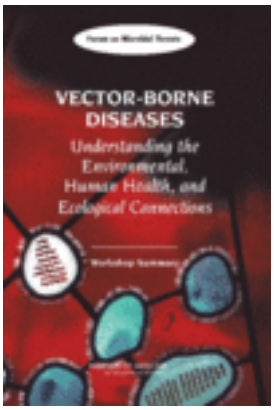

Vector-Borne Diseases: Understanding the Environmental, Human Health, and Ecological Connections, Workshop Summary (Forum on Microbial Threats)

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

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VECTOR-BORNE DISEASES

Understanding the Environmental, Human Health, and Ecological Connections

Workshop Summary

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

Forum on Microbial Threats
Board on Global Health

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

COVER: A detailed section of a stained glass window 21" × 56" depicting the natural history of influenza viruses and zoonotic exchange in the emergence of new strains was used to design the front cover. Based on the work done at St. Jude Children's Research Hospital supported by American Lebanese Syrian Associated Charities (ALSAC) and the National Institute of Allergy and Infectious Diseases (NIAID). Artist: Jenny Hammond, Highgreenleycleugh, Northumberland, England.

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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JAMES M. HUGHES, Global Infectious Diseases Program, Emory University, Atlanta, Georgia
STEPHEN A. JOHNSTON, Arizona BioDesign Institute, Arizona State University, Tempe
GERALD T. KEUSCH, Boston University School of Medicine and Boston University School of Public Health, Massachusetts
RIMA F. KHABBAZ, National Center for Preparedness, Detection and Control of Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
LONNIE J. KING, Center for Zoonotic, Vectorborne, and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
GEORGE W. KORCH, U.S. Army Medical Research Institute for Infectious Diseases, Fort Detrick, Maryland
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EDWARD McSWEEGAN, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
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TERENCE TAYLOR, International Council for the Life Sciences, Washington, DC
MURRAY TROSTLE, U.S. Agency for International Development, Washington, DC

Staff

EILEEN CHOFFNES, Director
SARAH BRONKO, Senior Program Assistant
ALISON MACK, Science Writer
KATE SKOCZDOPOLE, Senior Program Associate

*Deceased February 2, 2008.

Reviewers

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

Larry Granger, Centers for Epidemiology and Animal Health, USDA–Animal and Plant Health Inspection Services

James M. Hughes, School of Medicine and Rollins School of Public Health, Emory University Emory Program in Global Infectious Diseases and Emory Center for Global Safe Water, and Southeastern Center for Emerging Biologic Threats

Lonnie J. King, Center for Zoonotic, Vectorborne, and Enteric Diseases, Centers for Disease Control and Prevention

Mary Wilson, Department of Population and International Health, Harvard University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Melvin Worth.**

Appointed by the National Research Council, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

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

ABOUT THE WORKSHOP

Vector-borne diseases such as malaria, dengue, yellow fever, plague, trypanosomiasis, and leishmaniasis have been major causes of morbidity and mortality throughout human history. During the early to mid-20th century, the vectors for yellow fever, malaria, onchocerciasis, and other diseases were effectively controlled through a variety of intervention, prevention, and control strategies.

However, over the past 20 to 30 years, there has been an enormous resurgence of previously "contained" vector-borne infectious diseases for a variety of reasons as well as the global emergence, reemergence, and spread of new vector-borne diseases.

In addition to these threats to human health, new and emerging plant and animal vector-borne diseases have also greatly impacted regional ecologies and economies. Bluetongue virus, a disease agent transmitted to ruminants by insect vectors, costs the U.S. cattle and sheep industry an estimated $125 million annually in lost trade and in diagnostic testing. Citrus tristeza virus, spread to plants by aphids, has killed tens of millions of citrus trees in outbreaks worldwide and is currently threatening the orange crop in central California with an estimated $912 million in revenues at stake.

Because of their increasing economic and public health importance, coupled with their exceptional ability to cause large outbreaks of disease, vector-borne agents will continue to present significant threats to human, animal, and plant health in the future. Domestic and international capabilities to detect, identify, and control these diseases are limited for a variety of reasons.

To consider the importance of vector-borne diseases in terms of their human health, ecological, and environmental implications, the Institute of Medicine's Forum on Microbial Threats hosted a public workshop in Ft. Collins, Colorado, on June 19 and 20, 2007. Through invited presentations and discussions, participants examined factors associated with the emergence of vector-borne diseases, current domestic and international detection and control capabilities, and assessed the resource needs and opportunities for improving and coordinating surveillance, diagnosis, and response to vector-borne disease outbreaks.

ACKNOWLEDGMENTS

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

The Forum is indebted to the IOM staff who contributed during the course of the workshop and the production of this workshop summary. On behalf of the Forum, we gratefully acknowledge the efforts led by Eileen Choffnes, director of the Forum, Kate Skoczdopole, senior program associate, and Sarah Bronko, senior project assistant, for dedicating much effort and time to developing this workshop's agenda and for their thoughtful and insightful approach and skill in planning for the workshop and in translating the workshop's proceedings and discussion into this workshop summary. We would also like to thank the following IOM staff and consultants for their valuable contributions to this activity: Patrick Kelley, Alison Mack, Bronwyn Schrecker, Allison Brantley, Lara Andersen, and Heather Phillips.

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

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

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Summary and Assessment

VECTOR-BORNE DISEASES: UNDERSTANDING THE ENVIRONMENTAL, HUMAN HEALTH, AND ECOLOGICAL CONNECTIONS

Vector-borne infectious diseases, such as malaria, dengue fever, yellow fever, and plague, cause a significant fraction of the global infectious disease burden; indeed, nearly half of the world's population is infected with at least one type of vector-borne pathogen (CIESIN, 2007; WHO, 2004a). Vector-borne plant and animal diseases, including several newly recognized pathogens, reduce agricultural productivity and disrupt ecosystems throughout the world. These diseases profoundly restrict socioeconomic status and development in countries with the highest rates of infection, many of which are located in the tropics and subtropics.

