

GLOBAL DISEASE SURVEILLANCE, EMERGENT DISEASE PREPAREDNESS, AND NATIONAL SECURITY

Carleton J. Phillips, Anne M. Harrington, Terry L. Yates, Gary L. Simpson,
and Robert J. Baker



Cover: Earth from space, photo courtesy of NASA. Upper left, Drs. John Hay (University of Buffalo, New York State Center for Bioinformatics) and Roger Hewson (Health Protection Agency, Porton Down, United Kingdom) conducting zoonoses fieldwork in Central Asia with authors Phillips and Baker, photo by R. J. Baker; upper right, *Carios kelleyi*, a tick and potential vector parasitic on bats, photo by Jim Gathany courtesy of CDC; lower left, the deer mouse, *Peromyscus maniculatus*, a rodent that carries hantavirus in the United States, photo courtesy of CDC; lower right, two CDC microbiologists, Drs. Thomas Stevens, Jr. and Amy Hartman, preparing for work in a BSL-4 facility, photo by Jim Gathany courtesy of CDC.

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*CARLETON J. PHILLIPS, ANNE M. HARRINGTON, TERRY L. YATES, GARY L. SIMPSON,
AND ROBERT J. BAKER*

*Museum of Texas Tech University
Lubbock, Texas*

Layout and Design: Lisa Bradley
Cover Design and Plates: Carleton J. Phillips

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Museum of Texas Tech University
Lubbock, TX 79409-3191 USA
(806)742-2442

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Global Disease Surveillance, Emergent Disease Preparedness, and National Security is intended to provide background information and integrate a wide variety of scientific and technical sources relevant to strategic planning. Policy- and decision-makers in government comprise one intended audience, but we also believe that our paper will be valuable to citizens interested in infectious disease and its impact on society, economy, and security. With the foregoing in mind, this paper does not present a comprehensive review of the vast literature on the subject, and we apologize in advance to authors whose papers might not be cited.

The opinions, conclusions, and recommendations presented here are entirely the responsibility of the individual authors and may not be construed to represent any agency or any policy of the United States Government. All of the materials used in writing this paper, both those formally referenced and those that were used as general background but not cited, are publicly available.

AUTHORS' NOTE

As our monograph went to press, the attention of the global community was fixed on a pandemic outbreak of influenza A, H1N1. This outbreak is an example of the currency of the ideas expressed in our monograph. A central concept is that human morbidity and mortality must be continuously monitored, analyzed, and understood in context of dynamic interactions and perturbations of ecosystems that affect the health status of wildlife populations and biodiversity and threaten the economic stability of agriculture. The reality that approximately 60% of the estimated 1,461 known infectious diseases of humans infect both humans and other animal species, and the reality that 70-80% of emerging infectious diseases of the past 30 years have been of zoonotic origin, underscores the relevance of this perspective to human health and biosecurity.

The following highlights serve to illustrate how the influenza A, H1N1 outbreak can be viewed and assessed in the framework of our monograph.

Global infectious disease surveillance—In June 2009, the date of onset and exact origins of H1N1 remained unclear. Early event detection would be favored by implementation of a worldwide, systematic, syndromic surveillance system of known (or measurable) sensitivity and specificity. Because of the dynamic interactions of influenza viruses in humans, domestic animals, and wildlife, surveillance must span all of these species if it is to serve as a global biosecurity defense system.

Laboratory diagnostics—The absence of sophisticated, regional, diagnostic laboratories delayed virtually every aspect of the response to what became a global pandemic. Laboratory diagnosis of infectious diseases remains the “gold standard” of surveillance, although timeliness may be measured in days, weeks, or months.

Situational awareness—Understanding the susceptibility of any host species to a newly recognized and evolving influenza virus requires knowledge of age-specific seroprevalence in all species at risk. This will constitute a major challenge for the world community in coming months and years.

Molecular biology and genomics capabilities—The disciplines of molecular biology and evolutionary biology, in particular, are providing insights about the origin of the outbreak, the nature of transmissibility, the implications of a triple-reassortant influenza, and the virulence of the pandemic strain. One regrettable consequence of the contemporary characterization of the outbreak strain as a ‘triple-reassortant’ influenza A virus whose genome has human, swine, and avian genes (originating on at least 3 continents) has been the speculation (by some observers) that this is an engineered virus and that the outbreak is the result of an intentional release. Fortunately, this suggestion has been thoroughly debunked by the time of this writing.

Global data sharing—This issue is arguably the most important to the success of worldwide outbreak investigations. The contrast in the multinational transparency of data to the experience of the first global epidemic of the 21st Century (SARS) is notable. This success possibly is due to International Health Regulations instituted in 2005.

Public health, social, political, religious, diplomatic, and economic implications—The forced quarantine of foreign nationals is one example of a response with legal implications. Bans on importation of Mexican and U.S. pork products are examples of commercial impact on trade. A complex political and social impact occurred in Egypt because a government order to slaughter all swine affected the Coptic Christian minority, which led to clashes with police. A different kind of impact was felt in Mexico, where it was estimated that during the peak of influenza activity, Mexico City lost an estimated \$57 million per day in tourism and other revenues. Finally,

the general impact of the H1N1 virus can be described by the so-called “Katrina syndrome,” which holds that any major disaster or public health emergency will predictably expose social disparities in a population or society.

In June 2009, the Robert Wood Foundation (with Trust for America’s Care and the Center for Biosecurity) released a report on pandemic flu preparedness (available at <http://healthyamericans.org/report/64/pandemic-flu-frontlines>), which is consistent with themes covered in our monograph. Examples from the H1N1 experience include: inadequate resources at public health departments; the health care system was overwhelmed; communication was not well coordinated; WHO pandemic alert phases caused confusion; and international coordination was more complicated than expected. As we explain, such problems and short-comings would be expected based on the complexity of global disease surveillance in a biosecurity context.

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**GLOBAL DISEASE SURVEILLANCE,
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AND NATIONAL SECURITY**

Executive Summary

In March 2006, the White House released *The National Security Strategy*, which recognized that natural pandemics pose a risk to social order great enough to necessitate new public health strategies and responses. Moreover, this same document—and other recent government agency and congressional reports—also recognized the grave threat to national security posed by transnational bioterrorism, intentional disease outbreaks, or even accidental release of pathogens from laboratories not compliant with biosecurity protocols. Additionally, it is increasingly obvious that emergent zoonotic (animal-borne) diseases pose a general threat with implications for international cooperation and social and economic stability. Such outbreaks might increase over time because climate change, human population density, land use, and anthropogenic modification of habitat all contribute to the likelihood of zoonotic infectious agents entering the human population.

Global disease surveillance—the ability to detect, identify, and monitor disease on the broadest geographic scale—is a critically important challenge with political, social, and economic overtones for the United States and the international community. In theory, global disease surveillance could provide an important foundation for strategic response to natural outbreaks as well as to intentional or accidental misuse of infectious agents. And at the very least, a system of global disease surveillance could detect anomalies in prevalence of infectious diseases in human populations or in their livestock and in this way could trigger an appropriate, coordinated response.

The basic infrastructure for disease surveillance exists and versions of it are successfully functional within many nations. National systems thus contribute invaluable data for government planning and response in both the human and animal health sectors. In terms of international infrastructure, many organizations including UN-associated agencies and NGO's, already either monitor infectious diseases on a broad scale or provide assistance when outbreaks occur. At the same time there is no overall international coordinating leadership that covers both 'human' and 'animal' diseases, no centralized accessible system of databanks, and relatively few multilateral or bilateral agreements for data sharing. Implementation of an international system will require significant diplomacy, although it might be argued that the outcomes will warrant the effort. Improved biosecurity is one example.

On a global scale, diagnostic resources and reliability are highly variable. This especially is the case in regions that are economically depressed or politically unstable. International response to outbreaks can be swift and potentially effective on a high profile case-by-case basis (such as with influenza A, H1N1), but is incapable of responding to the broad range of public or animal health issues that arise regularly. Unanticipated outbreaks involving previously unknown zoonotic agents add yet another type of complexity that demands a well-coordinated response and transparent international data sharing. Historical experience documents the potentially dangerous political impact of natural outbreaks that occur by chance in regions of conflict or in regions that are socially or economically unstable.

Intentional outbreaks of disease or the potential for outbreaks that are the consequence of incompetent laboratory practices are matters of special concern. A disease surveillance system should be able to detect and distinguish such events, but currently it is unlikely that unnatural outbreaks would be recognized quickly. A global disease surveillance system could contribute to United States national security by serving as a stabilizing force in the face of a pandemic. At the same time, it might be too much to expect that a global system could recognize 'unnatural' events that could destabilize nations or large geographic regions.

The fact is that too little is known about the geospatial distribution, ecology, and biology of zoonotic diseases that have the potential to cause outbreaks in human populations or in the agricultural sector. Intensive research

over the past several decades has produced a substantial amount of information that substantiates the value of knowing about the geographic distribution, genotypic characteristics, and evolution of infectious agents. There also is substantial value in data about reservoir species and vectors. Mathematical modeling and remote sensing by satellite have advanced to the point where it is practical to monitor vast areas and predict outbreaks.

Our recommendation is that Emergent Disease Preparedness must be a high national security priority for the United States. The development of an accessible database with global coverage is practical, and would serve as the foundation for monitoring, assessing, and responding to outbreaks, especially outbreaks of unknown origin. Moreover, an Emergent Disease Preparedness Program would shift strategic focus from defense against the unknown to active engagement and acquisition of scientific information essential to security. The program that we envision will serve as a logical vehicle for international cooperation in biosecurity. It will create diplomatic pathways to agreements that support science, medicine, and disease surveillance. Finally, from our perspective, such a program can be seen as a maturation of nonproliferation and threat reduction strategic thinking in the field of biological sciences.

I. Introduction

Global disease surveillance—the ability to detect, identify, and monitor the occurrence of disease on the broadest geographic scale—is a critically important challenge with political, social, and economic overtones for the United States and the international community (1).

The basic concept of ‘surveillance’ is not new. In 1968, prior to the age of molecular diagnostics and powerful desktop computers and associated software, the Centers for Disease Control (CDC) defined surveillance as “ongoing systematic collection, analysis, and interpretation of health essential to the planning, implementation, and evaluation of public health practice (2).” Although not mentioned in this definition, the pathways of dissemination of acquired information or analysis is an essential aspect of surveillance. One obvious pathway is in the form of feedback to persons generating the initial surveillance data. This is the pathway that ensures that disease surveillance does not become merely a ‘collection’ and ‘archive’ process.

In the broad sense, surveillance programs can be applied to an array of health-related subjects ranging from infectious disease to occupational safety, injuries, and personal health practices. Over time, four types of surveillance have been applied to monitoring diseases: active, passive, sentinel, and syndromic. Among these types of surveillance, syndromic surveillance typically makes use of spatial (geographic) and temporal analyses. One example is the Syndrome Reporting Information System (SYRIS), which can provide an early warning to important disease outbreaks or bioterrorism events (3).

Regardless of the surveillance system, the significance of *global* disease surveillance to United States national security policy arises in part from the appearance of emergent or re-emergent zoonotic (animal-borne) diseases in human beings (4, 5). Most emerging infectious diseases in the past 40 years have had a zoonotic origin. Such outbreaks can be natural phenomena. Habitat modification, geographic changes in human population densities and land use, and climate change are examples of factors that can affect natural outbreak. Economic and social factors interrelate with the foregoing factors. But regardless of cause, zoonotic diseases

can have serious consequences for the United States (6, 7, 8). Several foundations privately fund one zoonoses surveillance system, called the Global Viral Forecasting Initiative (GVFI) (9). The United States Department of Defense also has a surveillance system for emerging infectious diseases—the DoD-GEIS (10).

Unfortunately, disease outbreaks also can be intentional, and the threat of transnational bioterrorism or even state-sponsored programs is a significant factor. Disease outbreaks also could be the accidental consequence of human manipulation of nature or even standard types of research on infectious agents conducted without adequate biosafety practices. The collective national security significance of disease outbreak is multiplied by the potential for intentional outbreaks to be masked as natural disease (11, 12). Under most circumstances it would be difficult for a nation to know if they were under attack or facing natural phenomena (13). Appropriate response to a disease outbreak of unknown origin thus is a major challenge, which begins with surveillance and detection (14). Unfortunately, our ability to respond and distinguish between natural and intentional outbreaks is limited by an absence of critical surveillance information on a global scale.

On a global scale, disease surveillance is an extremely large challenge. The international complexities are daunting. They include: working relationships among international organizations with overlapping jurisdictions; parochial, political, economical, and security interests of neighboring states; difference in average levels of education; access to adequate training and equipment within a particular country; and the reality that in some countries there simply are higher priorities, such as adequate food supplies, clean drinking water, and basic sanitation.

Regardless of complicating factors, many fundamental mechanisms for global disease surveillance are in place and functional. In the United States, the Centers for Disease Control detects, monitors, and reports on disease outbreaks in humans. A recent (2006) restructuring within CDC reflects the importance of emergent zoonotic diseases. Likewise, the Animal Public Health Information System (APHIS) within the Department of Agriculture monitors animal health—

especially livestock and poultry, but also wildlife to a limited extent—on a global scale and maintains a geospatial database of disease occurrence. Zoos are important sentinel sites. These institutions typically monitor the health of their animals on a regular basis. In the United States, state environmental and conservation agencies monitor and report on wildlife diseases, especially in game species frequently in contact with human beings.

Several national laboratories are positioned to respond to outbreaks linked to potentially exotic infectious agents. Although the trend is generally uncoordinated, academic institutions are gradually improving research facilities (typically by building BSL-3 laboratories) and monitoring the health of faculty, students, and technicians who work with animals or infectious agents. The National Institutes of Health (NIH) has funded Regional Centers of Excellence for Biodefense and Emerging Infectious Disease Research, which in turn fund research and career development and attract scientists into work that is relevant to both biodefense and response to emergent diseases (15). All of these resources are intended to be part of the network foreseen as a component of the National Biodefense Analysis and Countermeasures Center (NBACC) (16).

All developed countries and a substantial number of small, less economically developed countries have government agencies analogous to those in the United States. Many countries exchange at least certain types of health information. A good example is the network of national and international information systems devoted to tracking the annual outbreak of influenza. Many countries also link into central reporting databases such as the one maintained by APHIS in the United States. On an international scale, the World Health Organization (WHO) has the major role in monitoring diseases in humans. WHO also responds to selected international issues, including fielding teams of experts in response to outbreaks, linking countries to sources of financial aid, and providing training and technical assistance where needed (1). In a similar way, the World Organization for Animal Health (formerly Office International des Épizooties) (OIE) in Paris and the UN Food and Agriculture Organization (FAO) monitor and collect information on animal (generally livestock) diseases on a global scale. The OIE is linked to numerous regional organizations that usually emphasize diseases signifi-

cant to livestock in a particular geographic setting. The OIE database is called the World Animal Health and Information Database (WAHIS). The FAO Animal Disease Information System database is called EMPRES-*i* (17). These systems trigger an alert that includes disease diagnostic information and geographic data. The OIE missions are to: ensure transparency of global animal disease monitoring; disseminate animal disease reports and veterinary information; improve methods of disease control and eradication; and publication of standards for international trade in animals and animal products. The Federation of American Scientists developed a policy program for monitoring emerging diseases (called ProMED), which includes projects aimed at using disease surveillance as a mechanism for detecting agro-terrorism or economic sabotage potentially on a global scale (18).

The World Bank and a variety of non-governmental organizations (NGO) contribute to aspects of disease surveillance through loans or local medical assistance or data gathering and dissemination. In some countries, World Bank funding has been leveraged in order to develop political will and commitment from governments previously disinterested in infrastructure necessary to support disease surveillance.

The United States maintains bilateral agreements on joint disease surveillance projects through agencies such as the United States Agency for International Development (USAID), the Department of Health and Human Services, the Department of Defense, and the Department of State. The US-Japan Common Scientific Agenda and EU-US task force on emerging diseases are two additional platforms that support disease surveillance. Finally, Article X of the Biological Weapons Convention (BWC) provides incentive for countries to team on epidemiological research and surveillance (19). This latter system has potential value as a mechanism for addressing disease outbreaks, although it also requires that the outbreak is suspicious. This requirement in itself creates yet another layer of political complication, which might limit the usefulness of the BWC as a mechanism for international response to an outbreak (20).

In the overview, the mere concept of global disease surveillance is both ambitious and complex. Some of the complexity comes from the variety of organiza-

tions and divergent missions that in some way are a part of disease surveillance. Political and economic realities add another layer of complexity. Moreover, the nexus of disease surveillance, emergent zoonotic

diseases, and the potential intentional use of disease agents as weapons is a significant security issue for the United States (12).

Challenges to Global Disease Surveillance

Although fundamental technology and models for disease surveillance exist, the current system is inadequate for the task on a global scale, especially in context of United States national security. The reality is that national security is a priority. Because disease outbreaks could result from intentional misuse of biology or even carelessness in research laboratories, disease surveillance and United States national security are overlapped. But the perspective, priorities, and goals of the United States are not necessarily shared with all nations that might participate in a 'global' surveillance system. One of the most basic challenges, therefore, is to overcome such differences in perspective and priority. Engagement through the diplomatic community is a significant aspect of developing any type of global system.

The purely scientific complexities of emergent disease, the absence of critically important baseline information, the international variability in diagnostic capability, the realities of international politics and policy, the shared concerns over biosecurity and dual use capabilities, the involvement of the private sector, the facts of recent East-West history, and the limitations on coherent strategic planning and leadership all combine to make disease surveillance an enormous challenge on a global scale.

The spread of avian influenza H5N1, the appearance of a previously unknown syndrome (SARS-related coronavirus), and outbreaks of human encephalitis caused by Nipah virus in south-central and southeast Asia remind us of the dangers posed by lurking infectious diseases and the rapid mutation rates that will always produce new strains (21, 22, 23). In all three examples, the pathogens originated in wild animal 'reservoir' species and spilled over into domestic animals (24). Introduction of an infectious agent from wild species into domestic animals can result in a crisis because domestic animals often are densely congregated and in

contact with human beings. Herds of livestock, flocks of poultry, or pets kept by humans provide infectious agents with opportunities to multiply rapidly in proximity to humans. Rapid multiplication in a new host environment creates a situation in which new genetic strains are likely to appear. Outbreaks in humans can follow. Many nations have struggled to respond to complicated pandemic threats such as avian influenza and SARS, but politics, suspicion, and self-interest complicate cooperation and collective planning.

In the foregoing examples, purely technical issues also complicated the international response to outbreaks. In the case of SARS, the initial focus was on Chinese rural markets but the identity of the wild reservoir species was unknown. Establishing rhinolophid bats as the ultimate origin of SARS required a combination of basic biological fieldwork, systematic mammalogy, and laboratory research. In the case of avian influenza H5N1, an understanding of the role of migratory bird species and their interactions with domestic fowl is incomplete. Another complication is posed by the fact that strains of avian influenza H5N1 virus also have infected house cats in both Thailand and Iraq. Analysis of an infected cat obtained in Iraq revealed that the strain of H5N1 was 99% similar to a previously sequenced strain obtained from geese. Phylogeography is an analytical tool that enables scientists to combine a genealogy of viral strains with geographic locations from which the strains are known to occur. Using this tool, scientists placed the cat-derived viral strain isolated in Iraq in Clade II of H5N1 viruses. On this basis the Iraq strain was geographically associated with viruses circulating in geese in Qinghai, China (25). How a cat in Iraq contracted this strain of H5N1 virus is unknown, at least in an exact sense. Most likely, H5N1 entered northern Iraq in poultry, probably via the outbreak that occurred in Turkey. In the meantime, the phylogeographic analysis that revealed the connection between the virus in cats and Qinghai, China, illustrates

the value of linking nucleotide sequence data in both a phylogenetic and geographical context. Such a linkage provides information known as a “DNA/RNA postal code” and it is a powerful tool for tracking, predicting, and understanding zoonotic diseases in a geographic context (26). Phylogeographic analysis of nucleotide sequences—be they DNA or RNA—can be applied to infectious agents, their reservoir species, and any vectors involved in transmission. Combinations of such data can reveal historical and evolutionary interrelationships among zoonoses and hosts and is a basic step toward predictive models.

Recent outbreaks of emergent zoonotic disease underscore the fact that there is no current international capability to use accessible information about reservoir species to predict future outbreaks or geographic spread or even to identify geographic foci and local prevalence, or genetic diversity in most zoonotic viruses. Indeed, in many cases even the species identification and habitat of the natural host reservoir(s) is unknown and impossible to determine without field and laboratory research. In other instances the reservoir species of mammals or birds have been misidentified based on outdated field guides or undocumented by voucher specimens stored in research museum collections, or both (27). Voucher specimens are essential to the scientific validity of epidemiological research on zoonotic disease. Such specimens of mammals or birds collected in the wild must be accessioned into legitimate museum research collections where they can be identified to species. Once they are stored in such collection facilities, the voucher specimens provide a measure of scientific certainty as to reservoir species identifications because they can be analyzed or double-checked independently. Uncertainty about reservoir species identifications is unfortunate because such information is essential to understanding spatial epidemiology of disease and outbreak prediction (28, 29). In particular, once reservoir species have been identified, it then is practical to estimate geographical range, habitat requirements, and population densities in context of land use and a wide range of other variables. This in turn sets the stage for using remote sensing—including satellite imagery—to predict outbreaks of zoonotic disease (29).

On a global scale, governmental ministries and departments usually apply the term ‘wildlife’ to natural disease reservoirs. The alternative, which requires a

scientific foundation, is to seek an accurate understanding of the actual species that act as reservoirs. The term ‘wildlife’ connotes a level of uncertainty and provides such a low level of information that it is useless when it comes to prediction of ecological distribution, or monitoring of population densities and dispersal, or responding quickly to an outbreak. Currently available laboratory and field technologies can result in genetically-based species identifications. Preparedness for responding to outbreaks would be significantly improved if baseline data on reservoir species, their genetic signatures, their geographic and ecological distributions, and species associated with them were available and stored in accessible databases. Financial resources should be available for research on reservoir species and creation of such a database.

Infectious disease was the fundamental issue that prompted the creation and drove the development of the state and federal public health agencies and regulatory guidelines in the United States. Ironically, however, historical success in this realm might have bred institutional complacency. Educational training programs, research in epidemiology, perceived competency of the American medical profession, effective lobbying, and supportive legislation combined to make local and national capabilities appear to be adequate. But the occurrence of seemingly ‘new’ diseases in the last few decades has altered the political landscape and assumptions about preparedness. For example, the discovery in 1993 of a “new” hantavirus in the United States (with a fatality rate approaching 50%) led rapidly to the discovery and geographic localization of an additional 27 strains of the virus in the United States alone (30, 31). The original hantavirus outbreak was well publicized and captured public attention. Alarm over the outbreak predominated at first. Because many of those who fell ill were Native Americans, there also were social implications. Ultimately, questions were raised about public health preparedness. Although the outbreak of an unknown disease initially had political repercussions, the outbreak also led to a substantial technical response that included field biology, surveys of rodent specimens housed in museum research collections, and subsequent laboratory work.

The unexpected appearance of HIV/AIDS is another incident that altered public perception of infectious disease. Other emergent diseases such as tick-

borne Lyme disease in the northeastern United States, the rapid spread of West Nile virus in birds, livestock, and human beings, and rodent-borne hantavirus-associated respiratory disease have attracted attention, but their actual public and economic impacts have been far lower than those associated with HIV/AIDS.

