several book chapters.

Janet Shoemaker is director of the ASM's Public Affairs Office, a position she has held since 1989. She is responsible for managing the legislative and regulatory affairs of this 42,000-member organization, the largest single biological science society in the world. She has served as principal investigator for a project funded by the National Science Foundation (NSF) to collect and disseminate data on the job market for recent doctorates in microbiology and has played a key role in ASM projects, including the production of the ASM *Employment Outlook in the Microbiological Sciences* and *The Impact of Managed Care and Health System Change on Clinical Microbiology*. Previously, she held positions as assistant director of public affairs for the ASM, as ASM coordinator of the U.S./U.S.S.R. Exchange Program in Microbiology, a program sponsored and coordinated by NSF and the U.S. Department of State, and as a freelance editor and writer. She received her baccalaureate, cum laude, from the University of Massachusetts, and is a graduate of the George Washington University programs in public policy and

in editing and publications. She has served as commissioner to the Commission on Professionals in Science and Technology and as the ASM representative to the ad hoc Group for Medical Research Funding, and is a member of Women in Government Relations, the American Society of Association Executives, and the AAAS. She has coauthored published articles on research funding, biotechnology, biological weapons control, and public policy issues related to microbiology.

Brian J. Staskawicz, Ph.D., is professor and chair, Department of Plant and Microbial Biology, University of California–Berkeley. Dr. Staskawicz received his B.A. in biology from Bates College in 1974 and his Ph.D. from the University of California–Berkeley in 1980. Dr. Staskawicz's work has contributed greatly to understanding the molecular interactions between plants and their pathogens. He was elected to the NAS in 1998 for elucidating the mechanisms of disease resistance, as his lab was the first to clone a bacterial effector gene from a pathogen and among the first to clone and characterize plant disease-resistance genes. Dr. Staskawicz's research focuses on the interaction of the bacteria, *Pseudomonas* and *Xanthomonas*, with *Arabidopsis*, tomato, and pepper. He has published extensively in this area and is a one of the leading scientists in the world working on elucidating the molecular basis of plant innate immunity.

Terence Taylor is president and director of the International Council for the Life Sciences (ICLS). He is responsible for the overall direction of the ICLS and its programs, which have the goal of enhancing global biosafety and biosecurity. From 1995 to 2005, he was assistant director of the International Institute for Strategic Studies (IISS), a leading independent international institute, and president and executive director of its U.S. office (2001 to 2005). He studies international security policy, risk analysis, and scientific and technological developments and their impact on political and economic stability worldwide. At IISS he was one of the Institute's leading experts on issues associated with nuclear, biological, and chemical weapons and their means of delivery. In his previous appointments, he has had particular responsibilities for issues affecting public safety and security in relation to biological risks and advances in the life sciences. He was one of the commissioners to the United Nations (UN) Special Commission on Iraq, for which he also conducted missions as a chief inspector. He was a research fellow on the Science Program at the Center for International Security and Cooperation at Stanford University, where he carried out, among other subjects, studies of the implications for government and industry of the weapons of mass destruction treaties and agreements. He has also carried out consultancy work for the International Committee of the Red Cross on the implementation and development of the laws of armed conflict. He has served as chairman of the World Federation of Scientists' Permanent Monitoring Panel on Risk Analysis. He served as a career officer in the British Army on operations in many parts of the world, including counterterrorist operations and UN peacekeeping. His publications include

monographs, book chapters, and articles for, among others, Stanford University, the World Economic Forum, Stockholm International Peace Research Institute (SIPRI), the Crimes of War Project, *International Herald Tribune*, *Wall Street Journal*, the *International Defence Review*, the *Independent* (London), *Tiempo* (Madrid), the *International and Comparative Law Quarterly*, the *Washington Quarterly*, and other scholarly journals, including unsigned contributions to IISS publications.