From the perspective of infectious diseases, vectors are the transmitters of disease-causing organisms; that is, they carry pathogens from one host to another.[1] By common usage, vectors are normally considered to be invertebrate animals, usually arthropods, but they may also include fomites, which are defined as "[a]ny inanimate object that may be contaminated with disease-causing microorganisms and thus serves to transmit disease" (Hardy Diagnostics, 2007), or rodents, which

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

[1]The variations in efficiency of disease transmission in vectors fluctuates with climate and other environmental conditions. While this is an extremely important topic in epidemiology, it was not a major topic at this workshop.

carry the agent from a reservoir[2] to a susceptible host. Vectors of human disease are typically species of mosquitoes and ticks that are able to transmit viruses, bacteria, or parasites to humans and other warm-blooded hosts. For the purposes of this discussion, a disease that is transmitted to humans, plants, or animals by any agent, arthropod, or fomite is a *vector-borne disease.*

Over the past 30 years—following decades during which many mosquito-borne human illnesses were controlled in many areas through the use of habitat modification and pesticides—malaria and dengue fever have reemerged in Asia and the Americas, West Nile virus (WNV) has spread rapidly throughout the United States[3] following its 1999 introduction in New York City, and chikungunya fever has resurged in Asia and Africa and emerged in Europe (Gubler, 1998, 2007; Roos, 2007; Yergolkar et al., 2006). The world has also recently witnessed the emergence and spread of Lyme and other tick-borne diseases (Barbour and Fish, 1993), including bluetongue (a devastating viral disease, transmitted to ruminant livestock by insect vectors, that first appeared in northern Europe in 2006),[4] and the citrus tristeza virus (an aphid-borne disease that has killed tens of millions of citrus trees worldwide, and which currently threatens California orange crops) (Chung and Brlansky, 2006; Bar-Joseph et al., 1989).

The considerable economic, ecological, and public health impacts of vector-borne diseases are expected to continue, given limited domestic and international capabilities for detecting, identifying, and addressing likely epidemics.[5] Much remains to be discovered about the biology of these diseases, and in particular about the complex biological and ecological relationships that exist among pathogens, vectors, hosts, and their environments. Such knowledge is essential to the development of novel and more effective intervention and mitigation measures for vector-borne diseases.

The Forum on Microbial Threats of the Institute of Medicine (IOM) convened a public workshop in Fort Collins, Colorado, on June 19 and 20, 2007, in order to examine the global burden of vector-borne diseases of humans, animals, and plants, and to discuss prospects for successful mitigation and response strategies. Through invited presentations and discussions, participants explored the biological and ecological context of vector-borne diseases; their health and economic impacts; emerging domestic and global diseases; public, animal, and

[2]A reservoir is a source from which an infectious agent may be disseminated, such as the deer mouse being a reservoir host for hantavirus (Hardy Diagnostics, 2007).

[3]And Mexico and Canada, as well.

[4]See Osburn in Chapter 2 and http://www.iah.bbsrc.ac.uk/John_Gloster_3apr07.htm.

[5]An epidemic, often synonymous with an outbreak, is the occurrence of more cases of disease (or injury, or any other health condition) than expected in a given area or among a specific population during a particular period. Outbreaks are sometimes defined as highly localized epidemics. Pandemics are epidemics that occur in multiple countries or continents, usually affecting a substantial proportion of the population (HHS, 2006).

plant health preparedness; prevention, control, and therapeutic measures; scientific and technological advances; and integration strategies to address current and future threats.

ORGANIZATION OF THE WORKSHOP SUMMARY

This workshop summary was prepared for the Forum membership in the name of the rapporteurs and includes a collection of individually authored papers and commentary. Sections of the workshop summary not specifically attributed to an individual reflect the views of the rapporteurs and not those of the Forum on Microbial Threats, its sponsors, or the IOM. The contents of the unattributed sections are based on the presentations and discussions at the workshop.

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

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

THE VECTOR-BORNE DISEASE THREAT: PAST, PRESENT, AND FUTURE

Resurgence and Emergence of Human Vector-Borne Diseases

Infectious diseases transmitted by insects and other animal vectors have long been associated with significant human illness and death. In the 17th through early 20th centuries, human morbidity and mortality due to vector-borne diseases outstripped that from all other causes combined (Gubler, 1998). The early 20th century discovery that mosquitoes transmitted diseases such as malaria, yellow fever, and dengue led quickly to the draining of swamps and ditches where mosquitoes bred, and eventually to the use of pesticides, which reduced populations of these disease vectors. The adoption of vector control measures, including the

application of a variety of environmental management tools and approaches,[6] coupled with improvements in general hygiene, enabled much of the world to experience decades of respite from major vector-borne diseases in the first half of the 20th century. This success proved fleeting, however, and vector control programs waned due to a combination of factors including the development of pesticide resistance or—sometimes doomed by their own success—the loss of financial support when vector-borne diseases were no longer perceived as an important public health threat.

Today, vector-borne diseases are once again a worldwide concern and a significant cause of human morbidity and mortality, as Figure SA-1 illustrates (WHO, 2004c). Table SA-1 lists the disease burden (calculated in disability-adjusted life years, or DALYs) associated with each of several major human vector-borne diseases (WHO, 2004b).

Malaria accounts for the most deaths by far of any human vector-borne disease. The causative agents, *Plasmodium spp.*, currently infect approximately 300 million people and cause between 1 and 3 million deaths per year, mainly in sub-Saharan Africa (Breman, 2001). As described by keynote speaker Duane Gubler, of the University of Hawaii, malaria provides a particularly dramatic example of vector-borne disease reemergence (Gubler, 1998). As stated by Scott and Morrison (see Chapter 2), when done properly, vector control is a well-documented and effective strategy for prevention of mosquito-borne disease. Familiar examples of successful mosquito vector interventions include: the worldwide reduction of malaria in temperate regions and parts of Asia during the 1950s and 1960s (Curtis, 2000; Rugemalila et al., 2006); yellow fever during construction of the Panama Canal; yellow fever throughout most of the Americas during the 1950s and 1960s (Soper, 1967); dengue in Cuba and Singapore (Ooi et al., 2006); and more recently, dengue in parts of Vietnam (Kay and Nam, 2005). Following the drastic depopulation of its vector, the anopheline mosquito, in the first half of the 20th century, malaria began its resurgence in Asia in the late 1960s. In Sri Lanka, where only 17 cases of malaria were reported in 1963, an epidemic of more than 440,000 cases erupted 5 years later after preventive vector control strategies were replaced with case-finding and drug treatment. Similarly, by the mid-1970s, millions of new post-control cases had occurred in India. In Africa, a recent upsurge in infection, punctuated by several major epidemics, has erupted in endemic areas (Nchinda, 1998).

Explosive epidemics have also marked the resurgence of plague, dengue, and yellow fever, a situation that Gubler characterized as particularly worrisome.