One outcome of the foregoing is that the United States scientific community has focused substantial research effort on the ecology of emergent disease. Because this is a complex problem, scientific interest has been comprehensive. Zoologists, systematic and evolutionary biologists, virologists, and ecologists have found ways to work together to conduct multidisci-

plinary research on emergent zoonoses with financial support from federal and state agencies (32, 33). Federal governmental agencies have gradually recognized the economic, trade, social, and foreign policy significance of unanticipated kinds of human disease. The relationship between emergent diseases and biodefense has significant national security implications. Although this relationship is not yet fully appreciated in Washington, it has obvious implications for the nonproliferation and threat reduction community within the government. One challenge before us is to discover ways to integrate the scientific and technological components with United States foreign policy in the field of threat reduction.

An Accidental Confluence of Significant Events

Awareness of infectious disease as a national security threat gradually captured attention at the highest levels of the United States Government in the 1990's. Today the terrorism of mailed anthrax spores, the international impact of the SARS outbreak, and dire predications about avian influenza H5N1 have solidified the attention of the National Security Council, the White House, and Congress and also have brought these issues before the American public. Outbreaks of naturally occurring infectious disease are a phenomenon that overlaps with biosecurity concerns and has potential linkage to transnational bioterrorism. Collectively, these topics merge into a complex *mélange* that has significant foreign policy implications. Hopefully, this is understood in political circles and thus figures prominently in business conducted by the Department of State.

Despite long-time efforts of security and health experts, it probably was an accidental convergence of events that contributed most to the increased significance attached to the subject at the highest level of government. In addition to the unanticipated appearance and spread of a dramatic new disease—HIV/AIDS—with complicated social implications, in the early 1990's, West Nile virus unexpectedly appeared in major urban centers, hantavirus and Lyme disease made news, tuberculosis re-emerged as a global threat, and Ebola claimed a deadly toll in Africa. While these natural, emergent, zoonotic diseases captured headlines and created health, policy, research, and political cri-

ses, American troops returned from Operation Desert Storm, and, within a few months, an unknown health malady dubbed Gulf War Syndrome was reported. The ensuing debate seized public and governmental attention. Was this a real and previously unknown arid land disease, a manifestation of psychological stress attributable to the threat of chemical or biological attack during combat against the Iraqi army, or, in fact, an actual indicator of Iraq's use of chemical or biological weapons (CBW)? What was the likelihood that the troops had encountered a previously unknown disease? No existing database could be mined for hints about a potential naturally occurring emergent disease or reservoir species distributed in the desert along the Persian Gulf. It was not until November 2008 that the United States Veteran's Administration issued a report concluding that overuse of pesticides and pyridostigmine bromide, a prophylactic drug that confers protection from nerve agents, were likely causative factors (34).

While emergent zoonotic diseases and Gulf War Syndrome occupied public attention, another set of circumstances unfolded independently. First, after the collapse of the Soviet Union in 1991, the capability of their bioweapons (BW) program gradually became known through defectors and other former weaponeers who now were free to talk and write about some of their experiences. The full scope of this massive program became clear as nonproliferation programs engaged dozens of laboratories scattered across the former

Soviet Union. Second, the United Nations in 1995 uncovered and revealed the Iraqi BW program, thus confirming the existence of anthrax and other weaponized biological agents and their means of deployment and delivery (35, 36). By 1997, the potential interplay among regional instability, transnational terrorism, and primitive, but frightening, attempts at bioterrorism also was increasingly obvious. Most important, all of these seemingly far-flung subjects shared enough in common to coalesce under a single heading—**infectious disease and surveillance**—and added up to a significant national security issue.

The confluence of events had an impact on the United States government by gradually overcoming the inertia associated with its vast bureaucracy. Disease, human and animal health, foreign policy, biosecurity, and counter-terrorism could no longer be conveniently parceled to federal agencies and treated as business as usual. The potential relationship of nonproliferation programs aimed at redirection of former Soviet weapons and concerns about natural emergent zoonotic diseases were noticed at the agencies managing the programs. Moreover, public health specialists in the United States and abroad agreed that global disease surveillance systems were inadequate.

In 1996 President Bill Clinton issued a Presidential Decision Directive that called for a more ‘focused’ United States policy on infectious diseases (37). President Clinton also announced \$1.4 billion in Federal spending to develop urban response teams, protect government facilities, develop and stockpile vaccines, and enable the nation to detect and diagnose outbreaks caused by biological agents.

Collectively, presidential directives and funding legislation related to disease surveillance had measurable results. For the first time since early in the Cold War, the public health sector became directly linked to national security. The Department of State listed protection of human health and reduction of the spread of infectious disease as national strategic goals. The National Institutes of Health increased funding for research on emergent diseases and in early 2000 the National Intelligence Council produced an intelligence estimate on the threat of global infectious disease and its implications for the United States (38). In 2000 and again in 2001, the General Accounting Office (GAO) issued its own reports to Congress on challenges in improving infectious disease surveillance systems (1, 39).

SECTION SUMMARY

- Global disease surveillance is a critically important but complex international issue.
- The current system is inadequate for the task on a global scale and in context of national security.
- Recent events serve as reminders of lurking infectious diseases and the rapid mutation rates that produce new strains.
- Increasing human population size and, therefore, local densities, along with international movement of substantial numbers of people on a daily basis, contribute to evolution of new strains of disease, contagion, and rapid spread.
- There is no current capability to use information about reservoir species to predict emergence, spread, foci, prevalence, or genetic diversity in most zoonotic viruses.
- Disease, human and animal health, foreign policy, biosecurity, and counterterrorism cannot be treated as business as usual.
- Our knowledge of global pathogens even in the Western Hemisphere is woefully inadequate.
- Our ability to forecast disease emergence and spread is technically and mathematically possible, but lacking.

II. The 2000 National Intelligence Estimate

The National Intelligence Estimate (NIE) of 2000 reflects the thinking and analysis of the United States Government at that time in regard to security issues raised by infectious diseases (38). Because it was developed prior to fall 2001, this NIE does not reflect the emotional impact and uncertainty following the anthrax mailings and terrorist attacks on the United States. For these reasons, it is an excellent historical starting point for a discussion of where we are and where we should be in terms of global disease surveillance.

The NIE for the year 2000 concluded that, “development of an effective global disease surveillance and response system is probably at least a decade or more away, owing to inadequate coordination and funding at the international level and lack of capacity, funds, and commitment in many developing and former communist states.” The NIE also predicted that international progress in responding to infectious diseases would continue to deteriorate for several years before measurable progress might occur. This scenario was deemed the most likely—the alternative scenarios being the extremes of steady progress versus stymied progress—but all three scenarios were over-shadowed by concurrent caveats. All bets were off if a deadly and highly infectious new disease were to appear, if HIV/AIDS increased catastrophically, or if a contagious biological agent were to be released by human beings.

In terms of United States national security, the NIE concluded that emerging or re-emerging infectious diseases would continue to kill at least 170,000 Americans annually. Significantly, the NIE also con-

cluded that many of these new diseases would originate overseas. Infectious disease also was seen as a threat to U.S. and NATO military operations, especially in developing countries. HIV infection rates were predicted to increase in Sub-Saharan Africa, in the former Soviet republics (the ‘newly independent states’ or NIS), and in unnamed rogue states. Such events were predicted to affect military capabilities and recruitment pools. Politically, infectious diseases were predicted to have a heavy socioeconomic impact on developing countries (including the NIS), and this impact in turn would affect the United States through the cost and delivery of humanitarian aid and responses to regional or local instabilities. Finally, the NIE also highlighted difficulties due to embargos or travel restrictions and the interplay between infectious diseases and the potential for BW or bioterrorism.

Three specific aspects of the NIE report merit retrospective consideration. First, the report focused on a short list of human diseases – referred to as the ‘deadly seven’ – given priority based on their mortality rates and significance as assessed by the World Health Organization (WHO) and the U.S. Armed Forces Medical Intelligence Center (AFMIC). Second, the NIE report scarcely accounted for so-called animal diseases that (a) can infect human beings and (b) have major economic impact within the United States. Third, the NIE assumed that new diseases would most likely emerge in developing countries, the Russian Federation, or in the newly independent states, but not within the United States.

The Deadly Seven Diseases

Focusing on the deadly seven diseases makes sense in statistical terms. HIV/AIDS, tuberculosis (TB), malaria, hepatitis B and hepatitis C, lower respiratory infections, various forms of diarrhea, and measles accounted for the highest number of deaths worldwide in 1998. At the same time, however, each of these diseases is well defined, all are diagnosable, and most are treatable to some extent. Moreover, massive amounts of funding, research, and drug and vaccine development

are already devoted to each of the “deadly seven.” One consequence of such focused support is that international cooperation on reporting has been achieved and treatment has steadily improved. Given the current resources, response capability, and successes with the deadly seven diseases, is additional surveillance of these particular diseases required? The answer probably is no given the cost and other expensive priorities. But do any of these seven diseases constitute an unusual

threat to national security? Again the answer is no if one assumes that lesser known or previously unknown infectious agents constitute a greater threat than well-known, well-studied diseases. But there might be exceptions. One exception is hepatitis, which often is a co-infective agent, and another possible exception is drug-resistant tuberculosis. Ultimately, the real prob-

lem is that a focus on the “deadly seven” is inadequate and potentially misleading when infectious diseases are thought about in context of national security or bioterrorism. Such a focus can lead to an over-commitment of financial and other resources and a false sense that national security priorities have been satisfied.

Animal-borne Diseases

Zoonotic (animal-borne) diseases were hardly mentioned in the NIE report (38). This was an important oversight that can be explained by the paradigm that ‘human’ and ‘animal’ diseases are somehow different and biologically unrelated. The historical and cultural division of medical practice between human beings and domestic animals is very likely the source of this artificial categorization. Academically, the division between animal and human health was reinforced in the United States by creation of separate human medical and veterinary medical schools and professional associations. It was further reinforced by the fact that in American universities, veterinary medicine is administered within agriculture and generally restricted to Land Grant institutions, which originally usually did not have medical schools. Literally, then, the traditional veterinary and human medical programs usually do not co-exist on a common campus or even within the same university. They are, in fact, still separate activities in most respects. The failure of WHO and OIE to integrate their respective surveillance systems was highlighted in the 2008 report of the Commission on Prevention of Weapons of Mass Destruction Proliferation and Terrorism (4).

As it grew and matured administratively in the late 19th Century, the United States federal government parceled subject matter, policy development, and regulation into different agencies with their own missions. Eventually, this led to the U.S. Department of Agriculture (USDA), the National Institutes of Health (NIH) and Public Health Service (PHS), the Food and Drug Administration (FDA), and the Fish and Wildlife Service (wildlife management and disease control). Today, historical priority, budget, physical property and facilities, congressional authorizations and other factors reinforce this administrative and managerial

canalization. The United States is not unique in this regard. Animal and human diseases are regarded as different in most countries and this difference extends to the way that governments are organized. Moreover, there is a widespread homocentric cultural bias: human medicine is typically given priority, regulated to higher standards, and provided more financial resources than animal medicine, which is relegated as a subset of agricultural issues.

In one response to the problem of the animal versus human disease mentality, the Federation of American Scientists created an Animal Health/Emerging Diseases Project (AHEAD) with a focus on developing nations (40). Under this umbrella, the Federation developed the International Lookout for Infectious Animal Diseases (ILIAD)-Tanzania project, which is an animal disease surveillance system for deployment to impoverished rural areas of Africa. The mission of the ILIAD-Tanzania project is to provide “timely and accurate disease detection, diagnosis, prevention, and control” but the rationale is that because many animal diseases—brucellosis being a good example—can be transmitted to human beings, “their management and prevention are crucial to improving public health on a global scale” (40). Another example is the “one world, one health, one medicine” initiative, which aims to bridge veterinary and human medicine (www.wcs.org and www.oneworldonehealth.org).

It obviously is in the United States’ interest for human and veterinary medicine to strive toward a technically-based coalition. The only cautionary note is that such a revised relationship between two artificially distanced professions needs to somehow include an improved relationship with the biological sciences community. While the emphasis here is on

medicine, an understanding of emergent disease and zoonoses requires specialized scientifically-based expertise not found in the American medical communities. Mammalogy, medical acarology and entomology, and parasitology are examples of academic disciplines needed to provide the expertise required to conduct comprehensive research and promote preparedness for dealing with zoonotic diseases. There also are obvious roles for ecologists, specialists in geospatial analyses and satellite imagery, and mathematical modelers, just to point out a few more examples.

The arrival and spread of West Nile Virus in the United States illustrates complications that can arise from dividing infectious diseases into “animal” and “human” illnesses. In this instance, failure to recognize the relationship between bird die-offs and sick human beings misled the CDC and was one factor that delayed the correct identification of the infectious agent behind the epidemic (10). It also was the case that the initial human cases were attributed to St. Louis encephalitis virus because of geographically-based expectation.

Viewing the world as though ‘animal’ and ‘human’ diseases are separate biological entities might be more disrupting and limiting for developing nations than it is for the United States. In the United States this artificial distinction is mistakenly seen as merely a bureaucratic annoyance. But it is imperative to know that even for the United States this artificial world view has national security implications because it has become a paradigm that affects communication, expectation, and ability to think strategically. In developing nations it hinders progress, squanders resources, and misses opportunities for international financial and technical assistance. At a Regional (Kyrgyz Republic, Kazakhstan, Uzbekistan, and Tajikistan) Central Asian Disease Surveillance Workshop held in Bishkek, Kyrgyz Republic in 2006, one of us (CJP) moderated a working group on ‘Integrating Human and Animal Disease Surveillance’ (41). The working group included scientists, health specialists, representatives from WHO, FAO, U.S. Naval Medical Research Unit-3 (NAMRU-3), and governmental representatives from the Kyrgyz Republic, Tajikistan, the United States, Canada, and the UK. The private business sector was represented by Black & Veatch, a company that has developed software for disease surveillance. The

working group recommended a strategic approach with several specific steps.

- Create an inter-ministerial committee on zoonotic disease that meets on a regular schedule and is empowered to develop common reporting standards and goals.
- Define stakeholders (*e.g.*, public health officials, physicians and veterinarians, agriculturists, local and regional political and economic interests) and develop respect and shared interests.
- Develop an inter-ministerial reference laboratory for diagnostics, reporting, and emergency response.
- Create a regional scientific association that focuses on zoonotic diseases
- Bring higher education into the process through development of curricula that focus on biology of disease and ensure that public health integrates the human medical interests with veterinarian and agricultural interests.
- When resources are scarce, focus should be on monitoring zoonotic diseases in known geographic foci rather than the country at large.
- When outbreaks occur, WHO and other international organizations with field response teams should be quickly invited to assist on the ground.

The human- and animal-disease issue is a case in which common sense and scientific data must take precedence over political considerations, turf and resource issues, and homocentric traditions. Approximately 75% of diseases that have emerged over the last 30 years have been zoonotic (animal-borne) diseases that are transmitted to human beings. Moreover, ~60% of all infectious diseases typically associated with humans actually are shared with other mammal species. None of this is surprising from the perspective of evolutionary biology. Although evolution primarily is

regarded as an academic subject, evolutionary theory actually has broad applicability (42). In this instance, phylogenetic analyses result in ‘trees’ that illustrate historical relationships and these trees are the starting point for understanding the biological distributions of infectious agents.

Additional, new, emerging zoonotic diseases of concern will inevitably have wild animal reservoirs. Development of research teams with combined expertise (human health, veterinary medicine, and biology) would be a valuable strategy for dealing with this challenge (43, 44, 45). Zoonotic diseases can be adapted to use as biological (and economic) weapons. For the United States, a successful bioterrorist attack on the agricultural sector could have dire economic consequences.

One can easily gain a sense of this by exploring the economic impact of natural outbreaks. The rapidly evolving virus associated with blue-ear disease (porcine reproductive and respiratory syndrome—PRRS) in southeastern China and Viet Nam is a case-in-point. This swine disease has affected international relationships and led to a 1% decline in China’s GDP (46).

With the foregoing in mind, any program for global disease surveillance must integrate all of the resources and information about disease without regard to the unnecessary and artificial separation of diseases into ‘animal’ and ‘human’ disease. The term ‘species-neutral’ has been applied to the idea of such integration, which must be a priority when it comes to United States national security.

The Role of Emergent Disease According to the NIE

Emergent zoonotic diseases constituted the single major assumption in the NIE, which anticipated that developing countries would be the likely sources of previously unknown infectious agents. Emergent disease represents the unknown, and experience to date with HIV/AIDS, Ebola, Marburg, and Nipah encephalitis, hantavirus and arenaviruses in North and South America, a wide variety of Asian hemorrhagic fevers, and SARS is not encouraging (39, 47, 48). In most of these examples, reservoir species—the species of animal in which the virus resides over long time periods and the geographic limits of distribution of these “reservoir” species—are either unknown or imperfectly known (27). In most cases, environmental factors and mode(s) of transmission also are scientific mysteries. The same things can be said about potential vectors, which usually are the insects or ticks and chiggers (or both) that can transmit disease agents from a host reservoir species to another animal, including human beings. To a variable degree these emergent diseases are being “managed” within reasonable statistical limits. But because of an absence or paucity of data and analyses, the next new outbreak cannot be predicted geographically or epidemiologically. Even though scientists think they have identified the chimpanzee reservoir of HIV-1 virus and that with phylogeographic analysis have developed a robust hypothesis for the origin of HIV/AIDS, it still took 25 years to make that discovery. Given the rate at which new diseases emerge, 25 years is far too long a

timeline to provide adequate opportunity to prevent significant impact on humans, nations, and economies.

The United States presumably is better studied geographically, and potential reservoir species for emergent zoonotic diseases are better known, than is the case with most other politically defined regions of the world. But even in the United States we know very little about how infectious diseases are transmitted directly or indirectly to people from wild reservoir species. Not only have 27 new hantavirus strains been discovered since 1993, but two additional hantaviruses pathogenic to humans have been discovered just in New Mexico since that time (30). On a global scale, zoonotic diseases generally are associated only with domestic livestock or ‘wildlife’ rather than with particular species of wild mammals or birds. There are several reasons why this is the case, beginning with a lack of voucher specimens that specialists can use to identify species. Globally, it also is the case that local specialists are scarce and outbreak response is in the hands of agencies that are strictly associated with either public (human) health or agriculture and veterinary medicine.

It is important to know that technically it is feasible to detect, isolate, and genetically characterize previously unknown infectious agents. Both SARS in Asia and hantavirus-associated pulmonary syndrome in the United States are good examples of successful

technical response to unexpected outbreaks. At the same time, it also is true that in both examples the outbreaks document how political priorities can complicate the process of responding to a new disease (31, 49). But regardless of the political challenges, it is possible to determine the geographic patterns of viral circulation, genetic diversity and virulence, prevalence of an agent in natural populations, and identifications of reservoir species and vectors. Moreover, the scientific expertise also is available to identify and genotype reservoir species (such as mammals and birds) and vectors (such as ectoparasites or mosquitoes) and to predict ecological or climatological factors influencing emergent disease. Although U.S. government agencies and the scientific community are engaged in these kinds of projects, there is no centralized program to systematically acquire and integrate the information into databases that can be interactively interrogated in the United States. Integrating these efforts and being able to model the impact of global climate change on reservoir species, their evolution, their geographic and ecological distribution, and their migration or other movements will be a critical requirement in coming decades (50).

Emergent zoonotic diseases are an extreme contrast to some common non-infectious human diseases such as hypertension and most cancers. In the latter case, many human beings succumb every year and there is a massive technological response. In the former case, relatively fewer people die, but the disease constitutes a greater public health threat because (a) the mortality rate in new outbreaks can be high, (b) very little is known about their epidemiology, (c) we have no ability to predict the emergence of a new variety, and (d) the national security risk includes the need for redirection and rapid response and the possibility of terrorism or some other international complication. In comparison to hypertension or cancers or most of the “deadly seven” diseases, only emergent pathogens have special national security implications. There is a realistic potential for them to be harvested or acquired during legitimate research projects and from there be used in bioterrorism or state-sponsored biological weapons (BW) programs (51, 52). The potential for intentional release of a previously unknown but naturally occurring infectious agent should be a matter of concern. Acquisition of such a novel agent does not require sophisticated laboratory manipulation, and such novel agents will always be

available in nature. Based on the experience in the United States, the known infectious agents probably represent only a fraction of those that are available in natural reservoirs. The compelling question is: could a disease surveillance system be developed to recognize potentially dangerous but still emergent zoonotic diseases, and, if so, how could it be done?

Although the NIE focused on specific important but well-known diseases, the report included a brief section on ‘Economic Development and Land Use,’ which addressed factors that influence emergent disease. The NIE drew the following conclusions (38).

- Changes in land and water use patterns will remain major factors in the spread of infectious disease.
- The occurrence of Lyme disease in the United States and Europe has been linked to reforestation.
- Conversion of grassland to farm land in Asia encourages growth of rodent populations carrying hemorrhagic fever and other viral diseases.
- Human encroachment on tropical forests will bring populations into closer proximity with insects and animals carrying diseases.
- Close contact between humans and animals in the context of farming will increase the incidence of zoonotic diseases.
- Water management and agricultural irrigation will encourage spread of water-breeding vectors such as mosquitoes and snails that have contributed to outbreaks of Rift Valley fever and schistosomiasis in Africa.

Technical and scientific issues can be raised with all of these sweeping generalizations but it is nevertheless noteworthy that the NIE recognized the threat of emergent diseases and concluded that environmental factors and human activities were important considerations.

SECTION SUMMARY

- The National Intelligence Estimate (NIE) concluded that emerging or re-emerging infectious diseases would kill at least 170,000 Americans annually.
- The NIE assumed that new diseases would most likely emerge in developing countries, the Russian Federation, or in the newly independent states.
- Animal diseases are hardly mentioned by the NIE, which is an important oversight.
- A program for global disease surveillance must integrate all resources and information and should be a priority for United States national security.
- Emergent diseases constitute a significant threat because (a) very little is known about their epidemiology, (b) we have no ability to predict the emergence of a new variety, (c) these infectious agents frequently are deadly when contracted by human beings, and (d) these agents are potential resources for transnational bioterrorists.
- Since 1973 at least 30 deadly new diseases have been identified on a global scale.
- The NIE recognized the threat of emergent diseases and concluded that environmental factors and human activities were important considerations.
- Global climate change will have a profound impact on reservoir species.

III. Global Disease Surveillance: Problems and Concerns

The National Intelligence Estimate (NIE) of 2000 and General Accounting Office (GAO) reports to Congress in 2001 identified several specific challenges to global disease surveillance (38, 39). In 2008, the Commission on Prevention of Weapons of Mass Destruction Proliferation and Terrorism concluded that:

Disease surveillance and reporting remains a difficult and demanding task...and outbreak information is not always provided by WHO member states on a timely basis. Today's international surveillance networks are not comprehensive in their coverage...[and] reporting delays may result from political or bureaucratic hurdles as well as the lengthy laboratory analyses needed to confirm a disease diagnosis (4).

Although there are many challenges to the system, to a large extent previously identified problems were focused on the differences between developed and developing countries, with the conclusion that emergent diseases are most likely to appear in developing countries (38). Rather than begin by focusing on the developmental status of different countries, we prefer to first establish the goals and priorities of global disease surveillance and then identify the problems and challenges.