[6]Some of these approaches include improvements in drainage and sanitation systems; filling standing water areas (pits/ponds/lagoons/irrigation ditches, etc.) that can be breeding sites for vector larvae; and the use of treated mosquito nets and covering of domestic water tanks and other potable water sources. The effective application of these environmental control measures greatly reduces the reliance on pesticides for vector control (Center for Science and Environment, 1999).

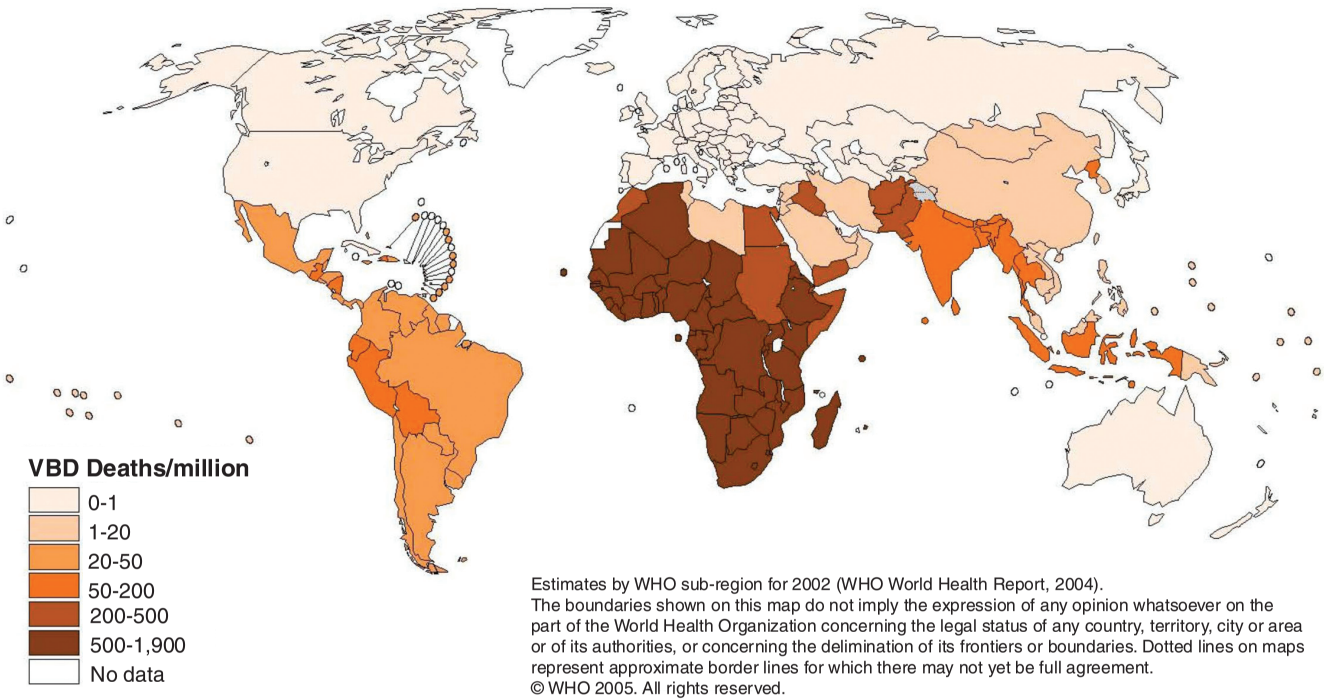

FIGURE SA-1 Deaths from vector-borne diseases.
SOURCE: Reprinted with permission from the World Health Organization (2004c).

TABLE SA-1 Estimates of the Global Burden of Disease Caused by Major Vector-Borne Diseases

Disease	Million DALYs[a]
Mosquito-borne infections	
Malaria	46.5
Lymphatic filariasis	5.8
Dengue	0.62
Japanese encephalitis	0.71
Others[b]	
Onchocerciasis	0.48
Leishmaniasis	2.1
African trypanosomiasis	1.5
Chagas disease	0.67

DALY = disability-adjusted life year.

[a]Total of DALYs for these diseases represent 17 percent of the global disease burden due to parasitic and infectious diseases.

[b]Synanthropic* flies play a major role in the transmission of trachoma and diarrhoeal diseases, but the attributable burden is not readily estimated; other arboviruses and typhus organisms may be of major public health significance but accurate data are not available.

*Animals that live in close association with humans (Montana State University Entomology Group, 2007).

SOURCE: Reprinted from Townson et al. (2005) with permission from the World Health Organization.

Plague is carried by rodent fleas, which transmit the pathogen *Yersinia pestis* when they bite animals or humans (CDC, 2005a). Millions of people in Europe died from plague in the Middle Ages; today, antibiotics are effective against plague when administered promptly following infection. A 1994 plague epidemic in Surat, India, produced one of the first health emergencies that had a major documented impact on the global economy,[7] Gubler said. When inadequate public health and government response to initial cases led to panic, nearly a quarter of the city's population fled Surat to other Indian towns and cities, carrying the disease with them. For the first time in 33 years, the World Health Organization (WHO) implemented the International Health Regulations (IHR) to contain the potential pandemic, resulting in a ban on shipping and travel that cost India an estimated $3 billion and the global economy nearly twice that sum.

Dengue's resurgence has been marked not only by epidemics, but also by the emergence of a more severe form of disease, dengue hemorrhagic fever (DHF) (Gubler, 1998). Ecological disruption in Southeast Asia, brought on by World

[7]The 1918-1919 influenza pandemic undoubtedly had worldwide economic repercussions; however, little data are available quantifying the immediate and long-term economic consequences of this disease event.

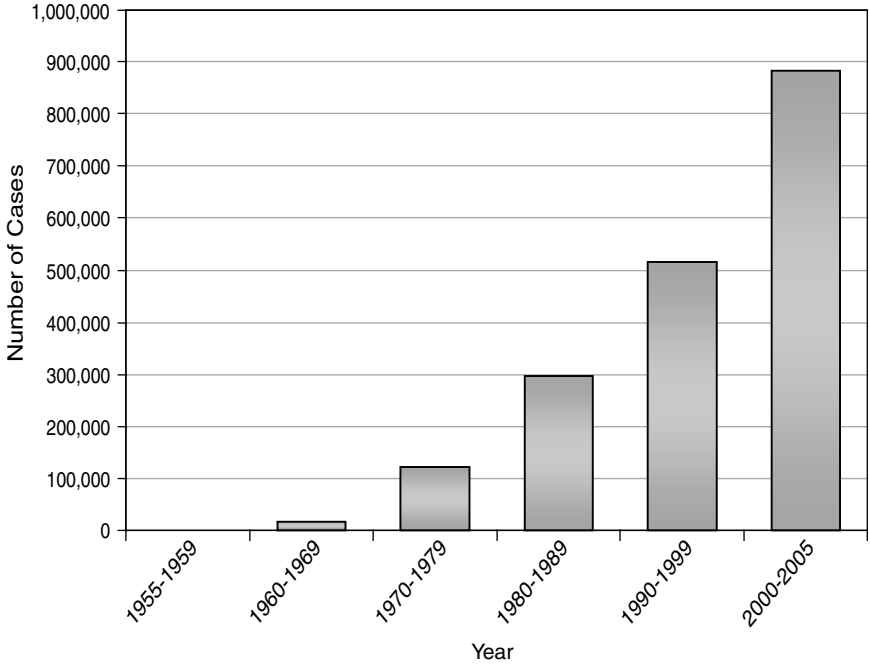

FIGURE SA-2 Dengue/dengue hemorrhagic fever, average annual number of cases reported to WHO, 1955-2005.
SOURCE: Courtesy of WHO.

War II, led to increased transmission of dengue and, eventually, a pandemic. As illustrated in Figure SA-2, dengue/DHF is one of the world's fastest-growing vector-borne diseases (see Gubler in Chapter 1) (WHO, 2007a).[8]

The summer of 2007 brought the worst dengue epidemic in nearly a decade to Asia (Mason, 2007). By July—well before transmission was expected to have peaked—Indonesia alone had experienced over 100,000 infections and 1,100 deaths. The epidemic was apparently spurred by weather conditions: a period of drought, during which water stored around homes provided an ideal habitat for mosquitoes to breed. This was followed by unusually hot, humid weather, in which adult mosquitoes thrive (ProMed-Mail, 2007; Anyamba et al., 2006).

Yellow fever, which along with dengue was controlled in the Americas by a variety of mosquito abatement techniques through the mid-20th century, remains

[8]However, chikungunya, hantavirus pulmonary syndrome, and Lyme disease may have a higher percentage of new cases based on local populations that are immunologically naïve being exposed to and acquiring these newly emerging diseases (IOM, 2003; Chretien et al., 2007).

a constant threat, with concerns that it might make its first appearance in Asia (see Gubler in Chapter 1). Yellow fever virus has caused major epidemics in Africa and South America (Gubler, 2001; Monath, 2001), and sylvatic reservoirs in these areas provide an ongoing threat for its reintroduction into *Aedes aegypti*-infested metropolitan areas throughout the world. *Ae. aegypti* is also the principal vector of the dengue viruses (IOM, 2003). The virus was apparently carried by infected birds (and possibly mammals as well) abetted by a vast and diverse population of mosquitoes (see Gubler in Chapter 1 and Petersen in Chapter 2). Indeed, Gubler concluded, nearly all of the most important vector-borne human diseases have exhibited dramatic changes in incidence and geographic range in recent decades.

Impact of Vector-Borne Animal and Plant Diseases

The majority of emerging, reemerging, and novel human infectious diseases are zoonoses (diseases that can be transmitted from animal reservoirs to humans), of which vector-borne diseases comprise a large percentage (IOM, 2003). Rift Valley fever (RVF), an acute mosquito-borne viral disease, primarily affects livestock (e.g., cattle, buffalo, sheep, goats) but can also be transmitted to humans through direct contact with the tissues or blood of infected animals, as well as by mosquito bites (see Linthicum et al. in Chapter 1 and Peters in Chapter 2) (CDC, 2007a). Outbreaks of RVF among animals can spread to humans; the largest reported human outbreak, which occurred in Kenya during 1997-1998, resulted in an estimated 89,000 infections and 478 deaths (CDC, 2007b). African trypanosomiasis, also known as African sleeping sickness, causes estimated losses in cattle production of more than $1 billion per year, and perhaps five times that amount in lost opportunities for development (FAO, 2007a). The disease currently affects an estimated 500,000 people in sub-Saharan Africa but threatens an estimated human population of 60 million, as well as 50 million head of cattle (FAO, 2007a). Given the rapid growth of human and domesticated animal populations, and their increasing contact with each other and with wild animals, the zoonotic disease threat is expected to increase (Karesh and Cook, 2005; Murphy, 1998; NRC, 2005).

Vector-borne diseases have the potential to cause enormous economic harm when they affect livestock and crops, and even the threat of infection can severely limit trade. For example, bluetongue, a viral disease transmitted among sheep and cattle by biting midges, results in annual losses of approximately $3 billion due to morbidity and mortality of animals, trade embargoes, and vaccination costs (see Osburn in Chapter 2) (FAO, 2007b; Osburn, 2007). Although considerable attention and resources have been committed to agriculturally important vector-borne diseases such as bluetongue, RVF, and African trypanosomiasis, relatively little is known about the vast majority of vector-borne disease-causing organisms that currently infect only wild animals. Yet such diseases can disrupt entire

ecosystems and, under the right conditions, could potentially expand their host range to include livestock, pets, or humans (Marin/Sonoma Mosquito and Vector Control District, 2005).

Vector-borne plant diseases profoundly affect agricultural productivity and ecosystem dynamics (Gergerich and Dolja, 2006; Purcell, 1982; Weintraub and Beanland, 2006). Examples include the bacterium, *Xylella fastidiosa,* which damages a wide range of plant species; in grapevines, it causes Pierce's disease, a significant threat to California's table grape and wine industries (see Almeida in Chapter 1) (Fletcher and Wayadande, 2002; NRC, 2004). Emerging vector-borne viral and bacterial diseases of citrus, most of which were introduced into the Americas since 2000, threaten 85 percent of the world's orange juice production, which resides in the United States and Brazil (Almeida, 2007; Woodall, 2007). Due in part to the difficulty of discerning whether damage to plants has been caused by disease, insects, or adverse weather conditions, the overall impact of vector-borne plant diseases cannot be accurately estimated (Almeida, 2007; Gergerich and Dolja, 2006); however, annual losses in crop quality and yield associated with certain vector-borne viruses are measured in the billions of dollars (Bowers et al., 2001; Gergerich and Dolja, 2006; Hull, 2002; Sherwood et al., 2003).