Presently, the term “disease surveillance”—defined by us as the ability to detect, identify, and monitor the occurrence of disease on a broad geographic scale—is widely used but typically is treated as if it represents a single unified international goal. In fact, the Centers for Disease Control (CDC) in the United States and the World Health Organization (WHO) and numerous other ministries and agencies in various nations constitute a patchwork of resources that more or less monitor disease occurrence in human beings. The central international theme, if there is one, is information gathering. The secondary theme, especially recently, is response.

Information gathering is used for such things as statistical summaries, analysis of trends, allocation

of resources (especially through the WHO), early warning of influenza strains, geographic spread of the deadly seven, re-emergence of old diseases (dengue, measles, polio, and drug-resistant TB being examples), and notification of new, emergent, diseases. If the international goal is to access this array of information, the current patchwork assembly does a modest job of accomplishing the goal. But at the same time, there are evident weaknesses and problems (53). The most obvious problems are driven by political or economic factors and can be conveniently organized as a set of questions:

- How reliable and available are laboratory and chemical diagnostics, especially in developing countries?
- Under what political, economic, or social circumstances are data withheld?
- What diseases are of greatest public significance, how are they diagnosed or recognized, and how does this vary across countries or regions?
- If emergent diseases first appear in rural or remote regions (especially in technologically underdeveloped nations), what is the likelihood of their detection or recognition, or both?
- Should information gathering be coupled to international response and health care delivery?
- Is it misleading or misguided to focus on certain diseases—such as the deadly seven—common to human beings and virtually ignore animal diseases?
- Does “syndromic surveillance,” which is based on pre-diagnoses data, offer advantages?

Diagnosics

Medical diagnostics traditionally was an ‘art.’ Eventually, however, laboratory-based diagnostics became feasible, rapid, and widely available, especially in the United States, Canada, and Western Europe. This technical advance gradually supplanted the largely (but not totally) subjective artistry of physicians. In countries where laboratory diagnostics became routine, the use of laboratories contributed heavily to the increased cost of health care. In the United States this cost increase was largely offset by economic strength and health insurance, two factors that do not apply to most of the world. Diagnostic costs have continued to increase as new technologies—such as real time PCR—have become available, making access to the tools increasingly difficult for developing countries.

Routine diagnostic capabilities in the United States have developed to the point that precise information is available and diseases and causes of mortality can be regarded as reasonably reliable as long as well-characterized diseases are involved. Data of similar reliability can be obtained from Europe, Canada, Australia, and Japan, but not from most of the rest of the world. In many places, diagnostics are simplified or improvised. The result is a lack of standardization of diagnostics, which increases statistical uncertainty and makes accurate analyses of data and trends very difficult. The idea of routine laboratory assays is not an option either because laboratories in many countries are unavailable, or ill equipped. Other factors also are at play. For instance, routine laboratory-based diagnostics often are impractical because of cost or because the laboratories are operated by technicians without equivalent levels of training as counterparts in more developed countries. Moreover, when it comes to human beings, economic reality and historical and cultural differences also inevitably intrude on any attempt at standardization in diagnostics.

Veterinary diagnostics exhibit a similar international pattern of variability in quality. Economic factors probably have the greatest impact, especially in developing countries where health ministries are often funded at a higher level than their agricultural counterparts. The historical divide between “human” and “animal” diseases probably exacerbates the challenge in developing countries.

In countries that are overwhelmed by health care challenges, precise diagnostics take a back seat to direct treatment of symptoms. In post-war Iraq, for example, years of poor sanitation, pooled runoff, and lack of potable water in the typical home is consistent with widespread diarrhea that takes a high toll on children. From a practical perspective, precise diagnosis of bacterial or viral agents is possibly less important than medical care directed at symptoms. From a resource perspective, significant improvements in infrastructure and public awareness might be immediately more important than sophisticated diagnostics. In terms of recent history and culture, the Iraqis—including their scientific community—frequently express the thought that cancers are on the increase. Quite sensibly, they point to environmental contamination as the likely source. In Iraq, however, there are no reliable data on the geospatial distribution of cancers prior to the first Gulf War, in most cases there are no local, regional, or national records that are accessible, and accurate diagnostics, especially in areas outside of Baghdad, probably do not exist.

In any country where political intention supersedes factual information, trustworthy diagnostic data, or acceptable statistical analysis, it is essentially impossible to conduct any type of disease surveillance. Also, under such circumstances the nation suffers because governmental decision-making regarding scarce financial and human resources will be affected. In Iraq, where infectious disease is a major challenge, the new (post-Saddam) government has had to address propaganda about depleted uranium ahead of infectious disease. Although no medical records or disease surveillance reports exist, the propaganda assertion was made that “elevated rates of cancers, congenital abnormalities, genetic defects, infertility, renal and hepatic dysfunction, cardiovascular diseases, malnutrition, spread of infectious disease, and death have all occurred” as a result of depleted uranium, electromagnetic fields, and “unusual oxygen ions” in the atmosphere (54). After several years of distraction, independent assessments of depleted uranium by the World Health Organization (55) and United Nations Environmental Programme (UNEP) (56) did not support the claims.

The foregoing paragraphs argue that reaction to recent history, culturally determined response to situation, a local sense of priority, international politics, and the struggle for resources can interact in ways that confuse priorities, diminish the role of science in

decision-making, and dissipate scarce resources. All of these inter-related factors can affect the capability of obtaining trustworthy diagnostic data to support any type of internationally standardized disease surveillance system.

Information Gathering

A global disease surveillance system presumes that countries will willingly share health information from within their borders. However, it is important to appreciate that this frequently is not the case. A classic example is the East African refusal in the 1980's to admit the dramatic impact of HIV/AIDS. Economic factors such as tourism, trade, and investment along with cultural and political expediencies interact to make it unlikely that nations will continue to share information in the absence of treaties or other binding legalities.

Ironically, however, it is possible that some countries, especially some of the former Soviet republics, will share disease information with the United States or the EU or even the Russian Federation more readily than with neighboring states. Information sharing is a complex problem in which critically important data might reach a central database before being exchanged between neighboring states. One might predict that regardless of the causes, impediments to data sharing will hamper local decision-making and response.

Emergent Disease, Reservoirs, Vectors, and Geographic Hotspots

It is important to know that new, emergent zoonotic disease is not just a phenomenon of developing countries. In the United States Lyme disease is vector-borne, transmitted by a species of tick. Lyme disease was first recognized in Connecticut, not far from New York City, and now either has spread or has been diagnosed for the first time across much of the nation (57). Species of small rodents in the genus *Microtus* (often called voles) are the usual reservoir of this disease. Arenaviruses are another example. Although arenavirus infections in human beings were well-known from South America, it was unknown in the United States. Indeed, the first human cases in the United States were diagnosed in California within the last decade. In this instance a species of woodrat (genus *Neotoma*) is the most likely reservoir. Yet another example is hantavirus-associated pulmonary syndrome. This disease was first recorded in New Mexico, but Black Creek Canal virus (a strain of hantavirus associated with a species of cotton rat, *Sigmodon*) infected people in Dade County Florida, and the *Sin Nombre* strain of the virus carried by deer mice (*Peromyscus*) has infected people in more than 20 states and several Canadian provinces (31, 58). A final example is West Nile virus. This virus, which arrived recently and then

quickly spread across the United States, is associated with wild bird species, especially crows (59).

In China, an unanticipated outbreak of the deadly SARS virus in late 2002 was first detected in Guangdong Province, but not reported. By March 2003, the disease had spread to the United States and Europe and by April confirmed cases were reported from India and Africa. Epidemiologists traced SARS to markets and concluded that the virus occurred in palm civets, which were brought to village markets and thus created a pool of potentially infected animals in contact with large numbers of people. In 2005 it was discovered that a species of horseshoe bat (genus *Rhinolophus*) is the natural SARS reservoir (60). If bats are the natural reservoirs, palm civets probably are accidental hosts.

In Patagonian Argentina a unique strain of hantavirus (Andes virus) was transported to human beings from a species of wild rice rat (genus *Oligoryzomys*), and the outbreak seriously affected the economy of the ski resort city of Bariloche, where it was first detected. Unlike the cases of hantavirus in the United States, a subset of the Argentine cases possibly resulted from person to person transmission (61).

Examples of emergent zoonotic disease are found throughout Latin America, Africa, northern Europe, Australia, and Asia. Although it might be the case that infections are most likely to occur in remote or rural areas where human beings come into contact with wild animal reservoirs, good data on incidence are scanty. It is likely that the first deaths from such events occur fairly commonly in remote areas where medical care is essentially non-existent or, if it exists, there is no routine reporting or diagnostic capability and no epidemiological or public health services. The local or regional scientific infrastructure often is ill-equipped to respond to outbreaks or to genetically characterize new agents or conduct other relevant research. One exception to this was seen in Southeast Asia where talented local (Malaysian) scientists teamed with international collaborators to respond to an outbreak of human encephalitis and identify a new virus (Nipah) responsible for the disease (62, 63). More typically, such a response is impossible. Even with good infrastructure it is possible for an emergent zoonotic disease to be a surprise. In the United States, hantavirus was first diagnosed in 1993, and although 27 additional strains have been characterized since then, undiagnosed deaths surely occurred at some unknown rate in the thousands of years that humans in the American Southwest have shared living space with deer mice prior to 1993.

Factors such as global climate change, habitat degradation, human population density and distribution, and landscape conversion to agriculture (or from agriculture back to a feral status) are logical contributors to increased contacts among human beings, reservoir species of mammals, and vectors (64, 65, 66). But additional scientific data are still needed to establish relationships and develop predictive models with reasonable statistical value (29). Such research is underway in a variety of laboratories that approach the problem from multiple perspectives—environmental degradation, remote sensing, molecular biology, field biology and reservoir natural history, and systematic biology. In reality, however, one of the major challenges is that the mechanisms and factors that facilitate interspecies transfers by pathogenic viruses are unknown.

Given the complexities involved, how can any global disease surveillance system account for emergent diseases? If the NIE is correct, and remote or even rural areas of developing countries are indeed the places

most likely to be sources of emergent diseases, how will cases be recognized? Who could identify a new disease in the absence of suitable diagnostics for an unknown infectious agent, or the absence of diagnostic capability to eliminate alternative, previously known, pathogens? It is unrealistic to think in terms of sentinel stations in remote or rural areas on a global scale, and with the lack of diagnostic capability the challenge is reduced very little by restricting sentinel stations to select developing nations. On the other hand, these are the circumstances under which the syndromic surveillance system might be well-suited to detect an outbreak of disease.

Several aspects of emergent zoonotic disease must be considered in order to develop a strategy for disease surveillance that includes previously known or future unknown emergent diseases. Although a research track record exists, the fact is that essential information about reservoir species—such as their identity (and ability to identify them), geographical distribution, ecology, and historical relationships to the infectious agents that they harbor—is unknown with few exceptions. The best available comprehensive data come from North America and Western Europe, where it is more convenient to conduct the necessary field studies. Vast areas of Asia, Africa, and South America, all of which are significant to understanding emergent zoonoses, are essentially unknown.

A far better understanding of infectious agents and their complicated biological relationship with their hosts is needed. Problems exist in understanding the instances in which vectors are involved in the transmission of disease from the reservoir animal to human beings. Ectoparasitic vectors—such as fleas, ticks, and chiggers—are incompletely known, taxonomically. Undescribed species are involved in transmission of infectious agents, especially in remote regions, and taxonomists with the expertise to identify them are becoming scarce throughout the world's scientific community. Reservoir and vector species identification is a critical and powerful piece of information. When placed in a geospatial database, such data can be used to predict the distribution of pathogenic viruses in context of land use, regional climate and local weather patterns, ecology, and human population densities and movements. Moreover, such information can lead to outbreak prediction.

The term ‘biological informatics’ applies to geospatial databases with biological information that can be queried in regard to emergent disease (67). Such databases already have been used to understand and predict the geographic spread of rabies virus in Texas. Although global scale databases do not currently exist, basic essential resources and technologies are available.

Even if the NIE conclusion that emergent diseases are most likely to occur in remote regions is correct, such a conclusion by itself cannot be converted into a strategic response. Therefore, alternative thinking is required. In this instance previous and ongoing scientific research can help. A biogeographic survey of known reservoir species, vectors (where applicable), and infectious agents can be used to strategically identify geographic ‘hot spots’ and select them either for surveys or sentinel stations. Such hot spots could be regions for which data are completely lacking, or regions where species related to known reservoir species probably occur. Hot spots also could be places where preliminary information suggests the presence of rapidly evolving infectious agents in wild animals, or, finally, places where wild species are known to be reservoirs for agents that infect domestic stock and, occasionally, human beings.

After geographic hot spots are identified on a technical or empirical basis, they can be assembled in priority order on the basis of their relative potential to contributing to fundamental scientific questions about disease emergence and transfer between species. Hot spots also can be given priority for foreign policy, national security, or other political considerations. But whatever technical, scientific, or political factors are combined to create priorities, such an approach does provide a logical pathway to strategic decision-making and sentinel placements. By way of contrast, the NIE generalization that emergent diseases are most likely to appear in “rural regions in developing countries” does not provide an adequate foundation for a logical response or for realistic planning. A far more precise

and predictive framework is needed. Localities of previous outbreaks, or localities where known reservoirs occur, can be monitored and modeled in several ways. Most important, qualified specialists need to ‘put boots on the ground’ and estimate the prevalence of an infectious agent and estimate population densities, follow population dynamics, and explore the ecological factors at play. Modeling of pathogen transmission in the reservoir species is an essential part of the process because it provides logic for testable hypotheses about the relationship between population density and disease prevalence (66). But for algorithms to be useful the mathematical modeling ultimately requires field data. Models dreamed up in the office or laboratory need to be tested in the field. Such data need to be coupled with remote monitoring—such as satellite imaging—for predictive purposes as has been done with *Sin Nombre* virus in deer mice in the Southwest United States (29,31). Finally, monitoring of commercial routes between rural villages and urban centers could be highly beneficial in countries where wild game animals, including potential reservoir species, are collected and transported to market.

The foregoing discussion of emergent disease highlights the need for new information. This in turn raises the question of whether or not information gathering through passive case detection and reporting is the ultimate goal of disease surveillance. Should surveillance be passive and linked to care delivery or medical or technical training, or all of these? Alternatively, should surveillance be active and driven by acquisition of new knowledge about geographic distribution and characteristics of disease-causing organisms? The NIE and GAO reports do not distinguish among alternative objectives but a functional surveillance system should be regarded as the primary resource behind decisions about preparation and care delivery and training, rather than as a combined activity. Such a step might enable us to keep a step ahead of disease progression, fill diagnostic, testing, and training gaps that could help stem an outbreak, and buy time to analyze and identify the causative pathogen.

Disease Selection and Surveillance Systems

Should a global disease surveillance system focus on particular ‘human’ diseases, say for instance the deadly seven, or should it be combined with ‘animal’ diseases or ‘emergent’ diseases, or both? In fact, although these disease categories are commonly used, in reality these categories are artificial. They are historical relics of cultural, economic, administrative, and political battles. In an ideal world a disease surveillance system would not be based on artificial categories. It might be comprehensive or it might focus on a set of diseases selected for surveillance on the basis of economic impact, or threat to regional stability, or importance to future generations. Moreover, when economics, regional stability, and international trade are considered, plant diseases also should come into the mix.

Realistically, the purpose of a surveillance system should drive the selection of diseases for monitoring. Viewed in this way, it is the disease surveillance systems that should differ according to their particular objectives. This approach avoids putting diseases into artificial categories or worrying about whether a particular disease is a ‘human’ disease’ or an ‘animal’ disease’ or ‘emergent’ disease. But this approach also might mean that the idea of a single comprehensive global disease surveillance system is too complex or unwieldy to be realized. Given the complications and complexities discussed thus far, it might be best to abandon a comprehensive global concept, at least in the near term, in favor of alternatives.

The subdivision of disease surveillance into individual systems tailored for specific goals has obvious advantages. For instance, when viewed in terms of United States foreign policy and financial assistance

to developing countries, a disease surveillance system could be developed around whatever infectious diseases are regional or national priorities for the country being assisted. The diagnostic issues, health care delivery, and training for local medical personnel can then be focused on priorities determined by public health, financial need, and infrastructural challenges specific to the country or region. In many instances this alternative approach will be compatible with humanitarian goals and should be attractive to UN programs and international NGO’s. Further, this approach to disease surveillance would separate United States national security concerns into smaller and more manageable subsets. It would have the effect of separating economic, developmental, and cultural issues—all of which have security implications—from disease issues that include everything from biosecurity and dual use problems to transnational bioterrorism.

Can disease surveillance be used strategically, or is it an activity that is more valuable to national security as a tactical rather than strategic device? The coalescence of events that attracted the attention of President Clinton and Congress in the late 1990’s was an artifact of the time. There were enough common themes—all associated with some aspect of pathogenic infectious agents and disease—to make it seem that all of these events could be addressed collectively. Global disease surveillance appeared to be the appropriate vehicle and appeared to have strategic value. The flaw, of course, is that coincidence of events is not a suitable rationale for making decisions in regard to United States national security and these events correspond to a moment in time that is unlikely to be repeated. This applies as well to events in the autumn of 2001.

SECTION SUMMARY

- Diagnostics are affected by history, culture, priority, international politics, and the struggle for resources.
- A global disease surveillance system presumes that countries will willingly share health information but compliance frequently is not the case.
- New, emergent disease is not just a phenomenon of developing countries.
- ‘Biological Informatics’ applies to geospatial databases with biological information that can be queried in regard to emergent disease.
- A biogeographic survey of reservoir species, vectors (where applicable), and infectious agents can be used to strategically identify geographic ‘hot spots.’
- After geographic hot spots are identified, they can be assembled in priority order on the basis of foreign policy, national security, or other political, economic, or social considerations.
- The purpose of a disease surveillance system should drive the selection of diseases for monitoring.
- The subdivision of disease surveillance into individual systems tailored for specific goals has obvious national security, policy, and management advantages.

IV. Intentional Disease—A Significant Layer of Complexity in Disease Surveillance

Human beings have engaged in warfare or war-like behavior from pre-history to today and are more likely to continue to do so than they are to cease in favor of peace and compromise. More importantly, humans have sought and then developed new weapons in relationship to technological advances and breakthroughs. Looking backwards in time it is easy to discover examples of ‘biological’ warfare even before germ theory or the advent of ‘biology’ as a scientific endeavor.

Biological weapons (BW) are based on infectious agents or biological toxins, and the main idea is to attack humans or their livestock or crops in ways that mimic or even exaggerate what can happen in nature. Weaponization and delivery are the major technical problems. If these are solved, defending against BW is a very serious challenge (4). Even a delivery method as simple as postal service poses a threat, as was demonstrated by the distribution of finely milled anthrax spores to businesses and the U.S. Congress in 2001 (69).

Intentional release of infectious agents is a significant threat to the United States. Once introduced in the human population, livestock, or our ecosystems, such pathogens could spread rapidly even before being detected. Simulations and modeling of aerosol dispersal provide a means of estimating that contagious BW

agents could have a devastating effect on civilian populations in urban areas. In fact, the Soviets calculated that their loaded BW warheads would kill up to eight million Americans (70). The accuracy of their modeling is unknown, and that leaves uncertainty about such dire predictions, including an unknown level of probability that the outcome could be even worse.

There is no way to know for certain what agents a state-sponsored BW program might weaponize and the potential for synthetic genomic creations introduces further uncertainty. There is of course a list of likely candidates based on historical data, but even knowing what has been weaponized with certainty does not necessarily provide the data needed to prepare a defense. Geographic variation in pathogens, genetic engineering, and synthetic biology enables an aggressor to introduce exotic or new strains of a disease, thus potentially bypassing natural or acquired immunity. To further complicate the threat, modern biological technology provides the potential for creating ‘designer’ infectious agents that could cause an unknown disease and combination of symptoms perhaps involving the use of multiple pathogens (4). Portentive knowledge such as this must be factored into any discussion of disease surveillance and obviously is a significant complication.

The Role of Technological Advances

Dramatic advances in civilian science stimulate technological advances in both equipment and methodology, which in turn increases the pace of discovery. Two aspects of this process—transparency and simplification—are particularly important. Civilian science is generally transparent, which means that methodology and results and discussion of the significance and reliability of data are available internationally in public journals and on the internet. Moreover, detailed data too cumbersome to be included in publications often are ‘banked’ in internet accessible servers. Examples include information about proteins and DNA or RNA

sequences from bacteria and viruses. Bioinformatics is a relatively new discipline in which information technology is applied to biological datasets (71). More specifically, bioinformatics provides algorithms that enable users to access and analyze a vast array of information stored in public data banks. The information available in public data banks increases almost daily, in part because most scientific journals require that raw nucleotide sequence data used in research described in the published manuscript be archived in such banks. Publicly available raw data includes, but is not limited to, nucleotide sequences from viruses, bacteria, rick-

ettsia, vertebrate animals, and plants; data on protein structures and function; and geographic sources of infectious agents. Bioinformatics algorithms also enable analysis and mining of the vast storehouse of newly acquired, transparent, molecular data.

Science education—hands-on analysis and theory for students—which generally occurs without regard for politics or intent and crosses international boundaries is another critical aspect of transparency in civilian scientific circles. Virtually everything about science education, especially at the graduate level, is international. This means that information and data routinely flow through scientific networks, from one laboratory to another.

As a scientific discipline, molecular biology is regarded as complex. It can bewilder the non-scientist. The seeming complexity and inaccessibility of the subject matter can be misleading. Although it is true that molecular biology is a complex subject and data interpretation requires substantial skill, it also is true that the associated technology has become simpler to use. Automated equipment has eliminated many difficult, time-consuming tasks that previously demanded an experienced technician. Pre-packaged kits and disposable containers have eliminated much of the traditional laboratory inventory of glassware and stored reagents. Every step in simplification and every public data bank with built-in analytical capability means that it is easier for individual scientists or small groups to function independently of massive funding and technical support. Unfortunately, it is not ‘gene splicing’ in the sense that only a select few people can understand how to make sinister use of the theories, materials, and methodologies.

The rapid development of molecular biology has led to new industries collectively referred to as biotechnology. Biotechnology is the commercial exploitation of technology and knowledge generated through research in molecular biology. In a sense, the open literature generated by academic civilian research in molecular biology has become the R&D for commercial exploitation, although biotechnology companies also contribute some of the funding and control some of the results. Because biotechnology is both commercial and international it also is a vehicle for transfer of information and movement of samples, funds, equipment, and consumables across international borders. Biotechnology, transparency, and simplification could form a foundation for continued or future state-sponsored development of offensive biological weapons and could create clear opportunities for under-funded rogue nations, transnational terrorist organizations, and even individuals. In fact, the quality and use of biotechnology facilities is another legitimate international biosecurity concern. What mechanism insures that bioterrorists will not gain access to dangerous pathogens through lax security at private biotechnology facilities (4)?

When the intent to inflict harm is coupled with the most modern and sophisticated molecular techniques, the surveillance calculus becomes far more complex and unpredictable. It also is possible that human beings could be deliberately infected by pathogens that are completely synthetic constructs of old, previously known agents or new, totally novel, man-made agents.

SECTION SUMMARY

- The main idea of intentional diseases is to attack human beings or economically important livestock or crops in ways that exaggerate what happens in nature.
- There is no way to know for certain what agents already might have been developed for such a purpose.
- Geographic variation in pathogens or synthetic pathogens created by recombinant DNA technology gives an aggressor the potential to introduce exotic strains of a disease, thus potentially bypassing natural or acquired immunity.
- Without disease surveillance, the purposeful introduction of disease has the potential to devastate human populations, livestock, or crops before being identified as foreign rather than natural.
- If malicious intent is coupled with modern molecular techniques, human beings could be intentionally infected by pathogens that are naturally occurring or synthetically enhanced through technology.

V. Mining Nature for Biological Weapons

Biologists and conservationists and other specialists have long understood that natural, undisturbed environments are a rich resource. Botanists in particular have sought samples of plant germ plasm from native species related to domesticated varieties. In a sense, expeditions to the Amazon and other tropical environments have “mined” these regions for seeds that now compose both commercial and private collections. Seeds stored under suitable conditions for decades are available for manipulation or testing and study by the latest molecular techniques. With modern techniques it is possible to retrieve specialized genes from these exotic plants and insert them into domesticated plants.

Although botanists probably were the first biologists to employ mining as a strategy, biotechnology has made it practical to use a similar strategy based on microbes or animals. In one dramatic example of biological mining, an enzyme produced by the principal submandibular salivary glands of vampire bats have been isolated and characterized and developed into a powerful anti-coagulant medication for use in human beings for treating strokes, clots, and coronary artery disease (72).

Obviously, naturally occurring biodiversity is the foundation for the mining described above. In the context of disease surveillance, three basic facts need to be kept in mind. First, natural biodiversity varies geographically. Ordinarily, humid tropical habitat is thought to hold the greatest biodiversity. Second, biodiversity can change over time. Habitat destruction or modification can result in a loss or decline of biodiversity, whereas evolutionary processes can produce genetic diversity and increase biodiversity. Third,

infectious diseases are a game of biodiversity played out between microorganisms and their potential hosts. Spontaneous genetic mutations enable infectious agents to change constantly, potentially increasing their own biodiversity. Host immune systems try to respond to new infectious genotypes.

There are numerous positive virtues to mining nature. Agricultural and human health applications are obvious. The cumulative experience of those who conduct scientific research in this discipline clearly supports the potential values of mining. But these positive virtues are offset by the potential for mining to be used as an access to dangerous, genetically unique pathogens. Indeed, for many geographic regions the naturally occurring zoonotic viruses are essentially unknown. For other regions the zoonotic viruses are known locally, but their genetic features and animal associations are unknown to the international scientific community. In both instances we also would expect a steady supply of genetic variants thanks to mutations and evolutionary processes (73). Virulence is one of the variables associated with mutant versions of infectious agents. Some habitats and geographic localities are more important—valuable in a negative sense—than others. Expertise in evolutionary theory, biogeographic principles, and an appreciation of the global distributions of genetic strains would enable the potential misuse of natural biodiversity in microorganisms. Biological mining requires knowledge about environments and evolutionary theory and systematics and an ability to undertake fieldwork, but does not require laboratory manipulation of genes or artificially constructed DNA or RNA sequences.

Understanding the Soviet Zoological Paradigm

During its lengthy and most active period (~1954-1989), the Soviet biological warfare community displayed a particularly profound understanding of the interrelationships among reservoir species, geography, variation in nature, and evolution of immunity in hosts

and pathogenicity in infectious agents. The parallel (but much briefer) U.S. program followed a similar path in the period 1954-1969 (before the offensive BW program was terminated in 1969 by President Richard Nixon).

The significance of the Soviet scientific thinking—the zoological paradigm—has both historical and current importance. The historical importance is that it helps explain the offensive and defensive strategies behind their massive state-run biological weapons program. Soviet strategic thinking is more than a historical curiosity. Its current importance can be seen in how it affects United States expectations. In particular, our understanding—or our misunderstanding as the case may be—of the Soviet approach is reflected in our preparations for defenses against other extant and potentially new state-run programs. An understanding of Soviet thinking also has important implications for nonproliferation programs that seek to reduce or eliminate lingering threats from the old Soviet Biological Weapons Program.

Regardless of the value in understanding Soviet thinking prior to 1991, this is a subject that is not fully appreciated by United States security circles. Why would this be true? Basically, the Soviet BW program was founded on traditional pre-1970's academic disciplines of zoology and evolutionary biology. United States thinking in national security and intelligence circles tends to track biological science 'of the moment' and tries to anticipate future technical capabilities. Consequently, the importance of basic biology and evolutionary theory is underappreciated. It is essential to understand capabilities created by high technology, but it is equally essential to not lose sight of the basics. This especially is the case when the basics of biological science were the theoretical underpinnings for real versus hypothetical preparations for biological warfare.

Ironically, the disciplinary roots of the original United States defensive thinking about BW were identical to the knowledge that founded the Soviet program. In 1944, for example, the United States Navy and the Army deployed counter-measure teams in Asia and the Pacific in response to high-level concern about Japanese 'bacteriological' warfare. Similar counter-measure teams also were deployed in Korea (1951-53) and Viet Nam (1965). In all three examples, the strategy involved deployment of personnel with traditional expertise in evolutionary biology, entomology, and mammalogy.

The thinking and ideas of E. N. Pavlovsky and G. F. Gause heavily influenced academic zoology in the

Soviet Union. Gause's seminal work, *The Struggle for Existence*, was published in English in 1934. In it, he laid out experimental approaches to understanding the significance of spontaneous genetic variation, population growth phenomena, and natural selection in populations (74). Pavlovsky primarily was a parasitologist. He worked in the Zoological Museum (later the Zoological Institute in St. Petersburg) beginning in 1924. Pavlovsky is credited with having created the Soviet Union's 'School of Thought' in the field of parasitology. Many of Pavlovsky's contributions were fundamental to his discipline. These contributions ranged from topics in ecology of parasitism to the basic taxonomy of parasites, which explains in part why Pavlovsky's name is associated with fundamental research on parasites. In modern perspective Pavlovsky's research interests might not seem relevant to disease surveillance but in fact he thought and wrote extensively on zoonotic disease. This work did not pass unnoticed. In 1965, coincidental with expansion of the Soviet biological weapons program, Pavlovsky received the Lenin Prize of the First Rank for his theoretical paper on "Natural Focality of Transmissible Diseases" (75, 76).

The ways in which scientists think about nature, the questions they ask, their interpretations of data, and their expectations—predictions based on theory and prior knowledge—are fundamental to the design and outcomes of scientific research. Such factors create scientific paradigms. Even within the United States, science is subdivided into different paradigms that affect everything from research topics, or priorities, to training of students and decisions by funding panels at the National Science Foundation (NSF), the National Institutes of Health (NIH), and other federal granting agencies. On an international scale, historical and cultural divergences accentuate the differences in the conduct of science. Strategic thinking and decision-making must account for such differences, which can have a profound affect on outcomes and expectations. It is essential for intelligence analysts to appreciate paradigm differences whenever a scientific discipline or its products become subjects of concern.

From the Soviet perspective, nature was the ideal laboratory and natural selection was the prime manipulative force. They understood that wild animals could be collected and 'mined' for infectious agents. More importantly, they understood that infectious

agents varied genetically in virulence over time and geographic space. It was unnecessary to understand or manipulate the genetic characters that underlie variability in virulence. It only mattered to know that virulent strains would appear naturally at geographic foci within the range of any animal species that served as a host for vectors or as a reservoir, or both. In a similar vein, the Soviet bacteriologists realized that if environmental contamination could trigger mutations in pathogenic bacteria, new strains of a previously weaponized bacterium—*e.g.*, anthrax—probably could be uncovered from contaminated soil. Thus, contaminated soil might be mined for new bacterial strains in such places as factory dumping grounds or among uranium mine tailings.

In terms of strategic thinking based on evolutionary theory, the Soviet academic scientists in Moscow served as strategic brains for the BW program. Georgyi Gause, who was required reading for all academic biologists, called their attention to Ronald Ross' early Twentieth Century mathematical modeling of malaria, which focused on introduction and spread of a disease (74). Ross, Gause, Pavlovsky, and other mathematically-inclined scientists, especially Sewall Wright in the United States, collectively laid the early scholarly ground work for estimating introduction of 'new' genes into populations, changes in gene frequencies, mutation rate and genetic variation in disease-causing organisms, origin and spread of new strains of pathogens, infection rates, and response of host populations. Most importantly, because of influential academic scientists such as these men, it was ordinary for the Soviet academicians to think about disease and infectious agents in evolutionary and mathematical terms. So, 'evolutionary' medicine or epidemiology became the paradigm behind Soviet strategic thinking well before it made broader inroads in the United States

medical and scientific communities in the 1980's and 1990's (73, 77, 78, 79).

The Soviet academic community knew that by definition potential new strains of any disease-causing agent would arise by mutation(s), would appear initially within a limited geographic space, and would either go extinct or slowly spread geographically depending on movements and population growth of the reservoir animal species. In terms of evolutionary theory, virulence and pathogenicity are expected to change over time as the infectious agent adjusts to using its host species for its own survival. Additionally, new strains with limited geographic distribution within one country would be unknown to a foreign enemy. In the absence of samples of strains, a defense—such as a vaccine—could not be developed in advance, at least under conventional means prior to 1990. If the United States, for example, was unaware of a particular infectious agent or a local strain, there would not be any pre-planned defense. The foregoing problem is illustrated by the current experience with avian influenza. In this instance the outbreak is a natural phenomenon rather than an intentional act by human beings, but vaccine development awaits the anticipated emergence of a new strain that is both virulent and contagious between human beings.

From the Soviet zoological perspective, an appreciation of individual genetic variation and evolutionary patterns in nature automatically extended to human beings. So, in their scheme of work, it was logical to investigate the variability in human immunological response. Such research had equally important implications for public health, their offensive BW program, and for their potential defense against an attack directed at the Soviet Union. An understanding of variation in human response to infectious agents is essential to understanding virulence and susceptibility.

The Soviet Anti-Plague System—A Model for Mining

The Soviet Union's anti-plague system began as a public health program but ultimately became the ideal way to tap into nature's endless supply of new, naturally-occurring strains of infectious agents (80). The Soviet Union's interest in plague as a potential weapon dates back to the 1930's. It is uncertain when it was first

weaponized by the Soviets, but the pre-World War II German intelligence assessment was that plague and anthrax were the foci of the Soviet BW capacity. Shortly before Japan's surrender in 1945, the Soviets attacked Japanese-held territory in China and captured several biological weapons experts from Unit 731, which was

the Japanese army organization responsible for the development, testing, and deployment of biological weapons (81). The men were tried for war crimes in 1948; the trial transcript (published in English by the USSR in 1950) reveals the extent to which the Soviets sought information about the weaponization of plague and results of Japanese field tests and experiments on civilian and military prisoners (82).

Regardless of the eventual role of the plague bacterium in the Soviet BW program, its original importance to government was in public health. Thus, the Soviet anti-plague system was (and the Russian Federation version still is) administered under the Ministry of Health. Under the Soviet Union, the anti-plague system consisted of main laboratories and rural field stations spread from Odessa in Ukraine, Kazakhstan, Kyrgyzstan, and Tajikistan on the western border of China to Vladivostok in the Far East. Technicians in the field drew blood from patients and trapped specimens of wild rodent species and collected their fleas. The technicians in some instances could do initial laboratory isolation locally where the plague bacterium could be characterized through standard bacteriology and the vector fleas and rodent(s) hosts identified by species. The bacterial cultures were stored as archival collections in the central laboratory. Samples of especially virulent strains were sent on to Moscow. Once identified in the field or central laboratory, the flea and rodent specimens were stored as ‘voucher’ specimens in a zoological reference collection. Voucher specimens consist of preserved remains of the actual mammal or parasite collected in the field. Associated records such as date and location and circumstances of how the specimen was obtained are kept with the specimen. Because voucher specimens can be re-examined at future dates, they provide some of the ‘repeatability’ required by the scientific method. Voucher specimens also make it possible to compare species taxonomies to data from previous outbreaks. Over time, a database of specimens and their species identifications, bacterial cultures, and field and laboratory experience was acquired. This enabled specialists to identify plague foci. Geographic foci could be defined in terms of bacterial strains and the geographic distribution and ecology of particular host rodent species and vectors. Such a strategy is an effective combination of fundamental zoological fieldwork, an understanding that in nature

certain species were reservoirs for particular genetic strains of disease, taxonomic sleuthing, fundamental bacteriology, and an appreciation of evolutionary processes. The resultant database was equally valuable to public health and BW.

The published history of the Anti-plague Institute of Irkutsk exemplifies the significant roles of such facilities between 1970 and 1988 (83). Although originally intended to focus on plague outbreaks, the Institute took on a broader role in disease surveillance, which included tularemia, brucellosis, and leprosy. When Igor Domaradskij arrived there as a young scientist in 1957, the older staff included zoologists, parasitologists, classical bacteriologists, and epidemiologists. Through his participation in the Institute programs, Domaradskij learned that plague virulence was reservoir-species-associated. It was not enough to know that ‘rodents’ or ‘rats’ or ‘ground squirrels’ were reservoirs. Instead, it was essential to know which species of rodent acted as a reservoir for which particular strain of plague. In Siberia, the most virulent plague strain was associated with a particular species of marmot locally known as a tarabagans.

The association of a virulent strain of plague bacterium with a particular species of rodent was a significant discovery for Domaradskij’s laboratory. If a virulent strain can be associated with a reservoir species and if a reservoir species can be identified and if its geographical and ecological range is determined, then scientists have a realistic starting point for predicting the geographic range of particular strain(s) of plague bacterium.

Marmots are just one kind of mammal that can serve as plague reservoirs in Central Asia. They are large-sized ground squirrels with a circumpolar distribution. There are at least 14 species of marmots worldwide. Little is known about many of the Asian species. As a consequence, it currently would be difficult or nearly impossible to accurately distinguish among species or subspecies with certainty. The problem of not knowing the species, or being unable to distinguish among species, is a consequence of the fact that fundamental research on systematics, which would allow them to be identified on a genotypic basis, has fallen behind what could be achieved through application of

modern molecular genetic methodology. Moreover, the geographic distribution and ecological associations of most of the Asian species are unknown—at least with certainty—by the scientific community in the West. Although species identification and naming is conducted under an international code, the combination of a closed Soviet society, limited scientific exchange, and lack of collaboration has meant that species—including important reservoirs of infectious disease—occurring in the vast former Soviet Union are very poorly known even among western experts. But, regardless of such problems the Soviet anti-plague experts knew that not all species of rodents or marmots are reservoirs of plague, and only particular species within particular geographic regions create foci of infection. The ability to decipher this zoological code was important to the Soviet BW program. The same is still true in the context of disease surveillance and biosecurity.

Under Domaradskij's leadership, the Irkutsk Anti-Plague Institute conducted new fieldwork at the margins of its geographic responsibility and even gained access to Chinese territory. Through this expansion of fieldwork, Domaradskij and his team uncovered new foci of plague associated with local species of rodents other than marmots (83). The realization that plague strains and foci could be linked to particular species of rodents and that these rodents had definable geographic distributions led Domaradskij to develop testable hypotheses about the evolution and persistence of plague in rodent populations. Through his research at the anti-plague institute, Domaradskij ultimately became interested in cross-immunity, which explores mechanisms under which immunity to one disease confers protection against a new disease. He also developed a keen interest in toxins produced by the plague bacterium. Later, in the leadership of the Soviet BW program, he pushed for a program to genetically engineer infectious agents with potent toxins (83).

The work by Igor Domaradskij and his colleagues resulted in a geographic database of select pathogens, reservoir species, and vectors across a vast stretch of Siberia and Central Asia. Although this database was not computerized, the zoological collections of specimens of reservoir species and vectors and the bacteriological culture collections collectively constituted a rich resource. These combined collections also provided a theoretical foundation for understanding foci and persistence of infectious agents over time, and created an interest in the evolution of virulent strains and of changes in pathogenicity over time. The anti-plague system linked fundamental field biology to epidemiology and to microbiology (80). The search for new foci of virulent agents also created networks of collaborators—for example the Irkutsk Institute, the Anti-Plague Institute in Alma-Ata (now called Almaty), Kazakhstan, and the Saratov Anti-Plague Institute 'Mikrob'—that was unusual for science under the Soviet system.

Regional scientific interest in work similar to Igor Domaradskij's continues today. Chinese scientists working at the Academy of Military Medical Sciences in Beijing published a geospatial analysis of plague foci in China. In their paper, the Chinese reported on the evolutionary genetics and virulence of plague strains and documented the relationships among geography, reservoir species, and virulence (84). This particular project serves as an excellent example of why knowledge of mammalian reservoir species and evolutionary relationships among species is essential to understanding geospatial distribution of disease foci. The research by the Chinese team also illustrates how an understanding of reservoir species can be integrated with information on plague genomics and the evolution of the plague bacterium, *Yersinia pestis* (84, 85).

Lessons Learned about Mining and Disease Surveillance

Taken in a broad context, it should be obvious that scientific paradigms have strategic and technological consequences. More important, a failure to recognize differences among scientific paradigms can have major consequences whenever scientific underpinnings are the key ingredient in foreign policy or national security decisions.

Biological weapons development in combination with scientific paradigms adds a significant but specialized complexity to the subject of disease surveillance. Given the harsh realities of bioterrorism, a disease surveillance system presumably would have to include forensic molecular epidemiological capability to do all of the following tasks:

- account for unusual outbreaks,
- distinguish between naturally occurring and purposely induced outbreaks, and
- in the case of a purposely induced outbreak provide a mechanism for attribution of the infectious agents to a particular source—natural or intentional—and to a particular geographic origin—naturally occurring in a particular region or introduced to the region by human beings.

SECTION SUMMARY

- The Soviet community understood the interrelationships among reservoir species, geography, variation in nature, and evolution of pathogenicity in infectious agents.
- Strategic thinking and decision-making must account for differences in scientific paradigms.
- The Soviets knew that virulent new strains of any disease would appear initially within a limited geographic space.
- Current research in China has documented the relationships among the evolution of plague virulence, differences in virulence, geography, and mammalian reservoir species.
- An understanding of variation in human response to infectious agents is essential to understanding virulence.
- The Soviet Union's anti-plague system was the ideal way to exploit nature's endless supply of new strains of infectious agents.
- Natural local or regional immunity in the human population provides plausible deniability and is a strategic reason to use naturally occurring infectious agents as offensive weapons.
- Being able to decipher reservoir species and vectors is important to disease surveillance and security.
- The anti-plague system produced a geographic database of select pathogens, reservoir species, and vectors across a vast stretch of Siberia and Central Asia.

VI. Disease Surveillance, Intentional Disease, and Transnational Terrorists

In the current decade, the American public mood and behavior of decision-makers has been shaped by events that were unimaginable to the public in the summer of 2001. Since then, a terrorist attack on New York and Washington, D.C., an anthrax attack on the U.S. Congress and American media; a war in Afghanistan; inter-related but local conflicts with radical Muslim terrorists in the Philippines, Indonesia, Pakistan, Saudi Arabia, and elsewhere; and a second war in Iraq have dominated American political life. These events have impacted the American economic calculus into the foreseeable future and have complicated the most ordinary of activities from Washington, D.C. to the community level. Each of these events in some way can be linked to efforts to eliminate stockpiles of biological weapons. Al-Qaeda—the common thread running through most of these events—is known to have sought access to biological, chemical, and even nuclear weapons and expertise. Indeed, news reports and journalism have described how the Al-Qaeda leadership has called for biological attacks on the United States, Israel, or European countries. In defense of terrorism, Al-Qaeda has employed radical ‘scholarship’ to justify such attacks as consistent with Islamic beliefs. The veracity of stories in the public press or gleaned from fundamentalist Islamic websites is uncertain. However, the leader of Al-Qaeda in Iraq, Abu Hamza al-Muhajir, was explicit, saying, “The field of jihad can satisfy your scientific ambitions and the large American bases [in Iraq] are good places to test your unconventional weapons, whether biological or dirty (86).” Generally, the available information is consistent with the commonly-held conclusion that given opportunity Al-Qaeda will attempt to use biological weapons against the United States and allies, especially the UK.

There is no way to know for certain whether or not transnational terrorists are actually capable of obtaining and weaponizing infectious agents or bacterial toxins. Generally it seems unlikely that they could do so on their own, but the expertise does exist in various countries and presumably could be purchased. In Iraq, the United States Department of State foresaw the potential for Saddam’s weapons personnel to sell their services,

or perhaps adhere to radical Islamic beliefs, and two of us (CJP and AMH) led development and implementation of a WMD Personnel Redirection Program for Iraq in 2003 (87). The Coalition Provisional Authority issued a de-Ba’athification policy (CPA Order 1) in summer of 2003 that might have left some former WMD biologists and chemists unemployed and beyond the reach of the nonproliferation program. Thus, there were (and still are) reasons to be concerned about Al-Qaeda’s call for biologists to join their jihad.

Accessible capability, the potential for hired expertise, and the undoubted terrorist intent and willingness to use biologically-based weapons demand attention on the part of the United States. An additional factor is the existence of collections of viable dangerous pathogens, some of which possibly are in private hands or stored with inadequate security at many types of facilities around the world.

Confronted with the threat of bioterrorism, the United States primarily has chosen to react defensively through development of an array of biosecurity initiatives. For example, the Federal Project BioShield legislation was signed by President Bush in 2004 and has grown into a major program in the Department of Health and Human Services (88). In 2005 Federal spending on BioShield reached \$7.6 billion; by mid-2007, the projected funding reached \$50 billion. Within this amount, BioShield planned to spend \$877 million on an improved anthrax vaccine. With the American Recovery and Reinvestment Act of 2009, an additional \$2.2 billion was expected for Project BioShield. Among all of the potential weaponized agents, BioShield is thus far most focused on botulinum, smallpox, and anthrax and on significant improvements in United States vaccine research, development, and production capabilities. Infectious agent detection capability, particularly in aerosol concentrations that realistically might occur in an urban area, is another high priority.

Generally speaking, a defensive strategy such as BioShield is not always popular. Historically, the idea of defending against state-run biological weapons

programs has had substantial political baggage, which overshadows the science involved (89). Project BioShield also has been criticized (90, 91).

Superficially, at least, a defensive position on biological agents associated with BW can be integrated into a disease surveillance network. In the United States, any diagnosis out of the ordinary—and smallpox obviously is one extreme example—should immediately set off alarm bells from the local medical community all the way to Capital Hill. The unexpected outbreak of monkey pox virus in May 2003 provides an

example of response to a real-world situation along with an idea of both the amount of time needed to respond, and the results of research triggered by the event (92, 93). Previously unknown or unrecognized infectious agents are troublesome because a diagnosis would not be easy and there would be no way to quickly determine if it was natural or purposefully induced. The ability to determine the source of an infectious agent is a key requirement for national response to an unanticipated outbreak. In most instances under current circumstances attribution would be impossible or slow because appropriate geospatial databases are incomplete.