Vector-borne plant diseases also cause immeasurable damage to ecosystems, which may not be recognized until it threatens human health, safety, or prosperity. For example, Sudden Oak Death (SOD)—an emerging infectious disease that has been spread across wild lands by hikers, mountain bikers, and equestrians (i.e., human "vectors")—was recognized after it caused widespread dieback of several tree species in West Coast forests (see subsequent section, "Lessons Learned: Case Studies of Vector-Borne Diseases" and Chapter 2) (California Oak Mortality Task Force, 2004; Rizzo and Garboletto, 2003). These losses are likely to reduce shelter and food sources for wildlife, increase fire frequency and intensity, and compromise water quality due to soil surface exposure. Moreover, such ecological effects can be long-lasting. For example, changes in forest composition in the Canadian Rocky Mountains, which resulted from the deaths of lodgepole pines due to an infestation of bark beetles, have persisted for as long as 65 years (Current Results, 2007; Dykstra and Braumandl, 2006).

Back to the Future

Infectious diseases have always accompanied humans, animals, plants, and goods in their travels. "Since the beginning of recorded history, disease epidemics have been associated with trade," Gubler observed, noting that the plague epidemic that killed one in every four Europeans in the 14th century is believed to have been introduced to the continent by commercial trade with Asia. The rapid expansion of global trade and transportation since 1700 has been associated with the spread of mosquito-borne diseases such as yellow fever and dengue. Dutch

Elm disease (so named because it was first described in Holland, in 1921) also originated in Asia and probably arrived in the United States on a shipment of lumber from Europe in the 1930s, after which it devastated American elms in forests and on city streets (Plant Disease Diagnostic Clinic, Cornell University, 2005; Riveredge Farms, 2004).

Today's integrated global economy has accelerated the transnational flow of capital, knowledge, people, livestock and animal products, and plant materials, as well as the introduction of pathogens and their vectors to new hosts and geographic ranges. Presented with these opportunities, several vector-borne diseases considered most problematic 100 years ago, such as malaria, dengue, plague, and yellow fever, once again pose serious threats to public health. While we have gained considerable insights into the biology and management of certain vector-borne diseases over the past century, limited capacity exists to apply that knowledge. In addition, as many workshop participants observed, much remains to be learned about the ecology and epidemiology of a broad spectrum of vector-borne diseases, including those that have recently emerged. Subsequent sections of this summary therefore explore both what we know and what we most need to understand about the biology of vector-borne diseases, the factors that precipitate disease emergence and resurgence, discussion about key research areas needed to fill the current gaps, and strategies for disease detection and response.

HALLMARKS OF VECTOR-BORNE DISEASE

Vector-borne diseases are transmitted among their human, animal, or plant hosts by arthropods,[9] usually insects. A broader definition of vector-borne disease recognizes that other animals can serve in the role of infectious disease vector by harboring pathogens that cause disease only in susceptible populations. These unconventional "reservoirs" include invertebrates other than arthropods (e.g., snails, in the case of schistosomiasis), rodents (which spread a variety of viral diseases, including hantavirus pulmonary syndrome [HPS]), and even humans (as noted earlier in the case of SOD).

Mosquitoes, ticks, and biting flies spread viruses, bacteria, and parasites within and among a variety of warm-blooded hosts. Arthropod-borne viruses (arboviruses) comprise the largest class of vector-borne human pathogens; over 500 arboviruses have been described, 20 percent of which are known to cause human disease (Gray and Banerjee, 1999; Gubler, 1998; Jacobson, 2007). These include dengue and DHF, yellow fever, RVF, and WNV (one among a number of arboviral causes of encephalitis) (CDC, 2005b; Gubler, 1998; WHO, 2005).

Vector-pathogen relationships are central to the epidemiology of many

[9]Arthropods (members of the phylum *Arthropoda*) are invertebrates with jointed limbs, segmented bodies, and exoskeletons made of chitin. They include insects, spiders, crustaceans (e.g., shrimp, lobsters), and centipedes.

important plant diseases (Gergerich and Dolja, 2006; Purcell, 1982; Weintraub and Beanland, 2006). While only certain bacterial pathogens of plants require a vector for transmission, most plant viruses are spread from infected to uninfected plants via a plant-feeding arthropod, or nematode. Several important bacterial pathogens are delivered directly into the plants' vasculature—either the sugar-transporting phloem or water-transporting xylem networks—by insects that feed on plant vascular fluids (Fletcher and Wayadande, 2002).

Workshop participants reflected upon the breadth and diversity of vector-borne diseases of humans, animals, and plants, but also sought to identify commonalities within and among them and to highlight the unique challenges these diseases present to science, agriculture, public health, and domestic animal and wildlife health. These discussions focused on the vector's paramount importance to the ecology and epidemiology of vector-borne diseases, a role which complicates transmission patterns, but which also provides opportunities for disease control.

Dynamics of Disease Transmission

A standard graphic representation of the ecology of infectious disease features host, pathogen, and environment as circles intersecting in a common zone that defines permissive conditions for disease transmission (see Figure SA-3).

The ecology and epidemiology of vector-borne diseases are particularly complex and often involve multiple disease cycles through alternate vectors and hosts, noted presenter Rodrigo Almeida of the University of California, Berkeley (see Chapter 1). His octagonal model, shown in Figure SA-4, depicts key influences on vector-borne plant disease; a similar diagram could illustrate the web of relationships governing animal and human vector-borne diseases. The inherently complex ecologies of individual vector-borne diseases are discussed in several case studies collected in Chapter 2.

A confluence of risk factors for a vector-borne disease may result in an outbreak, according to speaker Ned Hayes of the Centers for Disease Control and Prevention (CDC). An outbreak is a condition defined by an increase over background of disease incidence within a subpopulation of potential hosts. Epidemiologists investigating infectious disease outbreaks seek to determine the route of transmission; in the case of vector-borne diseases, their efforts necessarily focus on the presence, abundance, and ecology of the vector, which in turn may frequently be influenced by environmental conditions and human behavior. To illustrate these connections, Hayes described his experiences investigating three different vector-borne diseases in diverse settings: pneumonic plague in Ecuador, 1998; dengue at the Mexico-Texas border, 1999; and tularemia in Martha's Vineyard, Massachusetts, 2000 (see Chapter 2 Overview).