SECTION SUMMARY

- Although difficult to quantify the risk, it is likely that transnational terrorists are capable of obtaining and weaponizing infectious agents or bacterial toxins.
- Confronted with the threat of bioterrorism, the United States primarily has chosen to react defensively.
- BioShield focuses on botulinum, smallpox, and anthrax and on improvements in United States vaccine research, development, and production capabilities.
- A defensive position on BW agents can be integrated into a disease surveillance network.
- Rapid attribution of the source of an attack is a key to national response, but in most instances it would be slow or impossible because geospatial zoonotic disease databases are incomplete.

VII. Nonproliferation, Threat Reduction, and Disease Surveillance

The economic and political collapse of the Soviet Union left thousands of weapon-makers from the WMD programs without income or ability to seek new employment. These events created a security crisis for the West. What would be the role of weapons personnel if internal instability led to civil unrest? What was the possibility that weapons experts would flee to other nations, especially nations unfriendly to security interests of the United States and other nations that share our goals? Concerns and unknowns such as these led to the creation of international activities under the 'nonproliferation' rubric.

The United States responded in 1992 by passing legislation co-sponsored by Senators Sam Nunn and Richard Lugar. The Nunn-Lugar Program, as it became known, established a group of cooperative threat reduction programs, including nonproliferation programs to redirect former weaponeers into civilian science. Since then, at least \$5.7 billion has been spent in the former Soviet Union on purchasing and dismantling their nuclear weapons and delivery and support systems, destroying chemical weapons stockpiles, increasing the security of nuclear materials, and a variety of other related activities. The current annual expenditure is about \$590 million on nuclear weapon control and \$90 million on biological threat reduction. Agencies and offices within the Department of Defense (DoD), Department of Energy (DOE), and Department of State have all played major roles in developing and implementing international programs.

On the BW side, the Department of Defense programs in Cooperative Threat Reduction focused initially on dismantling laboratory and production facilities and on a small set of research grants. Defense programs also are creating secure facilities for collections of pathogenic or toxin-producing agents. The Department of State has worked through two international nonproliferation programs, the International Science and Technology Center (ISTC) headquartered in Moscow (www.istc.ru) and the Science and Technology Center in Ukraine (STCU; www.stcu.int) to support transparent civilian research projects at

former weapons institutes and provide other support and training appropriate to civilian activities. Another State Department program, the BioIndustry Initiative (BII), focused mainly on civilian commercialization opportunities for former Soviet BW assets. The FY 2006 BII annual budget was \$30 million. Some operational and implementation support for all of these nonproliferation programs is provided through a combination of contractors, including the United States Civilian Research and Development Foundation (CRDF). This NGO was created by congressional legislation in 1996 and is a sister organization to the National Science Foundation (www.crdf.org). Finally, the Biosecurity Engagement Program (BEP; www.bepstate.net) is a more recent initiative that takes a global perspective and provides assistance with disease surveillance and diagnostics within the framework of promoting nonproliferation through pathogen security and laboratory safety standards (94).

United States government nonproliferation funding through the ISTC and STCU has supported civilian research projects in many former Soviet BW facilities. Transparency is promoted through peer-reviewed scientific publication of the results of such research, site visits by collaborating scientists, and by programmatic and financial audits. Many scientific articles have resulted from such cooperative research. A phylogeographic analysis of Crimean-Congo hemorrhagic fever (CCHFV) is but one example of a successful scientific project relevant to threat reduction, disease surveillance, and public health (95). Some of the funding for this research came from the Defense Department's Defense Threat Reduction Agency (DTRA) through the ISTC in Moscow. The Ministry of Public Health in the Russian Federation also contributed funding, which made the project truly international and collaborative.

Most of the scientific team assembled for the CCHFV project worked at the former Soviet BSL-4 facility known as VECTOR (State Research Center of Virology and Biotechnology) in Koltsovo. In their publication the team reported on genetic variability

of CCHFV, which is an important emergent zoonotic disease that affects human beings (94). The geographical distributions of viral strains were analyzed based on evolutionary relationships among the strains and in terms of the ectoparasitic vectors (ticks) associated with them. The distributional data encompassed a huge geographic region—Russia, Central Asia, western China, and the Balkans. The distribution and evolutionary relationships among genetic lineages of CCHFV in Kazakhstan, Tajikistan, Uzbekistan, and western China turned out to be of major interest because these results were unexpected. One example is an unexplained relationship between a CCHFV virus strain isolated from Uzbekistan and a strain known from western China, a significant distance to the east (94). Unintentional human transport of infected ticks might move strains of CCHFV from one place to another. From the disease surveillance perspective, the

geospatial distribution of viral strains and their vectors is a major aspect of preparing diagnostic capabilities for disease surveillance. Knowledge of the existing geographical distributions and evolutionary (phylogenetic) interrelationships among viral strains is essential from the perspective of national security, nonproliferation strategies, and threat reduction. Although the scientific research arising from nonproliferation programs might be the most important contribution, it also is the case that the various international nonproliferation and threat reduction programs created an atmosphere in which other types of joint projects can flourish. One example is the inter-academy activities between the U.S. National Academies of Science and the Russian Academy of Science. The workshop held in Moscow in 2007 resulted in a joint publication on countering terrorism, and included a paper on disease surveillance and international biosecurity (95, 96).

TADR—A Threat Reduction Version of Disease Surveillance

The Department of Defense Cooperative Threat Reduction program includes the Threat Agent Detection and Response (TADR) project, which qualifies as a type of disease surveillance. TADR currently is active in Kazakhstan and Georgia with plans to expand into Uzbekistan. In the 2005 report to Congress, the TADR goals were described as “[to]...strengthen dangerous pathogen detection and response networks, enabling discovery of diversion or accidental release of biological materials. The focus...is on dangerous pathogens posing particular risks for theft, diversion, accidental release, or use by terrorists.” Essentially, TADR focuses on two legacies of the Soviet BW program in Central Asia—left-over collections of dangerous infectious agents and the possibility that BW agents will be released accidentally or intentionally in this region of the world. The TADR program is not inexpensive: the original budget estimate was \$122.9 million, whereas the revised estimate in the report to Congress was \$586.1 million. The FY 09 budget request was \$185 million but included TADR as well as a Bio Threat Reduction Program and Cooperative Biological Research projects. A number of problems with the TADR program were identified in an invited National Research Council study and preliminary letter to the TADR program office (97, 98).

Biological mining in Central Asia resulted in large collections of endemic infectious agents, and Soviet interest in virulent strains for BW purposes increased the probability that many of these specimens are dangerous. Under the Soviet system physical security was highly effective. Indeed, the United States intelligence community apparently was unaware of the scope or magnitude of the BW program and its geographically far-flung resources. Uncontrolled access to pathogen collections would have been unthinkable prior to the collapse of the Soviet Union in 1991. But when the Soviet Union did collapse, its security systems dissolved and its laboratories were poorly secured and vulnerable. To further complicate the problem, the BW laboratories were in abysmal condition. In the West, research laboratory standards had been progressively strengthened from about 1970 onwards. Institutional environmental health and safety programs and Occupational Health and Safety Administration (OSHA) regulations dominated laboratory working conditions. Protocols, reporting, HVAC systems (heating, ventilation, and air conditioning), chemical storage, safety training, and reviews became major aspects of doing science in Western countries. Any new laboratories were built to exacting standards imposed by both Federal and State regulations. None of this occurred in

the Soviet Union. Thus, when the entire political and economic system collapsed, the typical Soviet laboratory at best resembled a shabby version of a late 1940's Western laboratory of an equivalent type. Soviet-era laboratories were typified by: exposed, substandard wiring and electrical supply; unreliable power; unsealed window casements; nonfunctional chemical fume and biological biohazard hoods; and absence of functional HVAC systems. Secured, reliable freezers with backup generators were nearly nonexistent. Cultured pathogen collections sat on open shelving and frozen infectious agents occupied any available freezer space within a facility. Ironically, although the Soviet-era BW laboratories were abysmal and dangerous places to work, the program maintained huge special facilities such as the BSL-4 laboratory at the viral institute in Koltsovo known as VECTOR. But even at VECTOR there was a contrast between functional suitability and façade, which typified Soviet science.

The TADR program is intended to assist newly independent states (former Soviet republics) as they secure collections of dangerous infectious agents left over from Soviet era. After the Soviet BW program ended, the only argument for retaining legacy collections is that they are needed for development of diagnostic protocols and vaccines. The TADR program has sought opportunities to consolidate collections into centrally secured facilities and eliminate their importance by importing diagnostic capabilities. One of the TADR

tactical approaches was to import and make available 'state of the art' diagnostic tests that provide definitive results and minimize transport of dangerous pathogens. Such diagnostic tests might eliminate the need for collections of pathogens for diagnostic purposes at multiple locations.

In terms of disease surveillance, TADR intended to create a computer-based system with networked sentinel stations and personnel trained to detect and respond to suspicious outbreaks among human and animal populations. Because TADR coupled its disease surveillance with its goal of securing pathogen collections, it is difficult to avoid the impression that the TADR system primarily is intended to monitor the effectiveness of collection security. The sentinel stations are intended to alert simultaneously the regional governments and the United States in event of an outbreak of one of the monitored dangerous pathogens as specified by the U.S. Department of Defense. Subsequently, the idea was that local scientists trained through TADR projects should be able to conduct forensic microbiology.

In its review of the TADR program, the National Research Council of the U.S. National Academies of Science pointed out that TADR's focus on particular pathogens of interest to the U.S. Department of Defense limited opportunities for broader scientific collaboration on infectious agents (97, 98).

SECTION SUMMARY

- The collapse of the Soviet Union left thousands of WMD weapon-makers without income and created a security crisis for the West.
- This has led to the creation of international ‘nonproliferation’ programs.
- United States federal programs in the Department of Defense, Department of Energy, and the Department of State provide leadership in implementation of nonproliferation programs.
- The Department of Defense Threat Reduction program includes the Threat Agent Detection and Response (TADR) project, which is a highly specialized and limited type of disease surveillance in Central Asia.
- Soviet-era biological mining in Central Asia resulted in large legacy collections of dangerous endemic infectious agents, which are a primary concern for TADR.
- TADR coupled its disease surveillance with its goal of securing pathogen collections.
- The main purpose of importing diagnostic capability to former Soviet republics in Central Asia is to eliminate the need for local scientists to use BW legacy collections to create their own diagnostic kits.
- The ‘state-of-the-art’ diagnostics favored by TADR are specialized for a small group of pathogens.
- The TADR disease surveillance system will not recognize emergent diseases or create geospatial databases of reservoirs and agents that would be valuable for attribution.
- A requested study by the NRC raised a series of concerns about the TADR program: these included narrow focus; financial sustainability; reliability of raw data; and access and international use of information derived from host countries.



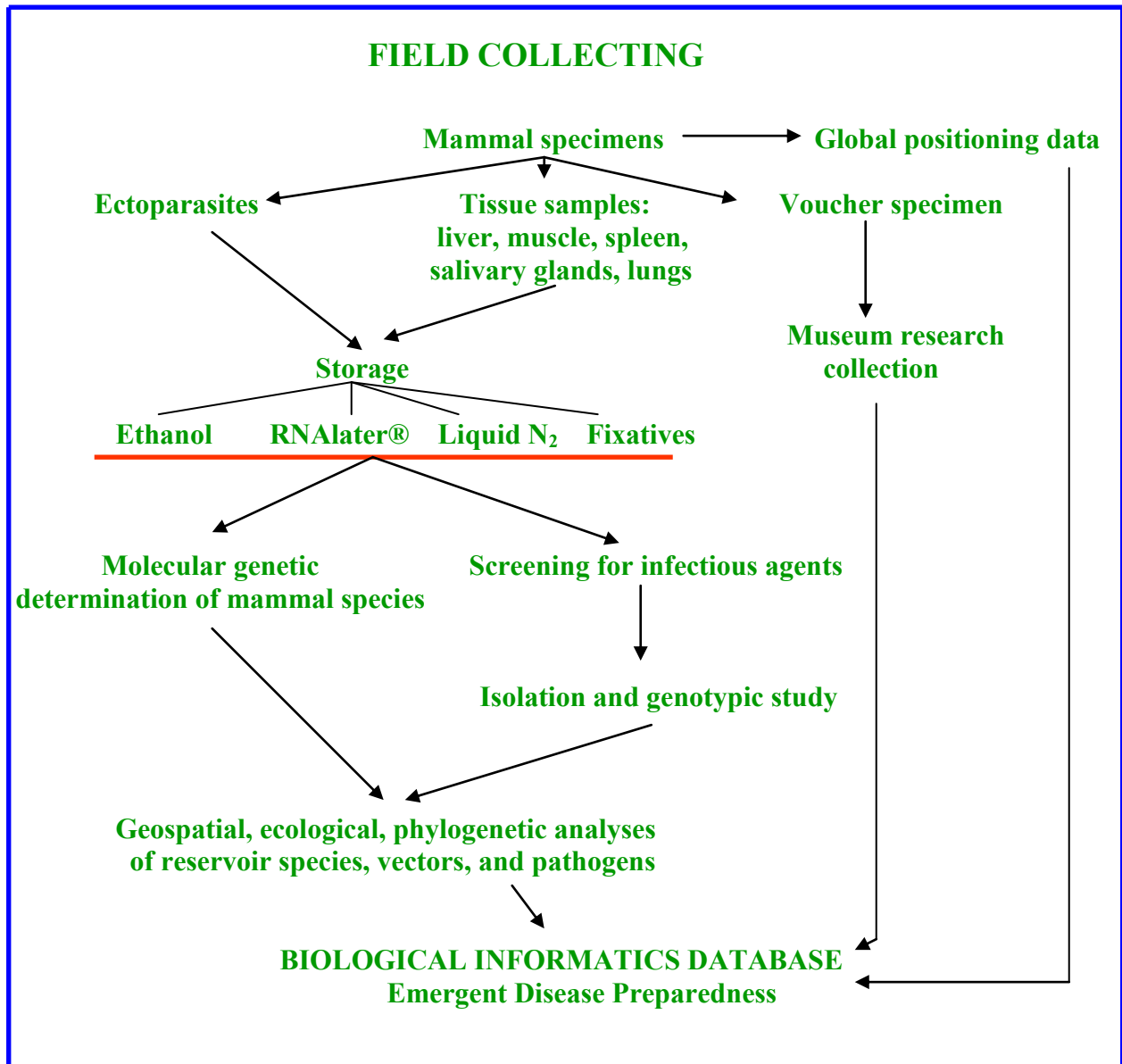
The collapse of the Soviet Union and end of the Cold War left thousands of WMD weapon-makers without income and created a security crisis for the West. The United States responded by creating Nonproliferation and Threat Reduction Programs with the goal of integrating former Soviet Biological Warfare (BW) labs into civilian science. In cooperation with Canada and European nations, such programs now provide a foundation for collaborative international research on infectious diseases and disease surveillance. Here, two virologists, Roger Hewson of the Health Protection Agency at Porton Down, UK (left) and John Hay of the University of Buffalo Medical School and the New York State Center for Bioinformatics (right), demonstrate the attire they wear while handling tissue specimens in a Soviet era laboratory where they are conducting collaborative research on zoonotic diseases in Central Asia. Fieldwork and cooperative international research projects such as this one are essential to emergent disease preparedness on a global scale. From the perspective of United States national security, this type of joint project constitutes a significant return on the original U.S. investment in Nonproliferation and Threat Reduction Programs that targeted cooperation with the defunct BW institutes in the former Soviet Republics. Moreover, projects like this produce new data of direct value to the Ministries of Health and Agriculture in the host country and exemplifies the process of converting former BW scientists and laboratories into civilian service in the newly independent republics. Research is essential because the geospatial distributions of genetic strains of zoonotic agents in most instances are either poorly known or unknown. Credit: image provided by J. Hay.

PLATE I.



Top left: wood mouse, *Apodemus pallipes*. This species, which occurs from the Kyrgyz Republic to Nepal and Kashmir, has been implicated as a reservoir for tick-borne encephalitis. Top right: white-toothed shrew, *Crocidura siberica*. This species occurs across Russia, Siberia, and the northern regions of Central Asia and has been implicated as a possible reservoir for hantavirus. Middle: international scientific team conducting laboratory work on zoonotic agents at the Kyrgyz National Academy of Science in Bishkek, Kyrgyz Republic. From the left, at the bench, are Benjamin Briggs (USA, Buffalo University Medical School) and Irina Breninger and Olga Gavrilova (Kyrgyz Republic, Republican Center for Quarantine and Especially Dangerous Diseases (RCQ)). In the background, Brazilian graduate student Cibele Caio prepares Sherman live traps (3x3x9 inch metal folding traps) that will be set to capture small mammals. Lower left: vampire bat, *Desmodus rotundus*. In the Neotropics, this species is associated with rabies. Globally, various bat species now are known to be important reservoirs of a wide range of viruses, including SARS, Ebola, Marburg, Nipah, and Tacaribe. Credits: top images, R. J. Baker; middle image, C. J. Phillips; bottom left image, Lynda Richardson.

PLATE II.

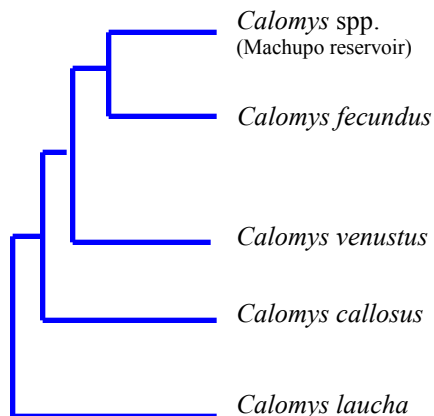
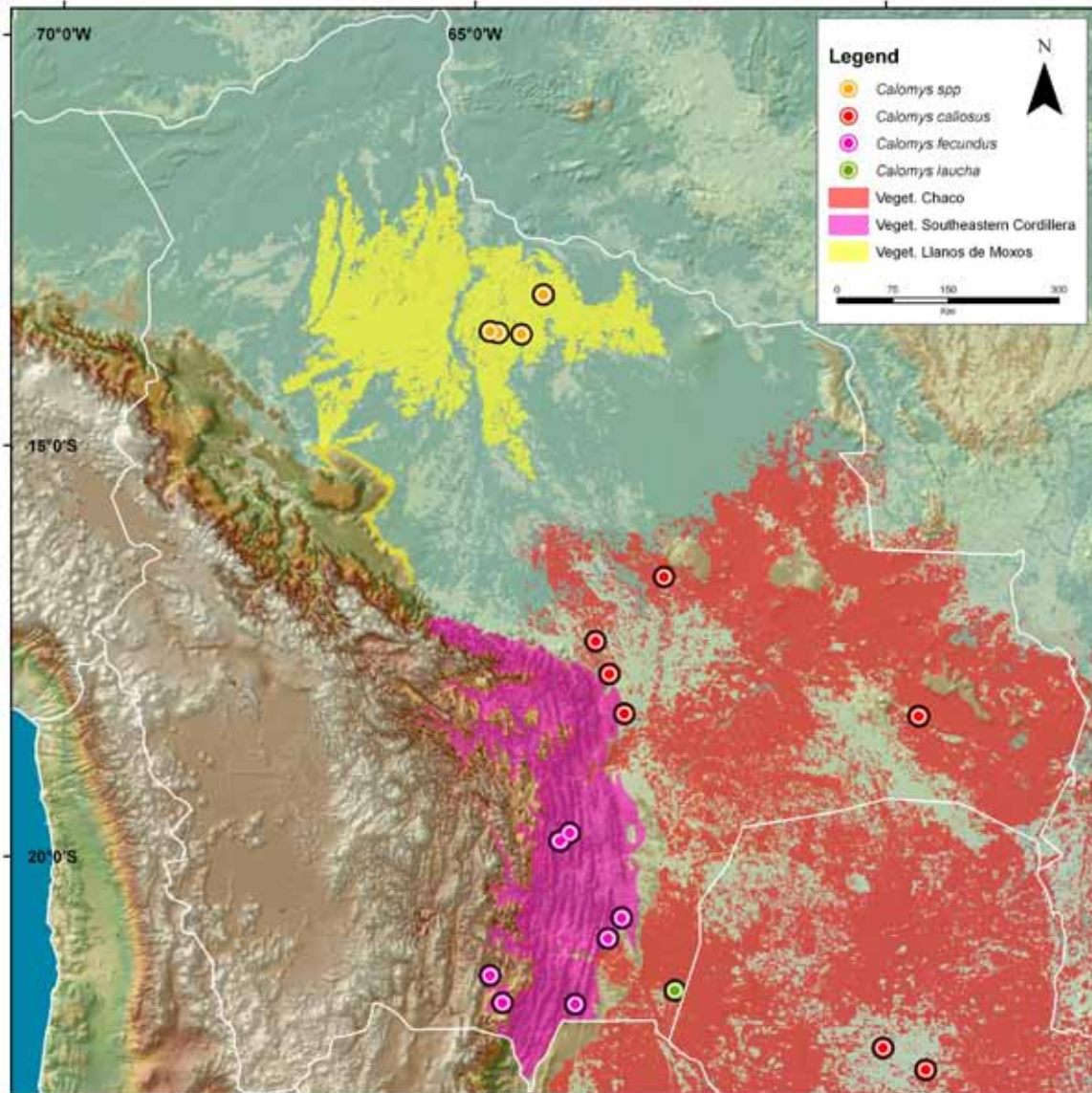


Emergent disease preparedness requires acquisition, assimilation, and application of new data. Some of these data can be obtained through fieldwork that involves collecting specimens of mammals or other suspected reservoir species. This flow diagram shows some of the activities that typically take place between the onset of a field program and the application of the data. Individual specimens are obtained by acceptable field methodology. GPS-based data for the collecting locality are essential, as is a numbering system that can be used to reliably associate an animal specimen with all other data and samples taken from it. The processing should include collection of ectoparasites (*e.g.*, fleas, chiggers, mites, ticks) from the animal (or, alternatively, from the collecting site or nests as well). Tissue samples (examples are shown in the flow diagram, but other tissues including blood, also can be taken) typically are stored in a variety of media, including RNAlater® or liquid nitrogen, or in standard fixatives for microscopic examination of tissue pathology. The skeleton, or body, of the animal usually becomes the ‘voucher’ specimen that ultimately is deposited in a museum research collection. Various kinds of processing can occur in the laboratory, following a field season. In this example, the species identity of the animal is determined through molecular genetic analysis and comparison to genetic databases. Screening tissues for infectious agents can lead to discovery of viruses, bacteria, or rickettsia, and once isolated they can be analyzed genetically and then compared to previously known species or strains. Collectively, the reservoir species data, geographic coordinates, information on ecological setting or land use, environmental variables (*e.g.*, temperature, precipitation, elevation), and all of the data about infectious agents can be stored in a database available for outbreak response.



Top left: Museum research collections are the foundation for scientific research on emergent and zoonotic (animal-borne) diseases. Specimens of birds and mammals are stored in an organized, accessible, collection so that field-caught specimens become the perpetual ‘vouchers’ associated with tissue samples that can be surveyed for infectious agents. In this way, future researchers can double-check all of the field data, the physical voucher specimens can be used to confirm species identifications, and GPS-defined collecting localities can be digitized for use in geospatial analyses. The research collection in this image is being used by Alejandra Camacho. The collection is in the Sección Mastozoología, Museo de Zoología, at Pontificia Universidad Católica del Ecuador in Quito. This collection is scientifically invaluable. In terms of understanding zoonotic disease in the Neotropics, it is one of the essential cornerstones for basic research and identification of reservoir species in northern South America. The museum is linked to similar academic-based research collections in other countries, including the United States, and is in position to support rapid responses to outbreaks in South America. In this way it is part of an informal network that could be formalized as a component of emergent disease preparedness. Top right: field collecting, especially in geographic ‘hot spots’ is an essential part of preparedness. Often times collecting must be done in localities that are difficult to reach. In this image, Peter Larsen (student, Texas Tech University) checks live traps that contain captured small mammals. His notes on species captured will enable his team to set priorities for processing the specimens. The Kyrgyz Republic project is an example of an international network of collaboration that will create a database on reservoir species and human diseases including tick-borne encephalitis and hemorrhagic fever. Lower right: shortly after collection, specimens of white-toothed shrews (*Crocidura*) are assigned numbers and photographed to document variation in external features. Credits: left image by Santiago Burneo; right images by R. J. Baker.

PLATE IV.

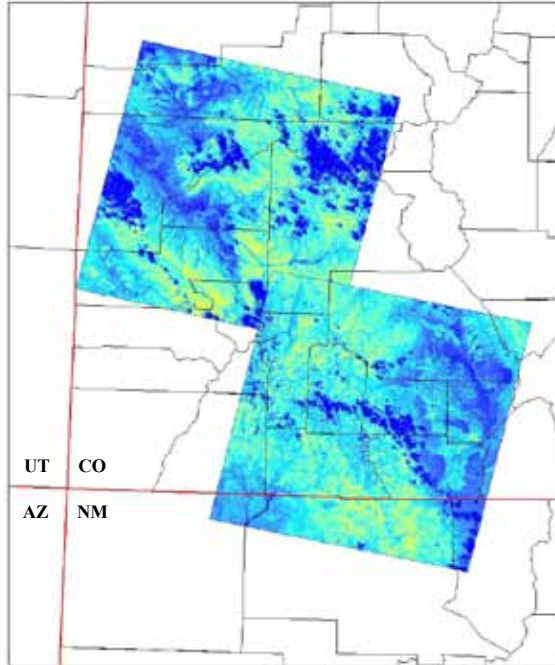


In Bolivia, Machupo virus is associated with Bolivian hemorrhagic fever (BHF) in humans. BHF is an acute disease. Samples of Machupo virus were obtained and studied by the Soviet BW experts, who were interested in its potential for weaponization (see pg 49 and ref 70). Originally, it was thought that a widely-distributed field mouse, *Calomys callosus* was the most likely reservoir of Machupo virus. However, it also was known that unlike *Calomys callosus*, the virus itself had a restricted distribution or focus, being isolated from mice only in Beni Province in northern Bolivia. Mice of the genus *Calomys* from throughout Bolivia were trapped and additional voucher specimens in museum research collections were studied. Molecular genetic analyses of the mice (phylogeny on left) revealed that Machupo virus is associated only with a particular genetic lineage of *Calomys*, which represents a previously unknown species. The distribution of these mice is limited to the Llanos de Moxos vegetation (shown in yellow, above), where BHF occurs. Other species of *Calomys* in Bolivia occur in the Chaco and Southeastern Cordilla regions and are not reservoirs for Machupo virus. This research is an excellent example of the kinds of fundamentally important information that can be obtained through field and laboratory work and is an example of preparedness. The GIS-based map was prepared for us by Dr. Hugo Mantilla-Meluk based on data published by Salazar-Bravo et al. (ref 122).

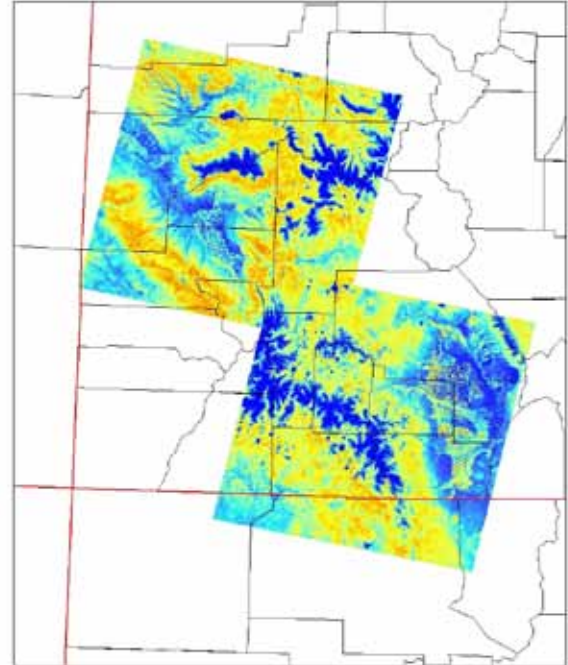
PLATE V.

Satellite Imagery

2004/2005



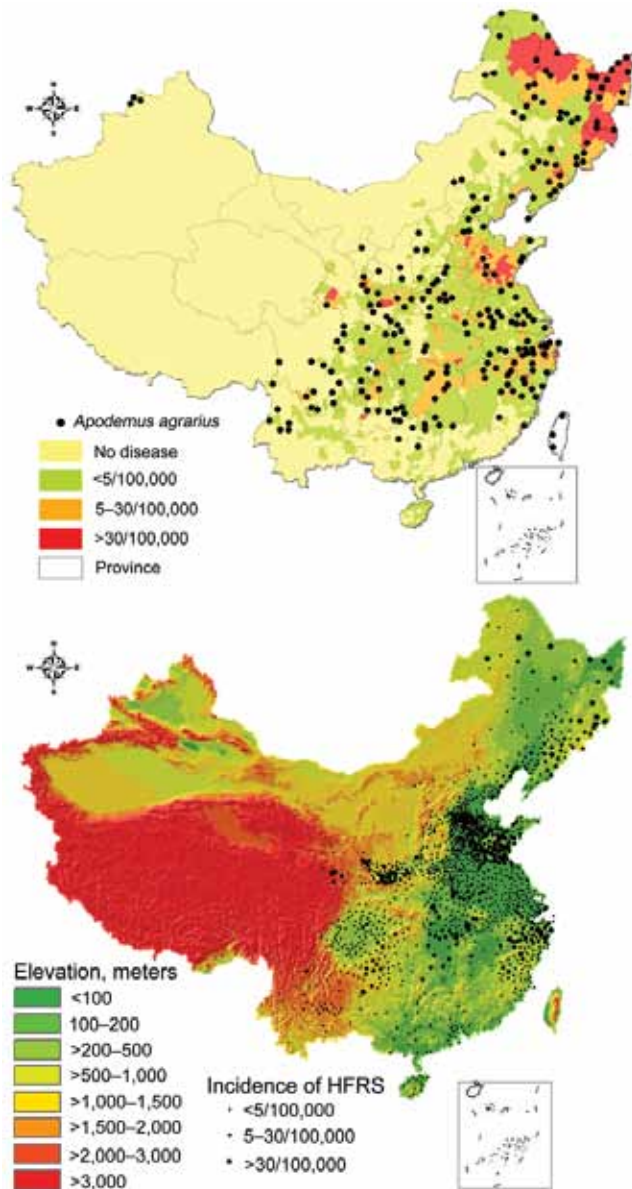
2005/2006



Emergent disease preparedness includes developing mathematical models, ground-truth verification, and collection and analysis of data about reservoir species and infectious agents. Collectively, such data can serve as the cornerstone for remote monitoring, response to outbreaks of unknown infectious agents, and outbreak prediction. Satellite imagery is pertinent because of its technical sophistication and potential for global coverage. In fact, it already is a key technology for monitoring weather patterns, shifts in land use, patterns and rate of deforestation, and impact of climate change. All of these factors are significant to the agricultural community, to forecasting, and to governmental strategic planning. This means that satellite imagery is well-suited to support emergent disease preparedness. It is practical to model the dynamic interplay among environmental factors (which can be monitored with remote imagery), reservoir species distribution and annual population densities (which requires direct measurement by fieldwork), and prevalence of infectious agents (also based on fieldwork).



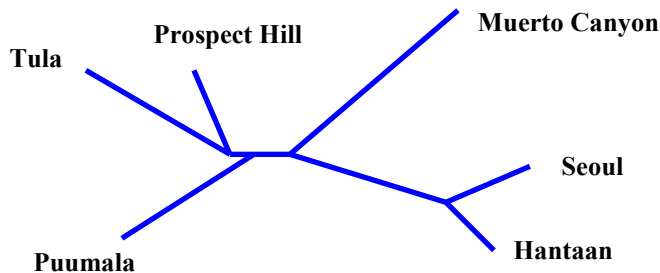
In 2006, Glass et al. (ref 29) used satellite imagery (logistic regression modeling of Landsat Thematic Mapper images, above) to predict an outbreak of hantavirus pulmonary syndrome (HPS) in southwestern Colorado and adjacent New Mexico. In the images shown above, outbreak risk ranges from low (blue) to high (red) and primarily is based on precipitation and deer mouse population dynamics, expressed in terms of density. The typical habitat monitored is shown on the left. The predicted outbreak held true for New Mexico, whereas in Colorado the typical number of cases were reported. Credits: satellite images were modified from Glass et al.; pinon pine habitat photo with permission, copyrighted by Al Schneider, www.swcoloradowildflowers.com.



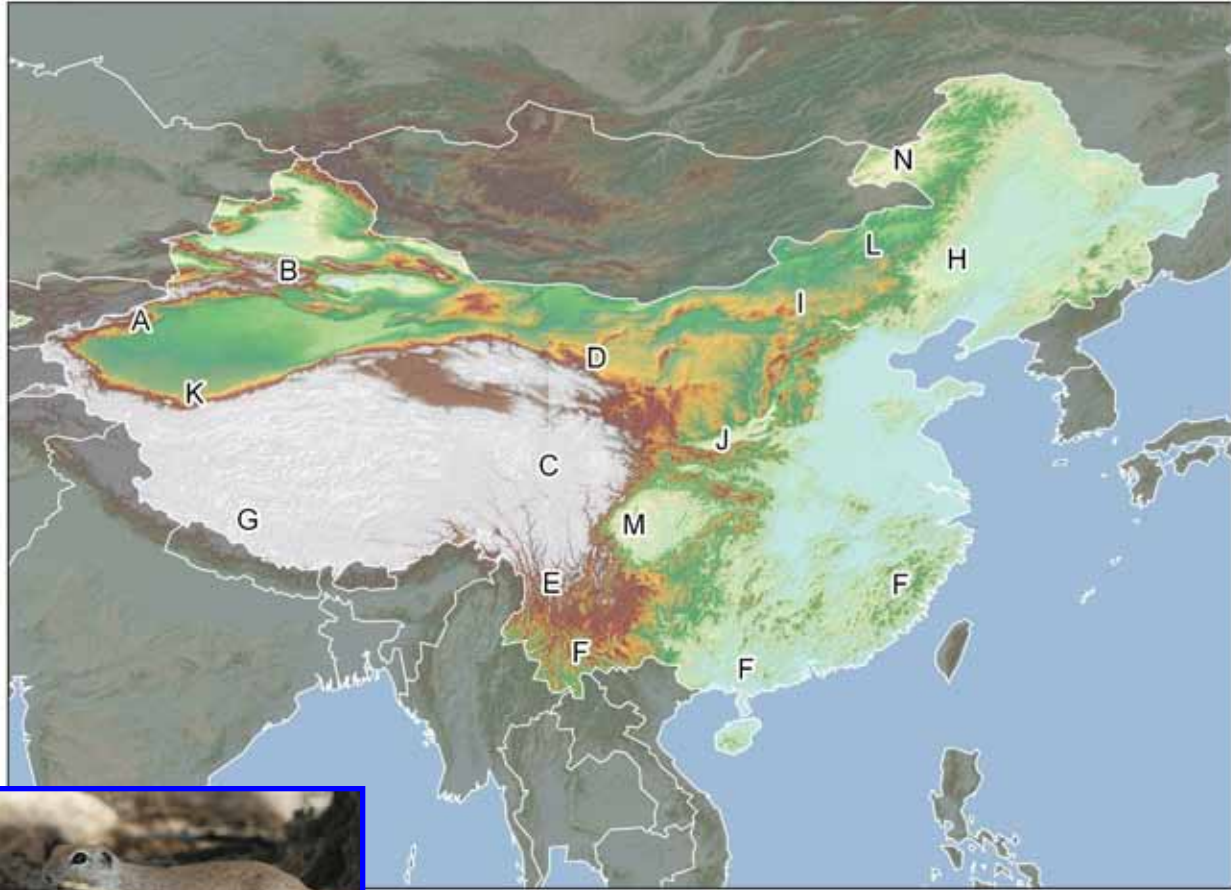
Hantaan virus-related hemorrhagic fever with renal syndrome (HFRS) is a significant public health challenge in China (maps at left). Hantaan virus was first isolated from the striped field mouse, *Apodemus agrarius* (above), on the Korean Peninsula (not shown). An outbreak of HFRS among combat troops and civilians during the Korean conflict (1951) caused considerable concern. Countermeasures included deployment of U.S. Army medical corps personnel with professional backgrounds in fieldwork and zoological disciplines including mammalogy and entomology. In China, recent field collecting of rodents, remote sensing (satellite data), and Geographic Information Systems (GIS) software have been used to analyze landscape and environmental factors that interact to influence the distribution of HFRS cases in humans. The GIS-generated maps at left illustrate the relationship of disease prevalence in humans to the localities where *Apodemus agrarius* was collected (top) and the relationship between prevalence (cases reported) and elevation (bottom). Elevation, vegetation, precipitation, and annual cumulative temperature are factors in disease prevalence. Other significant factors include soil type, timber (forest) land, and orchards frequented by striped field mice. This research serves as an excellent example of fieldwork, remote sensing, and GIS.

Credit: maps and mouse; CDC and Yan, L. et al., *Emerging Infectious Diseases*, 13:1301-1306, 2007.

Below, a phylogenetic analysis of 6 hantaviruses (based on sequenced viral RNA) shows the relationship of Hantaan virus to the Seoul, Muerto Canyon, Prospect Hill, Tula, and Puumala hantaviruses. These viruses are associated with a range of pathogenicity in humans. For the 3 viruses associated with HFRS, the striped field mouse is reservoir for Hantaan, 2 species of rats (*Rattus*) are reservoirs for Seoul, and the bank vole (*Myodes glareolus*) is reservoir for Puumala. Geographic distributions and evolutionary history of hantaviruses are correlated with their reservoir species.



In this phylogeny, the lengths of the branches (lines connecting viruses) approximates the degree of genetic relatedness. Credit: phylogeny based on Plyusnin et al., *Journal of Virology*, 68:7833-7839, 1994.



Natural foci of plague, caused by the bacterium *Yersinia pestis*, in China (foci labeled A-N). These data, from Zhou et al. (ref 84), illustrate how naturally-occurring disease foci can be visualized in a geographic context. Elevations on the satellite image shown above have been colorized so it is easy to see that plague foci occur at a wide range of elevations from seacoast urban areas (F) to the Qinghai-Tibet Plateau (C) to high Gangdisi and Tianshan mountain ranges (G and A, respectively). The foci differ in terms of the plague Biovar represented (plague bacteria from A, B, C, D, E, G, H foci are Antiqua Biovar; F is Orientalis Biovar; and plague bacteria from I, J, K, L, M, N are Medievalis Biovar). Not surprisingly, because this zoonotic disease spread over so large an area and at such diverse elevations and ecological settings, a variety of mammal species serve as principal reservoirs, depending on location. Examples of three rodent genera that have significant roles as plague reservoirs in China are shown at the left as follows: top, ground squirrel of the genus *Spermophilus*; middle, the Mongolian jird (gerbil), *Meriones unguiculatus*; bottom, species of this large alpine ground squirrel, genus *Marmota*, are important to the circulation of plague bacterium in Central Asia. Foci and their principal reservoir species are as follows: A, *Marmota caudata*; B, *M. baibacina* and a ground squirrel species, *Spermophilus undulates*; C, D, G, K, *M. himalayana*; E, two mouse species, *Apodemus chevrieri* and *Eothenomys miletus*; F, a rat, *Rattus flavipectus*; H, J, ground squirrel, *Spermophilus dauricus*; L, *Marmota brandti*; M, *M. fuscus*; N, *M. sibirica*. At plague foci L and M, Zhou et al. discovered plague bacteria with unique genomes; these new strains are not known to infect humans and are associated with mice of the genus *Myodes* (formerly, genus *Microtus*). Map prepared by Dr. Hugo Mantilla-Meluk based on Zhou et al. (ref 84). Credits: top left, image by T. Beth Kinsey; middle, image from magratknoblauch; bottom, image by unknown photographer.

PLATE VIII.

VIII. Emergent Disease, Geospatial Databases, and Reservoir Species

Disease surveillance theoretically can be divided into three generalized categories: 1) detection and data-keeping on established, common, infectious diseases that are important to human health; 2) determination and response to disease outbreaks that possibly are consequences of intentional rather than natural circumstances; and 3) detection of previously unknown 'new' diseases with emergent potential. Although it

is convenient to divide surveillance in this way, these are not separate categories and integration is the critical factor. Independently of any form of surveillance, new strains of infectious agents will continue to appear sporadically in geographic regions where the pathogens are endemic. Surveillance should establish the nature and importance of these emergent pathogens.

Technical Perspective on Emergent Disease

The existence of 'emergent diseases' is a significant and widely recognized phenomenon in which zoonotic agents, particularly viruses, are transferred unexpectedly to human beings. The biology of interspecies transfer is an important subject, but also one that is poorly understood. In addition to biological mechanisms, anthropogenic factors such as habitat destruction, expanding human populations, and climate change generally are regarded to have important roles (7, 8). On a global scale, at least thirty examples of emergent disease have appeared since 1973. Most of these examples are incompletely understood from a scientific and medical perspective. One example in the United States is hantavirus, which caused a public and political stir in 1993 (31). Deaths from hantavirus pulmonary syndrome (HPS) at first were attributed to influenza, pneumonia, or were unexplained respiratory-related deaths. Next they were regarded as due to a mysterious and unknown agent, which in the absence of data caused some people to consider the possibility of a loose BW agent escaped from recently closed Ft. Wingate in New Mexico. Eventually the deaths in New Mexico were associated with a particular strain (*Sin Nombre*) of a type of hantavirus previously unrecognized as a pathogen in the United States, but within the family of a well described viral hemorrhagic fever (VHF) viruses, which constitute a public health menace in Europe and Asia. Related viruses also were known from a vast portion of the Old World, including the Middle East, northern Europe, and Central Asia. Collectively, hantaviruses cause a variety of diseases in humans including in the United States a pulmonary respiratory syndrome. In the United States, most

known hantavirus strains are associated with species of wild rodents in a single family that serve as their reservoirs. The association of the virus with particular kinds of rodents is ancient and the viral genealogy thus reflects the evolutionary history of their rodent hosts. For this reason, an understanding of the rodent species that are involved as natural hosts of hantaviruses is an essential piece of the epidemiological and human disease forecasting puzzle. It is of significance that Old World hantaviruses seem to easily infect human beings, but are far less lethal to humans than are the New World forms. Fatality in humans from Old World hantaviruses is 10-20%, whereas it is 40% from *Sin Nombre* virus. The significance of strain differences in virulence is obvious when it is realized that hantavirus has a small genome, which simplifies its potential for genetic engineering.

Although the epidemiology, ecology, and host-relationships of hantavirus infection in the United States are not completely understood, many viral strains have been uncovered and characterized, the phylogenetic tree of the virus has been partially resolved, and the rodent reservoir species have been identified for the most dangerous of the 27 strains that have been isolated and genomically characterized since 1993. Horizontal transmission, which is thought to be the primary pathway for hantavirus transfer among hosts, has been modeled mathematically (68). Such modeling has the potential of being useful to understanding prevalence in reservoir host populations. Overall, North American hantavirus is a good example of what can be accomplished when multidisciplinary teams

explore emergent disease. Integrated data sets can be used to focus surveillance in space and time. Moreover, the use of modeling, environmental data, and satellite imaging in predicting disease outbreaks was demonstrated in 2006 (29).

Scientifically, the hantavirus experience in the United States produced three relevant and highly significant findings that mirror the Soviet approach to mining strains with potential value to their BW program: 1) not all hantaviruses are equally virulent; 2) the evolutionary history of the virus corresponds with the natural history of their rodent reservoir species (*e.g.*, reproductive rate, population dynamics, behavior, dispersal); and, therefore, 3) viruses can be defined geographically, ecologically, and as a function of epidemiological characteristics. Armed with this information, an individual could select the geographic focus of a particular virulent strain, collect specimens of its reservoir species, and isolate the virus in the laboratory. The number of individual rodents carrying the virus will vary according to population density and other factors, but as is implied by the term ‘reservoir,’ the viral strain is maintained over time in nature by replicating itself and passing from one individual of the rodent reservoir species to another individual. The minimum population density (the minimum number of individuals per hectare) of a host reservoir species required to maintain a virus over time is an important factor, because small mammal populations wax and wane according to microclimate and ecological conditions.

Hantavirus research has been comprehensive. Because of this, it can serve as a model to demonstrate that risk of outbreaks in humans can be estimated, even from remote sensing data (29). Additionally, genomic information from the viruses reveals how the pattern of virulence, in humans, varies geographically and in conjunction with genetic variation within the reservoir species of deer mouse (30).

Scientifically-generated information has incredible potential for answering questions relative to United States biosecurity. The foregoing statement seems obvious but acquisition of new data that can answer high priority questions usually is not emphasized in strategic planning. Nevertheless, the scientific methodology is available for establishing programs that can be used

to determine whether an infectious disease outbreak is naturally occurring or has been introduced to a particular geographic setting. Although such data are neutral and not political, they have value to political leadership for shaping response and for strategic planning.

An interesting historical example of the power of scientifically generated geospatial information about reservoir species and viruses is available from work on hantaviruses and associated hemorrhagic fever in Korea. In 1951, during the war on the Korean peninsula, there was an outbreak of an unrecognized disease. In less than one month (28 June to 23 July), the 8th U.S. Army combat units reported 55 cases of a significant disease syndrome. Most of the cases occurred in a single regiment. Because the symptoms were described as ‘leptospirosis-like,’ leptospirosis was one of the preliminary presumptive differential diagnosis (99). Consultations with the Japanese raised the possibility that the disease outbreak in Korea had common features with a disease seen in the Japanese army in Manchuria in the 1940’s (99). But aside from natural outbreaks, it also seems likely that the United States at least considered the possibility that an intentional BW release—possibly by the Soviet Union—was involved. Such an explanation was consistent with the facts that (a) the disease initially seemed unknown and (b) appeared first in a group of infantrymen who had been engaged in combat with North Korean and Chinese forces. It also was known that during the Second World War the Japanese bio-weapons organization in Manchuria had conducted research on a disease that produced a similar syndrome. Moreover, the Russian medical literature addressed hemorrhagic fevers that also were similar. Cumulatively, all of this information reinforced in at least some minds the potential for a disease outbreak being the consequence of an intentional release of an imported infectious agent. Given the ideological and strategic circumstances at play in the Korean conflict, could the outbreak perhaps involve a field test of a Soviet BW product? If it did, this would be a critically significant factor. If it did not, and the outbreak was natural, the potential health impact on combat units still was extremely important. In response to the problem, the United States quickly organized and deployed an array of civilian specialists and scientific and medical experts assigned to the military. The assembled expertise included traditional bacteriologists and virologists, entomologists, and mammalogists. Just to give a few

examples, the U.S. Army team included Col. Robert Traub, a renowned expert on Asian fleas (the vectors for plague) and Lt. J. Knox Jones, Jr., a mammal specialist from the University of Kansas (99, 100). David Johnson, a mammal specialist at the Smithsonian served as a backup collaborator to Lt. Jones. Johnson previously had served in the Pacific in 1944-45 as a member of NAMRU-2. Specimens of mammals—species that were potential disease reservoirs—were sent to the Smithsonian research collections at the United States National Museum (now called the Museum of Natural History) and studied taxonomically by Jones and Johnson (101). In the search for hemorrhagic fever reservoir species, Lt. Jones also conducted joint research with Japanese experts on scrub typhus and mammals (102).