Approximately 80 percent of vector-borne disease transmission typically occurs among 20 percent of the host population (Smith et al., 2005; Woolhouse

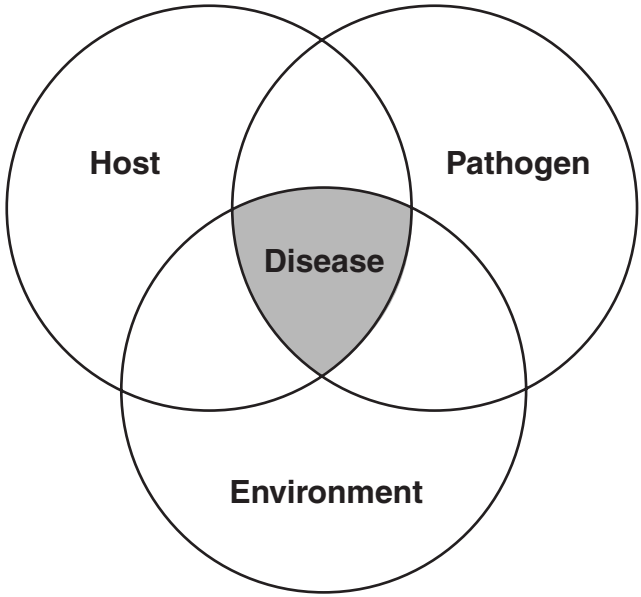

FIGURE SA-3 The epidemiological triad. The familiar "epidemiological triad" concept (host-pathogen-environment), as illustrated in the famous diagram of Snieszko (1974), neatly illustrates the complex interplay of factors that result in disease at the individual and population levels. The presence of a pathogen is a necessary but not sufficient cause of a particular disease.
SOURCE: Reprinted with the permission of Blackwell Publishing Ltd. from Snieszko (1974). Copyright 1974.

et al., 1997). The distribution of the incidence of vector-borne diseases is grossly disproportionate, with the overwhelming impact in developing countries located in tropical and subtropical areas (CIESIN, 2007). Using his work on dengue as an example, presenter Thomas Scott of the University of California, Davis, described the challenges—as well as the potential rewards—of investigating the dynamic relationships between vector population density and risk for disease transmission. His findings, which are discussed in detail in Chapter 2 (see Scott and Morrison), as well as in a subsequent section of this summary, "Lessons Learned: Case Studies of Vector-Borne Diseases," support the notion that heterogeneity in exposure to infection can be exploited to optimize vector control. He cautioned, however, that such efforts cannot succeed unless they are tailored to the local epidemiological and ecological conditions that influence disease transmission.

Disease Prevention Strategies

Vector control is the primary means of preventing vector-borne disease. In the case of dengue, the goal of current public health policy is to prevent explosive epidemics by managing mosquito populations—a difficult proposition, given the intricacies of mosquito ecology and population biology, Scott said (see Scott and Morrison in Chapter 2). Seeking a more efficient alternative, he and colleagues used a simulation model to identify two important sources of heterogeneity in dengue transmission—age of infection and location—in their study area, the impoverished city of Iquitos, Peru. Based on these findings, they developed a cost-efficient spray plan that targeted those areas of the city that would have the largest impact; the timely implementation of this plan by local authorities appears to have averted an epidemic. This result, and those of similar studies, imply that careful modeling of transmission patterns and vector life cycles may suggest

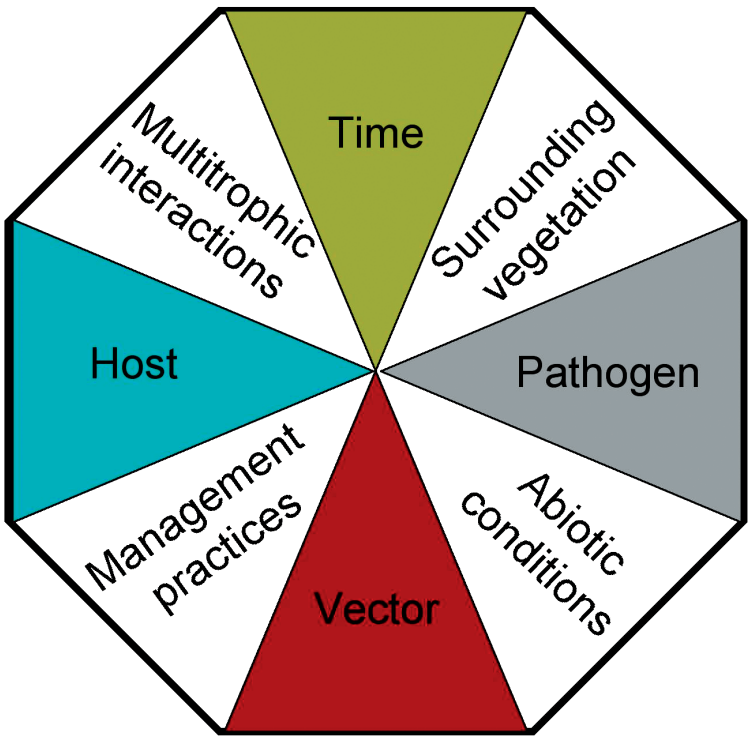

FIGURE SA-4 Factors affecting plant disease outbreaks.
SOURCE: Almeida (2007).

targeted interventions directed toward specific host subpopulations and locations associated with high rates of vector-borne infections. Such an approach may be far more effective than broad-spectrum, non-specific, vector control efforts (Getis et al., 2003; Morrison et al., 2004; Vanwambeke et al., 2006).

Recognition of shared features among vector-borne diseases—some broad, such as their ecological and epidemiological complexity; some narrow, such as a common vector—is prompting the development of guidelines for outbreak prevention and management. The purpose of these guidelines, as envisioned by Scott, would not be to prescribe universal solutions, but rather to help public health officials choose, apply, monitor, and evaluate pathogen detection and disease prevention methods that fit their particular circumstances. This is the underlying premise of decision support systems (DSSs) that have recently been launched for malaria and dengue and which could potentially be extrapolated to other vector-borne diseases, according to speaker Barry Beaty of Colorado State University. The development of both DSSs is supported by the Innovative Vector Control Consortium (IVCC), a private-public partnership funded by the Bill and Melinda Gates Foundation (see Eisen and Beaty in Chapter 2, and Beaty and Eisen in Chapter 3).[10]

Beaty, who has participated in efforts to establish the DSS for dengue, described it as a rationally designed, computer-based information system that serves three distinct purposes: to assist local and regional authorities in designing evidence-based vector control programs; to collect information on pesticide and insecticide resistance; and to provide proactive surveillance and modeling of dengue transmission. The malaria DSS, which is the predecessor and model for the dengue DSS, evolved from an interactive geographical information system (GIS) for insecticide resistance data that was developed to support malaria control in Africa (Coleman et al., 2006). The malaria DSS currently encompasses information on health and intervention management, entomology, geography, and surveillance.

Michael Coleman, a developer of the malaria DSS from the Medical Research Council of South Africa, focused on the crucial role of information on insecticide resistance in addressing malaria in his workshop presentation (see Coleman and Hemingway in Chapter 2 and the subsequent section, "Lessons Learned: Case Studies of Vector-Borne Diseases"). By way of introduction, he offered a concise rationale for the development of DSSs: vector control is difficult, but it can be made easier by providing resources for quality control, informed decisions, and evidence-based policy. In addition, workshop participants discussed the importance of predictive epidemiological models and the critical need for quality information that emphasizes strong surveillance, diagnostics, and evidence-based conclusions that are needed to support accurate modeling and/or DSS.

[10]See http://www.ivcc.com.

FACTORS IN VECTOR-BORNE DISEASE EMERGENCE[11]

Disease vectors and their associated pathogens have coevolved in discrete geographic locations with climates, hosts, and habitats that favor transmission. The once limited geographic and host ranges of many vector-borne diseases are expanding, spurred largely by anthropogenic factors. Epidemics of malaria, dengue, and other formerly "contained" vector-borne diseases are on the rise, as are outbreaks of previously unknown infections, such as Lyme disease. Workshop presentations and discussions described the effects on various vector-borne diseases of a range of local, regional, and global phenomena and considered the potential use of this information to construct predictive epidemiological models.

A Pandemic of Epidemics

Gubler described a "dramatic increase" in vector-borne disease epidemics over the past 30 years and identified several factors that underlie this trend (see Chapter 1).

Some recent epidemics have been associated with local surges in vector (particularly mosquito) density, but increased vector competence—a measure of a given vector's intrinsic capacity to be infected by a pathogen, to replicate it, and to transmit it—has also fueled outbreaks. Epidemics have arisen in naïve host populations, whose opportunity for exposure to vector-borne diseases has increased with the globalization of travel and trade, as well as with declining vector control. For viruses such as WNV and dengue that have recently expanded their geographic range, increased transmission has driven selection for strains with increased epidemic potential (see also Petersen in Chapter 2), while increased gene flow among vector populations has been associated with higher viral transmission rates. Climate change may also have contributed to the emergence of some vector-borne diseases, Gubler said, but it has not played a central role in the reemergence of malaria or dengue.

Adopting a broader frame of reference, Gubler traced the origins of emerging infections to human population growth, social organization, and technology. He identified demographic changes such as urbanization, along with human impacts on the environment and modern transportation, as principal drivers of the reemergence of vector-borne disease (see Figure SA-5). In his contribution to Chapter 1, Gubler presents case studies of three reemergent arboviral diseases—West Nile viral fever, dengue and DHF, and yellow fever—that illustrate the epidemiological effects of pristine populations and environmental change, which include animal and wildlife hosts.

[11]Emerging infectious diseases are caused by pathogens that (1) have increased in incidence, geographical or host range; (2) have altered capabilities for pathogenesis; (3) have newly evolved; or (4) have been discovered or newly recognized (Anderson et al., 2004; Daszak et al., 2000; IOM, 1992).

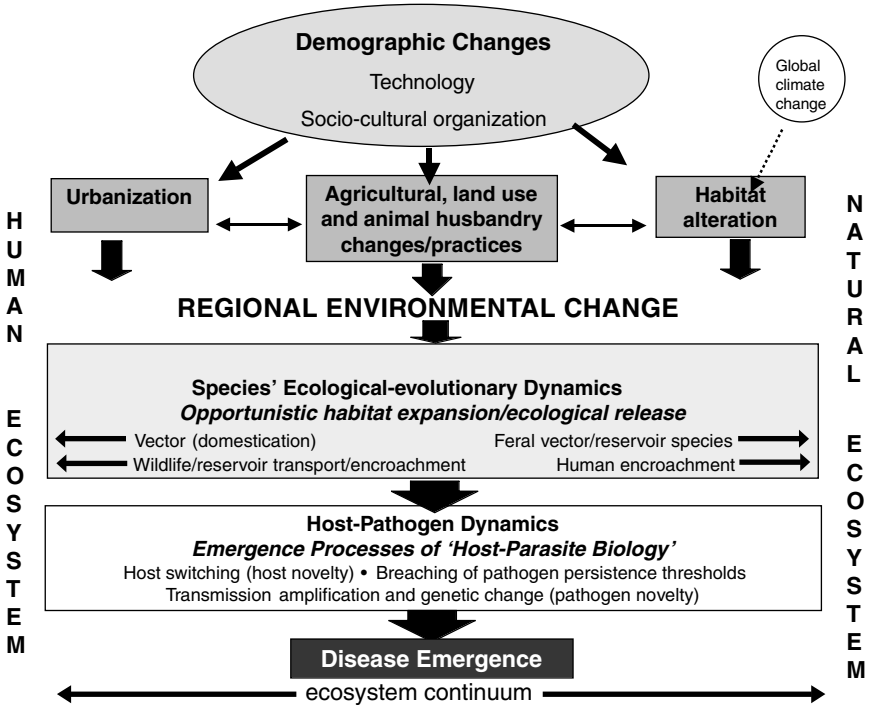

FIGURE SA-5 The epidemiological effects of urbanization and environmental change. SOURCE: Adapted from Wilcox and Gubler (2005) with permission from *Environmental Health and Preventive Medicine*.

Trade and transportation have greatly contributed to the global spread of plant disease vectors, as described below, but as Almeida observes in his contribution to Chapter 1, many emerging infectious diseases of plants—and indeed of humans and animals as well—can also be viewed as a byproduct of agriculture. "The expansion of agricultural land and increased pesticide, irrigation, and fertilizer use have been the major controllable inputs to increase crop yield," he states, but these gains have come at a price. "An increased human-natural vegetation interface may also result in new human and plant diseases, as pathogens may spill over from natural environments into new host organisms." Reversing this trend through sustainable agricultural practices "may reduce the impact of human pathogens from individual to population levels," Almeida concludes.