The assembly of a scientific team capable of conducting scientific research under combat conditions was based upon the counter-measure strategy developed in Southeast Asia and the Pacific late in the Second World War. One working hypothesis in Korea was that the disease outbreak was intentional. Another plausible hypothesis was that it was natural. If the latter were the case, the epidemiology was unknown. Perhaps the disease vector was an ectoparasite such as a chigger, and the reservoir species was one or more species of field rodents native to the Korean Peninsula. In a sense, these competing hypotheses and the critical need to rapidly determine scientifically which one was supportable encapsulates both the current United States national security need and the potential global scope of disease surveillance.

Given the field methods and laboratory technology available in 1951-55, it was challenging to test any hypothesis, much less the example given here. One huge technical challenge was to isolate and identify infectious microorganisms from species of tiny ectoparasites that might or might not be vectors and might or might not be infected at time of capture. Identifying and determining the geographic and ecological distributions of wild rodent species (certainly numbering in dozens) and further determining which one(s) might be the reservoir of an unknown disease was a separate, independent challenge. To a large extent, this second challenge was offset by the existence in the United States of research reference collections of mammal specimens at the Smithsonian Institution, American Museum of Natural History (New York),

the Field Museum (Chicago), and major university museums such as at the University of Kansas. Such collections were the single most important resource to identifying and estimating geographic distributions and habitats of potential reservoir species of Korean mammals. It is important to appreciate that the same thing was true in 1993 when the first recorded human cases of hantavirus-associated pulmonary syndrome caused substantial alarm. Within months of the first human cases, a species of deer mouse (*Peromyscus maniculatus*) was identified as the most important rodent reservoir (103).

Mice of the genus *Peromyscus* occur across southern Canada, throughout the United States, and deep into Mexico. Because of this broad geographic distribution and because there are dozens of species that occupy a huge range of habitats, identification of the species involved was both essential and insightful. Research collections with specimens of species of deer mice and other rodents that occur in the southwestern United States were an essential cornerstone to identification of the reservoir species (30, 31). In addition to the national collection at the Smithsonian, university mammal research collections in the Museum of Southwestern Biology at the University of New Mexico and the Natural Science Research Laboratory (NSRL) at the Museum of Texas Tech University were important repositories with relevant specimens (31).

The role of basic zoology—and research collections of specimens of mammals—in the Korean-era episode is largely forgotten except in scientific circles familiar with the personnel involved. But the fieldwork, reference collections obtained in the early 1950's, and the resulting scientific publications on Korean mammals ultimately were valuable to a research trail that led to Dr. Ho Wang Lee's discovery of Hantaan (HTN) hantavirus in Korea (104, 105). Karl M. Johnson has described his role as a part of 'serendipity' in the discovery of the Hantaan virus and its mammalian reservoir, the striped field mouse, *Apodemus agrarius* (106). Johnson was one of the first virologists to associate Bolivian Machupo virus with mice of the species *Calomys callosus*, a feat accomplished through intensive fieldwork, mouse trapping, and tissue sampling in the early 1960's (106). Similarly, with Johnson's support, Ho Wang Lee collected the key specimens of *Apodemus agrarius* in Korea.

Many of the voucher specimens of reservoir species that were collected during the Korean War and in following years still can be examined or used in research today because they are stored in the research collections of the Smithsonian Institute's National Museum in Washington, D.C.

The Hantaan virus story in Korea is worth understanding as history with great relevance to both disease surveillance and national security. One lesson is that the United States must maintain a biological forensics infrastructure capable of quickly responding to events similar to the one described here. The CDC, U.S. Army, and Naval Medical Research Units 2 and 3 are examples of organizations capable of response. Another, more important, strategic lesson is that prior knowledge of the Korean landscape, diseases, vectors, and potential reservoir species would have been extremely valuable. Today it still is the case that prior knowledge of this type is essential—and possible to obtain—on a global scale. Yet a third lesson is both scientific and political. During the Korean conflict, the People's Republic of China charged that the United States had deployed biological weapons on the peninsula. Ironically, the Soviet Union eventually announced that their analysis did not support the Chinese claim. In retrospect the failure of the Soviet Union to support her ally possibly was necessitated to ensure concealment of the developing Soviet BW program.

In 1998 two history professors at York University in Canada wrote a book, *The United States and Biological Warfare* (107), in which they elaborated on the original Chinese charges. Based on the authors' interpretation of previously 'classified' information they obtained from China and additional information obtained through the Freedom of Information Act in the United States, the professors took the Chinese side and argued that the hemorrhagic fever outbreak was evidence that the United States deployed and used biological weapons in Korea. As an example of polemic discourse this book illustrates the roles of emotionalism and political perspective as responses to disease outbreak associated with conflict. Most of the key claims were erroneous and even inconsistent with the official position of the Chinese government (89). Nevertheless, this book was successful at illustrating the substantial problems that can result from an unexpected disease outbreak coinciding with armed conflict.

The York University history professors postulated that the outbreak of hemorrhagic fever was unnatural. In the absence of any scientific data their rationale was inferential and based almost solely on their ideological position. They claimed that the disease previously had not been known in Korea and given the fact that the peninsula was engulfed in war they argued that the best conclusion was that the disease was intentionally imported. For ideological reasons, the authors ignored the scientific evidence developed during the Korean War or in following decades leading up to publication of their book in 1998. But in fact the scientific research conducted by the U.S. Army teams in Korea supported the hypothesis that the outbreak of hemorrhagic fever was a natural occurrence. The hypothesis that the disease was imported, or intentionally introduced to the battlefield, was rejected by the data.

Today, with modern molecular genetic methodology and algorithms for using DNA or RNA sequences to construct phylogenetic genealogies in a geographic context, significantly more scientific information is available about both hantaviruses and the mammal species that serve as reservoirs for these viruses (108). Modern data provide the scientific information that can dispel politically or ideologically motivated interpretations of historical events. Moreover, the modern molecular genetic data also clearly illustrate the power of current methods and their utility to understanding emergent zoonotic disease, distinguishing between intentional and natural disease outbreaks, and providing a basis for strategic planning and preparedness. Hypotheses about both geographic and phylogenetic (genetic lineage) origin can be tested readily.

In the evolution of the hantaviruses, one genetic 'clade' (a cluster of genetic lineages with a shared common origin) has a strictly Palearctic (Old World northern region) distribution. The viruses in this clade are associated with species of rodents that only occur in Europe and Asia. Among the European and Asian hantavirus strains, the Seoul and Hantaan varieties are found on the Korean Peninsula, hosted by striped field mice (*Apodemus agraius*) and black rats (*Rattus rattus*). Interestingly, these viral strains had independent evolutionary origins and histories: the Seoul strain apparently evolved with rats as their hosts, whereas the Hantaan strain originated from an ancestry in common with the Dobrava strain of the virus found in Europe

in association with two particular species (of more than five) of *Apodemus* (108, 109, 110). Wild mice of the genus *Apodemus* are a significant part of the hantavirus story in Korea, China, all of Central Asia, and Europe (111). The scientific research on hantavirus in Korea documents the value of geographical and genetic analyses of infectious agents and the mammal species that serve as their reservoirs. It also illustrates that important information for one country or region must be placed in a broader geographic context. Overall, the hemorrhagic fever story is an excellent example of the power of science as it can be applied to significant political and historical issues that have been distorted for propaganda purposes.

The extensive work on hantaviruses has led to models that can use remote (satellite-based) sensing for predicting outbreaks (29). Genetic signatures can be used to document the geographic distributions of the viral strains, and systematic mammalogy and phylogenetic analyses can be used to identify or even predict reservoir species (108, 112). Overall, hantaviruses and associated rodent species that serve as reservoirs (and those related species that do not seem to be reservoirs) provide a model for designing future research on naturally occurring zoonotic diseases. But although with proper data the resolution is excellent for many hantaviruses, the bad news is that for most examples the data are poor or non-existent. More studies are needed for identification of zoonotic agents and their reservoirs, knowledge of geographic distribution and ecology of the reservoir species, environmental and climatological factors involved in outbreaks, genetic variation in the virus and its relationship to the reservoir, and mode(s) of transmission within the reservoir and from the reservoir species to human beings.

Although much attention has been given to the role of wild rodent species as reservoirs for zoonotic agents, in 2005 an insect-feeding Asian bat was identified as a reservoir for the SARS-associated corona virus and three species of African fruit bats were identified as reservoirs of Ebola virus. Although still incomplete, these findings were major breakthroughs in highlighting the potential role of bat species as reservoirs (113, 114, 115). Bats now are known to be reservoirs for Henipahvirus, SARS corona virus, Ebola, and rabies. They also might be associated with Marburg virus. The Tacaribe virus (an arenavirus), originally was known

only from a species of Neotropical bat collected on Trinidad. This Neotropical bat (*Artibeus jamaicensis*) is geographically widespread (throughout the Caribbean and much of Central America and western South America) and has a very complicated biogeographic and genetic history (116). Thus it is not surprising that since the discovery of Tacaribe on Trinidad, the virus also has been reported in this bat species (and several other species) in Central America (117). Geographically, Tacaribe virus is widely distributed and potentially accessible through biological mining.

Emergent diseases are a national security threat because they are rare and poorly known, often highly virulent, capable of appearing virtually anywhere depending upon a variety of circumstances, and, most of all, they retain the potential for state-sponsored BW and even transnational bioterrorism. Indeed, in the case of bat- and swine-borne Nipah virus in Southeast Asia, articles have been published on (a) simple methods to isolate the virus from bat urine and (b) the potential for the virus as a weapon (51, 118, 119).

The Soviets also kept a close eye on emergent diseases as part of their global biological mining. Former Soviet weaponeer Ken Alibek described it as follows:

A strain of Marburg arrived in the Soviet Union a decade after it was first isolated, during one of our periodic global searches for promising material. It wasn't clear from the records whether we got it from the United States or directly from Germany, but it was immediately added to our growing collection of viral warfare agents. We were already investigating a number of microorganisms that weaken blood vessels and cause hemorrhagic fevers, such as Junin from Argentina and Machupo from Bolivia. Marburg quickly proved to have great potential. (70)

During Alibek's time, the Soviet Union sponsored extensive collecting projects aimed at obtaining specimens of mammals that were potential reservoirs and using them as sources of access to previously unknown strains of infectious agents. One example of this involved fieldwork in Guinea (Africa) during 1978-1989. In this instance the field team was led by

O. K. Konstantinov, who published the results of his work in open scientific literature in 2006, well after the collapse of the Soviet Union (120). Konstantinov reported that in Guinea reservoir species of mammals provide a reservoir for 18 arboviruses, 13 of which are

known to be pathogenic to humans, which the former Soviet Union added to their collection of infectious agents with implications for intentional misuse of zoonotic diseases.

Historical Factors, Infrastructure, and Preparedness

Emergent disease was unanticipated in the United States and there was no formal preparedness for such an event in 1993 (see pages 19-20). This also is the case on a global scale, although the international scientific and medical infrastructure is capable of mounting an *ad hoc* response to an unexpected outbreak, albeit with political stumbling blocks. The best example of an international response comes from the emergence of SARS in Asia in 2002. The respiratory syndrome initially was unrecognized by local Chinese health care personnel (22), although Zelicoff and his colleagues believed that a syndromic system of surveillance with the RSVP (Rapid Syndrome Surveillance Project) software would have been able to pick it up early in the outbreak (3). But with the absence of such surveillance, the disease had spread from the Chinese mainland to Hong Kong and Viet Nam by the time that the WHO issued its 12 March alert (22). A syndromic surveillance network is being developed in China at the present time.

When scientists obtained samples of the virus, they were able to use sequencing technology to determine that it most likely was a naturally occurring infectious agent rather than a synthetically manufactured product of a clandestine BW laboratory. Although this first question was answered quickly, the initial diagnosis that it was a Paramyxovirus (more specifically a Metapneumovirus) was incorrect and it was not until late 2005 that an Asian bat of uncertain species was finally documented as the likely reservoir for the corona virus associated with SARS (27). The announced discovery of a reservoir for SARS was an important event, although the identity of the bat species involved was not documented. There are at least thirty species within this bat genus and many are poorly known to biological science. This complication meant that there was no basis for determining how ecology, bat species genealogy, and geographic distribution contribute to epidemiology, and no basis for predicting the potential

that related strains of SARS might appear in humans. This shortcoming is significant because it severely reduced the epidemiological and strategic value of the information about the SARS reservoir. The shortcoming also was unnecessary inasmuch as species identity is knowable if the fieldwork is conducted correctly and produces voucher specimens for laboratory analysis.

An understanding of “species” is essential to disease surveillance when emergent zoonotic diseases are involved. The most appropriate version of the term must be applied to geographic reservoirs for infectious agents. Among the many options, the genetic species concept is more practical than a classical taxonomic definition because genetic data are testable and repeatable (121). Additionally, genetic data provide resolution to geographic source(s) and species biology. The genetic species concept already is applied to viruses and single cell organisms, so its application to reservoir species provides a better interface among data sets. Therefore, application of the genetic species concept to mammals that are potential reservoir species best fits with the research being conducted on the genomes of infectious agents and zoonotic diseases. Historically, species identification has been mistakenly regarded as an arcane skill and the application of the scientific concept to broader issues has been underappreciated, especially in the United States. Soviet BW program scientists understood the value of such information, however, and although they were limited to using old taxonomic methods for determining species identification they still were able to associate species with virulent infectious agents. With modern genotyping technology and genomics the ability to identify species, particularly species that are disease reservoirs, has become a powerful tool.

Collectively the determination of the interrelationships among reservoir species, genetic strains of

infectious agents, and vectors is an essential piece of any strategic approach to emergent disease. Machupo virus from South America, which was collected by the Soviets as part of their BW activities, is an excellent example (70). In this instance the geographic distribution of Bolivian hemorrhagic fever, for which the Machupo virus is the etiological agent, did not match the geographic distribution of the known rodent reservoir. Subsequently it was determined that the virus was associated with a genetic subset of mice (or possibly a new, previously unrecognized species) rather than with the entire species population (122). The methodology for understanding and defining “species” and how and why a species differs genetically in geographic space was critical to the work. In terms of disease surveil-

lance this finding could focus public health programs to geographic localities and habitats identified as the natural “nidality” (similar to the concept of disease ‘foci’) for Machupo virus in Bolivia. In terms of BW potential, this same information would be valuable to mining examples of the virus in nature. The term “dual use” is usually applied to laboratory equipment or methodology that can be used for both civilian science and weapons development; in this instance dual use applies to fundamental knowledge about nature. Interestingly, the rodent reservoir for Machupo virus is a member of the same subfamily as rodents that serve as hosts for hantaviruses, a finding that led to the discovery of the first arenavirus in the United States.

Preparedness versus Post-outbreak Response

Hantavirus, SARS-associated corona virus, and Nipah virus are three examples of how the scientific and public health communities responded to unexpected disease outbreaks. In all three instances the response was a qualified success given that there had been no formal preparation for handling these types of public health emergency. It also is true that in all three instances the outbreaks were natural. If human beings had intentionally triggered these outbreaks, the responses might not have been timely enough to be successful. Moreover, the absence of databases on genetic variation and distribution of naturally occurring zoonotic viruses would have made it difficult to distinguish quickly between natural infectious agents and man-made constructs.

It is possible and practical to think in terms of preparedness for outbreaks of emergent disease. In this instance preparedness means the development of a global geospatial knowledge base about reservoir species and the infectious agents they harbor. Data about vectors, when applicable, would be included. Such preparedness requires five activities: 1) aggressive, ongoing acquisition of new biological materials (viruses, bacteria, other infectious agents and potential vectors) through fieldwork; 2) creation of standard computer-catalogued collections of museum voucher specimens and tissue samples of mammals and birds; 3) molecular biological analysis of isolated infectious agents, potential reservoir species, and potential vectors; 4) creation

of accessible, interactive, geographic-based databases that ideally have the capacity to evaluate risks and support decision-making; and 5) integrative modeling. Versions of the first two activities are currently underway in a wide variety of academic institutions and in a few national laboratories. However, with few exceptions the individual projects and objectives are pure research rather than part of a centralized approach to preparedness. As a consequence, choice of geographic localities, infectious agents of interest, and experimental design is being driven more by scientific questions than by strategic or national security concerns. It is possible, however, to combine scientific objectives with national security priorities and public health goals.

Technically, post-outbreak response to zoonotic diseases requires the same capabilities as preparedness, albeit as a defensive reaction to an outbreak rather than as an on-going process of preparation. Because preparedness and defensive reaction require the same technologies, preparedness is favored as a strategy for dealing with emergent disease. Preparedness is more cost-effective because any defensive response is likely to be *ad hoc*. Moreover, preparedness requires active technical teams, ongoing data acquisition in the field, and laboratory coordination, all of which strengthen responsive ability if it is required. And none of these will have much impact without international collaboration and communication.

Preparedness for emergent disease would significantly reduce the time required to distinguish between natural outbreaks and bioterrorism, including the time it would take to conduct forensic analysis necessary for reliable source attribution. A prepared geospatial database of molecular genetic information about reservoirs, vectors, and infectious agents should substantially reduce response time and improve effectiveness of the response.

Preparedness is practical because emergent disease is not unpredictable. Proactive preparedness can be achieved on a global scale. The application of biological informatics—the integration of biological and geospatial information—provides a cost-effective solution to national security and public health challenges associated with emergent diseases.

Infrastructure for Preparedness

Although it is not organized under a coherent national plan, much of the infrastructure required for emergent disease preparedness either already exists in the United States or has historical precedent in government and the private sector. Likewise, analogous elements of required infrastructure exist in other countries, especially in the EU, Russia, other Eurasian countries, and, increasingly, in China and Southeast Asia.

Historically, United States governmental capabilities for collecting and studying specimens of infectious agents were developed publicly in context of public health and epidemiology by the Centers for Disease Control (CDC). The USDA (APHIS) has contributed a global geospatial database on animal health, the U.S. Geological Survey has a National Biological Information Infrastructure, and the United States Biological Survey (Department of Interior) and the United States National Museum of Natural History (Smithsonian Institution) and other research museums, including those at major research universities (especially Louisiana State University, University of California Berkeley, University of Kansas, University of Michigan, University of New Mexico, and Texas Tech University) have obtained specimens of potential reservoir species and vectors from a wide assortment of geographic localities. For example, the Natural Science Research Laboratory (NSRL) at the Museum of Texas Tech University holds a major collection built around the concept of vouchers for identifying and studying reservoir species (26).

Academic-based scientists have developed museum specimen-based databases on a global scale (accessible through MaNIS, the Mammal Networked

Information System supported by the NSF), have tissue collections available for research on reservoir species and vectors, and have implemented computer programs capable of surveying collections (including those held by the Smithsonian Institution) for geographic and systematic information about reservoir species. Many of the museum-based research collections are integrated with laboratories performing research on infectious agents (such as CDC and University of Texas Medical Branch at Galveston, UTMB) and geospatial modeling and remote sensing (Texas Tech University, University of New Mexico, and Johns Hopkins University).

In the past decade, the National Institutes of Health (NIH) and the National Science Foundation (NSF) have created individual and joint programs to support international research on evolution and ecology of emergent disease. United States infrastructure also is strengthened by university centers and institutes that focus research efforts on emergent zoonotic diseases, human health, and ecosystems. Some of these are newly created, whereas others are built on traditional academic programs. A few examples are: Center for EcoEpidemiology at Yale University; Institute of Ecology, University of Georgia; and the Center for Sustainability and the Global Environment (SAGE) at the University of Wisconsin.

United States military units operating in select regions since the 1940's have made significant contributions. Zoonotic diseases were a substantial strategic issue during warfare in the Pacific Basin and on the Asian mainland. United States Army (Medical Research and Development Command) and Naval Medical Research Unit Number 2 (NAMRU-2) staffed

by epidemiologists and field biologists operated in the Pacific Theater during the latter stages of the Second World War, where tropical disease epidemiology was a major challenge (123). The NAMRU-2 team helped solve the epidemiological puzzle of scrub typhus (tsutsugamushi disease), which caused substantial casualties among American and Japanese forces deployed on Pacific islands. Subsequently, as discussed previously, the U.S. Army fielded a team in Korea to investigate hemorrhagic fever with renal syndrome during the conflict there, and the Navy sent a NAMRU-2 team to Da Nang during the war in Viet Nam. All of these teams specialized in collecting, identifying, and creating scientific collections of voucher specimens of potential reservoir species and vectors, sometimes at the margins of combat operations.

Field research teams were not deployed to Iraq as a medical and BW counter-measure strategy in support of Operation Iraqi Freedom (OIF). But cases of both malaria and leishmaniasis were reported among Coalition troops. Field teams might have been able to survey and identify the rodent species that act as reservoirs for leishmaniasis. From this they might have predicted localities, habitat, and associated risks, had they been deployed in OIF. Following the invasion and collapse of the Saddam regime, the United States Department of State developed and implemented an Iraqi WMD Personnel Redirection Program (87). In 2006, this Cooperative Threat Reduction Program, represented in Baghdad, Iraq, by the International Iraq Center for Science and Industry (IICSI), supported a meeting on ‘Epidemiology, Zoonoses, and Disease Surveillance in Iraq.’ The meeting was organized by the U.S. Civilian Research and Development Foundation and one of us (CJP) served as a host. The meeting brought together relevant Iraqi scientific expertise in virology, bacteriology, parasitology, and reservoir species (rodents, primarily) along with experts from the United States, including NAMRU-3, CDC-Atlanta, Sandia National Laboratories, UTMB-Galveston, and Texas Tech University. The participants reviewed available data on the prevalence and distribution of the known,

significant, infectious diseases in Iraq and discussed ways to develop and implement a disease surveillance system as part of the reconstruction of science and technology in Iraq.

In addition to responding to specific disease issues in the midst of military operations, force threat reduction and preparedness requirements continue to involve the Department of Defense (*e.g.*, U.S. Army Center for Health Promotion and Preventive Medicine—USACHPPM—and the U.S. Army Medical Research Institute of Infectious Diseases—USAMRIID) working both alone and in concert with civilian scientists, often in the academic community or national laboratories, or both.

The overlap between defensive and offensive use of BW and conventional civilian field research on reservoir species, vectors, evolutionary theory, and infectious agents is obvious. It is reflected historically in the temporary creation of a CDC Epidemic Intelligence Service in the United States during the Korean War (124). The importance of evolutionary theory, which encompasses all of biology, is reflected in numerous papers, especially those that focus on species and population dynamics, phylogeny of infectious agents in geospatial context, and evolution of virulence (95, 112, 114, 125).

At one level the overlap between BW and conventional science involves typical biological mining. At another level, the personnel, technologies, and goals of such fieldwork reflect the unwritten history of offensive, defensive, and counter-measure approaches to BW. Thus, in the 1960’s United States civilian scientific teams conducted field studies on reservoir species and vectors of scrub typhus in northernmost Pakistan, just across the border from the Soviet Central Asian republics where numerous BW laboratories and biological mining field stations were located. In the post-Soviet years many of these institutes in Uzbekistan, the Kyrgyz Republic, and Kazakhstan have participated in United States and EU nonproliferation programs.

SECTION SUMMARY

- ‘Emergent diseases’ is a significant and seemingly new phenomenon in which zoonotic diseases are transferred unexpectedly from naturally occurring species to human beings.
- Regardless of research, more is unknown than is known when it comes to emergent diseases.
- Emergent diseases are a threat to United States national security because they are rare and poorly known, often highly virulent, likely to appear virtually anywhere depending upon a variety of circumstances, and, most of all, because of their potential for BW.
- An understanding of “species” as the term applies to geographic reservoirs for infectious agents is essential to emergent disease preparedness and risk assessment.
- It is possible and practical to think in terms of preparedness for outbreaks of emergent disease.
- Preparedness requires:
 - aggressive ongoing acquisition of new biological materials through field-work;
 - proper preparation, storage, and accession of tissue samples and reservoir voucher specimens in an accredited museum research collection;

SECTION SUMMARY (CONT.)

- molecular biological analysis of isolated infectious agents, potential reservoir species, and potential vectors; and
- creation of accessible, interactive, geographic-based databases.
- Although it is not organized under a coherent national plan, much of the infrastructure required for emergent disease preparedness either already exists in the United States or has historical precedent in government and the private sector.
- The availability of numerous university research collections and the available diversity of expertise is the consequence of previous investment and now is a relatively inexpensive asset.
- Strategic preparedness with geospatial databases and genetic information on infectious agents, reservoir species, and vectors provides:
 - capability of rapid determination of natural versus human-influenced outbreaks;
 - capability of attribution through geographic and genotypic information about infectious agents, reservoir species, and identification of vectors;
 - capability for predicting, monitoring, and responding to natural outbreaks of emergent disease.

IX. The Way Forward

By any standards, global disease surveillance is an extremely complex concept. On the one hand, some form of disease surveillance with record keeping, transmission of important findings, morbidity and mortality summaries, and response systems is commonplace around the world. But on the other hand, the goals and objectives, reliability, and overall quality vary dramatically. For many countries, diseases in human beings and livestock have staggering economic and social impacts but outbreaks can go unnoticed by outside parties. When resources are scant, the impacts of disease are magnified. Daily or monthly monitoring and information storage and accurate communications become secondary under such circumstances. Disease surveillance as it is practiced in the United States or other ‘western’ countries might be seen as a luxury for nations with limited economic and technical resources. Under such circumstances disease ‘priorities’ are set, and small nations tend to restrict surveillance to particular, selected, infectious diseases. From the perspective of the United States, where we believe that infectious disease is a matter of our national security, another nation’s priorities might or might not be compatible with our idea of priority. We might, for example, want to know about an outbreak of a zoonotic disease associated with potential intentional release as opposed to a common but economically important disease in livestock. Our concern with transnational bioterrorism is unlikely to dissipate in the foreseeable future. In fact, because national security is a priority from the perspective of the United States, national security considerations will trump every other consideration when it comes to global disease surveillance. This reality certainly will continue to be the case into the foreseeable future.

The immediacy of disease surveillance as a subject thus is compounded by the concept of ‘national security’ at least as it is practiced in the United States. It would be helpful if national security was a single issue, but in reality it comprises multiple issues that just happen to share the same umbrella terminology. In the 21st Century, opinions about what constitutes national security will influence every strategic decision and national security will be both the starting and the end point of any discussion about infectious disease.

Because disease surveillance is a matter of national security, disease surveillance has become a popular subject within government. This popularity is reflected in the number and variety of Federal reports generated by Congress, the GAO, the Intelligence Community, and other agencies. In a sense, disease surveillance has been adopted by the threat reduction, nonproliferation community. Indeed, the Threat Agent Detection and Response (TADR) program in the Department of Defense essentially is an attempt to create a special-case regionalized disease surveillance system. Interest in disease surveillance on the part of the Federal Government also is reflected by the amounts of money distributed by Congress to local levels (first responders, health departments), research grant programs, homeland security activities, and impromptu responses to influenza outbreaks. Although the national disease surveillance infrastructure is strong within the United States, there is no clearly identified lead agency when it comes to *global* disease surveillance. One might explain the absence of a lead agency by arguing that disease surveillance is not a single activity. Disease surveillance, as a topic, does not clearly fall within the authority of a single agency. One might also argue that any subject with significant national security implications will have a correspondingly large and diverse group of stake-holders. Levels of interest and Congressional funding activity probably correlate (in the statistical sense) with and in fact help drive the diversity and number of perceived stake-holders. In this way, disease surveillance (including funding generated by anticipated or actual outbreaks) has become a cash cow but not a coherent national program with agreed-upon goals and predictability.

The complexity of disease surveillance also can be explained at least partly in terms of a combination of historical and cultural factors and international relationships along with the very basic question of why such surveillance is needed in the first place. Disease surveillance on a global scale is a challenge in which local, regional, and international political factors dominate the scientific and technological demands. It is technically feasible to equip selected sentinel stations—even in reasonably remote places and economically marginal nations—to detect specific infectious agents.

But we can predict that politically such stations will function only so long as their output is unimportant and some other nation, or consortium of nations, pays the bill. If an important outbreak were detected, political considerations would take priority. There are ways to reasonably assure that the event occurrence will be known to the international community but the question is: what happens next?

When disease surveillance is discussed as a ‘global’ activity it makes sense to imagine a network that joins nations large and small into a shared enterprise. Some of the infrastructure, most notably the World Health Organization, is in place for a truly international approach to disease surveillance. At the same time, the single largest complication arises when the United States quite rightly brings up its own national security concerns, which is an American priority. The United States is concerned with transnational bioterrorism, state-sponsored biological weapons programs, legacy collections of infectious agents, and the possible misuse of biological research on infectious disease. All of these concerns obviously overlap with even the most routine disease surveillance and reporting. Collectively, the issues of most concern to national security specialists in the United States also are the issues that cloud the international discussion about how to create an equitable system of global disease surveillance. Moreover, the concerns that occupy the attention of the United States national security community are not shared by all nations. Indeed, for many nations the very basic elements of disease surveillance—diagnostics, quality control on reporting, guidelines for response and data-sharing—pose substantial financial, governmental, and political challenges. Ability to respond is yet another challenge. A system of global disease surveillance must account for significant international asymmetry in political interests, ability to carry out and finance a plan, and equity of outcomes (126).

The Egyptian response to the 2009 outbreak of H1N1 influenza is one current example of how politics and perhaps religious-based ideology and even simmering social and religious resentments can take priority. Although there was no scientific or medical basis for it, the Egyptian response to the outbreak in Mexico was to order the slaughter of thousands of swine (127). The international community questioned the decision and technically-based medical objections were raised.

The official excuse was that the swine industry in Egypt already had been slated for new regulatory control and the outbreak simply triggered what would have occurred in any case (127). The fact that the swine industry was in the hands of a minority Christian group might or might not have been a factor in decision-making. Untangling the politics of pandemic outbreaks will occupy academic historians and political scientists for decades. If such decisions are more emotional than political, a reliable understanding of the decision-making is unlikely. But in terms of disease surveillance, none of this has any direct value to the immediate problems created by a detected outbreak.

Expected outbreaks—as in the case of avian influenza (H5N1)—and actual outbreaks leading to pandemics—as in the case with H1N1—illustrate some of the challenges associated with global disease surveillance. With Avian influenza the expectation of a dangerous pandemic led to multiagency expenditures of billions of dollars focused primarily on the projected dangers of this particular virus. In the case of H1N1 the allocations authorized by Congress were bolstered by \$7.7 billion added to the ‘war supplemental’ legislation passed in June 2009. Whether anticipating an outbreak of a particular viral strain or reacting to an actual outbreak, the United States’ approach has been massive. At the very least such responses document the economic and political impacts of particular diseases and the ability of a democracy to respond to what is perceived as a ‘crisis.’ Other effects include the impacts of directed change in research activities at national resources such as the CDC in Atlanta. By any measure, the massive responses that typify the way in which the United States government usually reacts will have a ripple effect that persists years after an actual crisis, or, more important, a potential crisis that either fades away or is resolved.

One positive impact of potential or actual influenza outbreaks can be documented in terms of new knowledge that results from research stimulated and funded as a consequence of the alarm that is generated. Influenza virus, which is a threat in part because of its rapid evolution, is an excellent model for understanding evolutionary patterns and the relationship between specific genes and antigenic patterns in the virus (128, 129). These viral strains also have been modeled mathematically in context of both prediction of evolutionary

patterns and ecological factors that could influence the distribution and spread of the viruses (130, 131). Basic and applied science benefits from crisis when there is a perception that scientific knowledge can solve a problem or that scientific research might hold a solution.

Ultimately, the question for the United States is whether or not the concept of global disease surveillance is worth pursuing as a formal component of a national security strategy. Many agencies and stakeholders benefit from disease surveillance, so it would not be surprising to hear the question answered with a resounding ‘yes.’ But the reality is that global disease surveillance has too many stake-holders, too many components, and, most important, lacks a single point of leadership. Ironically, the purely social and historical division of infectious diseases into ‘human’ and ‘animal’ health is one of the factors that make it difficult to identify a lead agency. Presumably both CDC and the USDA see themselves as the most logical choice for leader. Similarly, the traditional health community focus on monitoring single diseases – polio, measles, smallpox, influenza – with each having its own surveillance platform, means that efficiencies of scale are not realized. For example, it would be useful to question how the global influenza monitoring and response system might be used as a backbone for building broader capability for multiple diseases rather than tracking, and heavily investing in, only one at a time.

On a global scale, disease surveillance is ‘possible’ to accomplish so long as it is satisfactory to have mixed results and imperfect communication and relatively uninformed decision-making well into the foreseeable future. If success is defined in terms of mixed results or other imperfections, then the value of disease surveillance is correspondingly weakened as an instrument of national security. This is the dilemma: as a stand-alone activity global disease surveillance has limitations and these limitations are exacerbated when national security decisions are dependent on data from disease surveillance. Even so, as a strategic instrument of national security strategy, global disease surveillance still qualifies as a ‘good thing.’ In the end, global disease surveillance is too large, too complex, and too cumbersome to meet national security requirements.

The way forward requires us to simplify the subject of disease surveillance. Continued haphazard

growth stimulated by Federal funding opportunities combined with unpredictable infusions of substantial amounts of money whenever an outbreak is anticipated, will compound the problem. Because natural disease outbreaks already are associated with habitat destruction and changes in land use, we can predict that disease outbreaks in future years will become an even larger challenge because global climate change will drastically alter landscape, animal and plant distributions, land use patterns, and habitats (28, 32, 48). Introductions of exotic species and commercial use of wildlife on a regional and international level will be another complicating factor (132). Responding to outbreaks, or anticipated outbreaks, will be necessary, but for the United States it will require leadership from the National Security Council. Such leadership must insure that funding and programmatic changes are not disruptive to other high priority activities.

Much of our emphasis in the present publication has been on the importance of understanding zoonotic diseases. Such an understanding is not simply a matter of ‘research,’ or increased funding for research from agencies such as NIH and NSF, which already have had joint and individual programs on zoonotic disease. It is true that research is critical—and must continue to be supported—but it is even more critical to create an integrated approach that coordinates future research and links it with international collaboration, intentional engagement, and clear strategic objectives.

Directed programs that result in accessible, interactive databases on the geographic distributions of zoonotic infectious agents and their reservoir species and associated vectors are essential to our national security. The Soviet BW Program, which used biological mining to locate and obtain virulent pathogens with limited geographical distributions, calls attention to the significance of such knowledge. An understanding of genetic or genomic variation in a geographic or ecological context is essential to rapid forensic analysis, which is a key capability in national preparation for natural or intentional outbreaks (132). And the fact is that many regions of the world that pose critical security concerns for the United States also are among the most poorly known in terms of potential reservoirs, vectors, and strains of zoonotic agents. In fact, some regions, particularly regions in Southeast Asia, Central Asia, the Middle East, and Sub-Saharan Africa, are

both poorly known and difficult localities in which to conduct the primary fieldwork that is needed. It is virtually impossible to conduct primary fieldwork in any of these regions without local collaboration and logistical assistance. On the positive side, many of the necessary scientific collaborations already exist. In Southeast Asia, for example, collaborations among universities, both local and foreign, and collaborations with the U.S. Navy Medical Research Unit-2 provide a foundation for substantial progress in understanding the ecology, reservoirs, and vectors involved in zoonotic diseases.

Collaborations among universities and a variety of research organizations have the added benefit of nearly always involving students. Training of new personnel is an essential but often overlooked aspect of national security. A perusal of responses to influenza,

either outbreaks or potential outbreaks, will document that the need for educating specialists is almost never mentioned. In order to aggressively pursue the fundamental scientific information required for United States national security, a new generation of biomedical scientists is needed. These people must have multiple skill sets and an interest in conducting technologically innovative fieldwork on zoonotic agents. Given the circumstances, they also must be capable of functioning in foreign lands, must understand the principles of international collaboration, and must be able to integrate their work with governmental goals (including the goals of foreign ministries of health or agriculture). Meeting the foregoing criteria will not be easy, but it is essential that we recognize the need and define the skill sets required to meet national security objectives in the field of emergent disease, bioterrorism, and disease surveillance.

SECTION SUMMARY

- Disease surveillance on a global scale is a challenge in which local, regional, and international political factors dominate the scientific and technological demands.
- United States national security interests must have priority, but it is necessary to appreciate the overlap with basic disease surveillance and remember that other nations do not share the same perspective.
- Asymmetry in the ability of nations to contribute to a global system poses a major challenge.
- The Egyptian response to the 2009 outbreak of influenza A, H1N1 is an example of how politics and perhaps religious-based ideology and even simmering social and religious resentments can take priority.
- One positive impact of potential or actual influenza outbreaks can be documented in terms of new knowledge that results from research stimulated and funded as a consequence of the alarm that is generated.
- It would be useful to question how the global influenza monitoring and response system might be used as a backbone for building broader capability for multiple diseases rather than tracking, and heavily investing in, only one at a time.
- On a global scale, disease surveillance is ‘possible’ to accomplish so long as it is satisfactory to have mixed results and imperfect communication and relatively uninformed decision-making well into the foreseeable future.
- Directed programs that result in accessible, interactive databases on the geographic distributions of zoonotic infectious agents and their reservoir species and associated vectors are essential to our national security.
- In order to aggressively pursue the fundamental scientific information required for United States national security, a new generation of biomedical scientists is needed.

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Key to Abbreviations and Acronyms

AFMIC – Armed Forces Medical Intelligence Center
AHEAD – Animal Health/Emerging Diseases project (Federation of American Scientists)
AIDS – acquired immune deficiency syndrome
APHIS – Animal Public Health Information System
BEP – Biosecurity Engagement Program
BII – BioIndustry Initiative
BSL – biosafety level
BW – biological weapons
BWC – Biological Weapons Convention
CBW – chemical and biological weapons
CCHFV – Crimean-Congo hemorrhagic fever virus
CDC – Centers for Disease Control
CPA – Coalition Provisional Authority (Iraq)
CRDF – Civilian Research and Development Foundation
DNA - deoxyribonucleic acid
DoD – Department of Defense
DoD-GEIS – Department of Defense Global Emerging Infections Surveillance and Response System
DOE – Department of Energy
DTRA – Defense Threat Reduction Agency (Department of Defense)
DU – depleted uranium
EMPRES-*i* – Global Animal Disease Information System (database of FAO)
EU – European Union
FAO – Food and Agriculture Organization (United Nations)
FDA – Food and Drug Administration
GAO – General Accounting Office
GDP – gross domestic product
GIS – Geographic Information Systems
GPS – Global Positioning System
GVFI – Global Viral Forecasting Initiative
H1N1 – influenza A subtype, also known as swine flu
H5N1 – influenza A subtype, also known as avian flu
HFRS – hemorrhagic fever with renal syndrome
HIV – human immunodeficiency virus
HPS – hantavirus pulmonary syndrome
HTN - Hantaan (virus)
IICSI – Interim Iraq Center for Science and Industry

ILIAD – International Lookout for Infectious Animal Diseases (Tanzania, Africa)
ISTC – International Science and Technology Center
MaNIS – Mammal Networked Information System
NAMRU – Naval Medical Research Unit
NASA – National Aeronautics and Space Administration
NATO – North Atlantic Treaty Organization
NBACC – National Biodefense Analysis and Countermeasures Center
NGO – non-governmental organization
NIE – National Intelligence Estimate
NIH – National Institutes of Health
NIS – newly independent states (of former Soviet Union)
NRC – National Research Council
NSF – National Science Foundation
NSRL – Natural Science Research Laboratory (Texas Tech University)
OIE – World Organisation for Animal Health (formerly Office International des Épizooties) (France)
OIF - Operation Iraqi Freedom
OSHA – Occupational Health and Safety Administration
PCR – polymerase chain reaction
PHS – Public Health Service
ProMED – Program for Monitoring Emerging Diseases (Federation of American Scientists)
PRRS – porcine reproductive and respiratory syndrome
R&D – research and development
RCQ – Republican Center for Quarantine and Especially Dangerous Diseases (Kyrgyz Republic)
RNA – ribonucleic acid
RSVP - Rapid Syndrome Surveillance Project
SAGE – Center for Sustainability and the Global Environment (University of Wisconsin)
SARS – severe acute respiratory disease
STCU – Science and Technology Center Ukraine
SYRIS – Syndrome Reporting Information System
TADR – Threat Agent Detection and Response Program
TB – tuberculosis
UK – United Kingdom
UNEP – United Nations Environmental Programme
USACHPPM – United States Army Center for Health Promotion and Preventive Medicine
USAID – United States Agency for International Development
USAMRIID – United States Army Medical Research Institute of Infectious Diseases
USDA – United States Department of Agriculture
USGS – United States Geological Survey

UTMB – University of Texas Medical Branch (Galveston, Texas)

WAHIS - World Animal Health Information Database (database of OIE)

VECTOR – State Research Center of Virology and Biotechnology (BSL-4 facility, former Soviet Union)

VHF – viral hemorrhagic fever

WHO – World Health Organization

WMD – weapons of mass destruction

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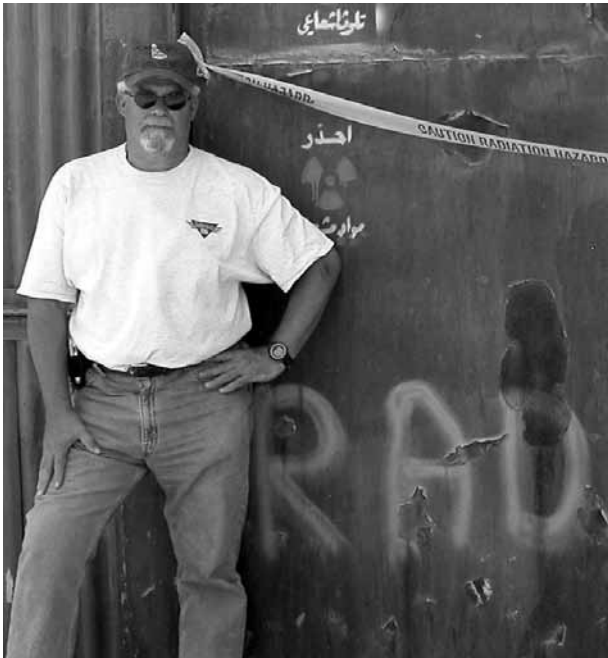
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About the Authors



Carleton J. Phillips is Professor of Biological Sciences at Texas Tech University. He previously served as Assistant Vice President for Research and Chair of Biological Sciences at Texas Tech. He also has served as William C. Foster Fellow, Office of Cooperative Threat Reduction, United States Department of State and Special Advisor on Nonproliferation, Coalition Provisional Authority in Iraq. He currently has field research projects in Central Asia and Iraq and has conducted biological research projects in Central and South America, the Caribbean, Central, South, and Southeast Asia, and Africa. Current address: Department of Biological Sciences, Texas Tech University, Lubbock, TX 79409-3131, carl.phillips@ttu.edu.



Anne M. Harrington is Director of the Committee on International Security and Arms Control, the United States National Academies of Science. Previously she served as Deputy Director of the Office of Proliferation Threat Reduction, United States Department of State. Harrington has had extensive experience with development and implementation of nonproliferation and threat reduction programs in the former Soviet Union, Libya, and Iraq. Her current portfolio is global but much of her focus is on Asia, including nonproliferation and redirection planning for North Korea. Current address: The National Academies, 500 5th Street, NW, Washington, D.C. 20001, aharrington@nas.edu.



The late **Terry L. Yates** was Vice President for Research and Economic Development and Professor of Biology and Pathology at the University of New Mexico. He previously had served as the Director of the Division of Environmental Biology at the National Science Foundation and represented that organization on the WMD Subcommittee in the Office of Science and Technology Policy in the Executive Office of the President. He also was a member of the Board on Life Sciences at the National Academies of Sciences.

Terry passed away unexpectedly during the preparation of this monograph. Fortunately for readers, Terry completed his contributions to the manuscript before he died. We want to give him credit for his writing and thus have kept his name on the author line. Terry was a major contributor to our scientific understanding of zoonoses and was recognized by the National Science Foundation for his research on hantavirus in the southwestern United States. Terry also was prominent in the science policy community, and we dedicate this paper to his memory (please see Baker, R. J., et al. 2008. Obituary Terry Lamon Yates: 1950-2007. *Journal of Mammalogy*, 89:1557-1569).



Gary L. Simpson was trained in internal medicine at the Peter Bent Brigham Hospital and in infectious diseases at the Radcliffe Infirmary (Oxford) and the Stanford University Medical Center. He has graduate degrees from the Rush Medical College, the University of Illinois, Balliol College (Oxford), and the Harvard School of Public Health. He has more than 30 years experience in academic medicine, infectious diseases, and public health and until recently was the Medical Director, Infectious Diseases, New Mexico Department of Health. Current position and address: College Master and Professor of Internal Medicine and Infectious Disease, Departments of Medical Education and Internal Medicine, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center at El Paso, TX, garylsimpson@comcast.net.



Robert J. Baker is Paul W. Horn Professor of Biological Sciences and Director of the Natural Science Research Laboratory (NSRL) at Texas Tech University. Baker was trained as a mammalogist with an emphasis on speciation, genetics, and chromosomes. He champions the genetic species concept and may have first published that DNA is analogous to postal codes that identify species and geographic origin. He has directed 40 Ph.D. students to completion, including Terry L. Yates who was a major contributor to this monograph. He has authored over 300 peer reviewed papers, and as Director of the NSRL he expanded the Museum mammal collection at TTU to rank 5th in the nation among academic institutions. The associated NSRL Genetic Resources Collection contains 240,000 tissues representing 87,000 voucher specimens from 900+ species. Current address: Department of Biological Sciences, Texas Tech University, Lubbock, TX 79409-3131, rjbaker@ttu.edu.



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