Follow the Vector

Where vectors go, diseases of both plants and animals follow. Norwegian rats, bearing plague-infected fleas from Asia, escaped from ships to deliver the Black Death to 14th century Europe.[12] In California, the emergence of Pierce's disease in grapes followed the introduction of a highly competent vector for an endemic pathogen (see Almeida in Chapter 1). The pathogen in this case, *Xylella fastidiosa*, is a bacterium with a wide host range; it had caused low levels of disease in California grapevines for over a century, where until recently it was transmitted by the blue-green sharpshooter (*Graphocephala atropuntata*) (Fletcher and Wayadande, 2002). After a new vector species, the glassy-winged sharpshooter (*Homalodisca coagulata*), was introduced to California from the southeastern United States in the late 1980s, Pierce's disease emerged as a major threat to the state's viticultural industries. In his contribution to Chapter 1, Almeida describes a suite of characteristics that make the glassy-winged sharpshooter a highly efficient vector for *X. fastidiosa*. Similarly, the introduction of an efficient Asian aphid vector to the Americas prompted the regional emergence of citrus tristeza virus, decades after the pathogen was known to be present in South America (Anderson et al., 2004).

"The jet airplane provides the ideal mechanism by which pathogens of all kinds move around the world in infected humans, host animals, and vectors," Gubler writes (see Chapter 1). For example, he noted, until recently, the African and American tropics had long been populated with single dengue viral serotypes, and multiple serotypes had only been present in Southeast Asia since the arrival of Allied and Japanese forces in World War II. Today, multiple dengue serotypes circulate throughout the tropics, where their ease of recombination, as well as the continued evolution, selection, and introduction of new serotypes and strains (Rico-Hesse, 2007), drives the evolution of viral strains with increased epidemic potential. In addition, the vectors themselves can also be transported. The used tire trade has recently been linked to the appearance of chikungunya in Italy, infecting almost 270 people in Ravenna province (Gale, 2007).

Land Use

As F. A. Murphy (1998) has observed, when ecosystems are altered, disease problems arise (Murphy, 1998). The usual vertebrate hosts for most vector-borne pathogens that infect humans are wild or domestic animals; people may also become infected when they intrude on habitats where pathogens exist (Marin/Sonoma Mosquito and Vector Control District, 2005). Similarly, many vector-borne diseases of wildlife have now spread to domestic animals. Bluetongue, for

[12]Of course there are other exposure routes, including localized dynamics—human fleas transmitting without rats and also human to human transmission via aerosolization leading to the pneumonic form of plague.

example, was first described after it devastated Merino sheep from Europe that were introduced to South Africa in the late 18th century (FAO, 2007b; Verwoerd and Erasmus, 1994). It is therefore not surprising that the initial human occupation of remote ecosystems has resulted in the emergence of vector-borne diseases, given the potential for such circumstances to introduce vector-borne pathogens to immunologically naïve hosts and vectors. Moreover, this is a two-way street: as vector-borne diseases emerge from formerly isolated locations, vector-borne pathogens enter new territories along with their human and animal hosts (Murphy, 1998).

Deforestation and Risk for Malaria

As presenter Jonathan Patz, of the University of Wisconsin, Madison, has observed, land use changes such as deforestation, road construction, and dam building can trigger a cascade of secondary factors known to exacerbate infectious disease emergence, such as forest fragmentation, pathogen introduction, pollution, and human migration (see Patz and Olson in Chapter 1) (Patz et al., 2004).[13] In a study they conducted along a road under construction in the Peruvian Amazon, Patz and colleagues determined that as forest density increased, the mosquito biting rate declined, regardless of human population density (Vittor et al., 2006). The change in biting rate, in turn was linked to the species distribution of mosquitoes, such that in deforested sites, the biting rate of *Anopheles darlingi*, the primary local vector of the malarial parasite *Plasmodium falciparum*, was more than 278 times higher than for forested areas. Thus, Patz concluded, the change in land use in this area appeared to reduce mosquito biodiversity, increasing the numbers of the malaria vectors and thereby raising the risk of infection. His group is currently investigating possible ecological explanations for the shift in mosquito biodiversity they observed.

Reforestation and Tick-Borne Disease

According to Durland Fish of Yale University, the reversal of deforestation led to the emergence of Lyme disease in the northeastern United States (Barbour and Fish, 1993). Black-legged deer ticks (*Ixodes scapularis*) carry the bacterial pathogen *Borrelia burgdorferi* that causes Lyme disease. The adults of this tick species feed exclusively on white-tailed deer; only the nymphs feed on and transmit disease to humans. As long as the deer population of the eastern United States was limited by farming and hunting to a few small, isolated bands, Lyme disease—though probably present—was unrecognized. The decline of agriculture

[13]Human-induced land use changes are the primary drivers of a range of infectious disease outbreaks and emergence events and also modifiers of the transmission of endemic infections (Patz et al., 2000).

in this region and its subsequent reforestation over the last several decades, however, provided an ideal habitat for increasing numbers of white-tailed deer and their attendant ticks. Thus Lyme disease, unknown in the United States before 1975, had by 1991 become the country's most common vector-borne disease (Barbour and Fish, 1993).[14] In order to anticipate whether and where Lyme disease might spread, Fish and colleagues developed a model based on climate and vegetation to predict the spatial distribution of *I. scapularis* in the United States (Brownstein et al., 2003). Their findings suggest that *I. scapularis,* and therefore Lyme disease, will continue to expand its range.

In a survey study conducted on Block Island, Rhode Island—where Lyme disease is endemic—27 percent of residents reported receiving at least one tick bite per year (Burke et al., 2005). Fish noted that black-legged ticks serve as vectors for human pathogens other than *B. burgdorferi*; these include *Anaplasma phagocytophilum*—a bacterium that causes a flu-like illness called human granulocytic anaplasmosis—and the protozoan *Babesia microti*, which causes babesiosis, resembling malaria in its symptoms as well as its ability to contaminate blood that is used for transfusions. He added that this list of pathogens could potentially expand to include the Powassan arbovirus, which now is transmitted by an *Ixodes* species that feeds almost exclusively on members of the mammalian family *Mustelidae*[15] (e.g., skunks and fisher martins). Fish also observed that various non-native tick-borne arboviruses could potentially infect any of several hundred human-feeding species of ticks present in the United States.

Weather, Climate, and Prediction

Weather refers to short-term fluctuations in the atmosphere, whereas climate describes average weather over long periods of time (IOM, 2003: 64; NRC, 2001: 20). Climate tends to affect the geographic distribution of vector-borne diseases, while variations in weather such as temperature, rainfall, and humidity influence disease transmission dynamics, and thereby the timing and intensity of outbreaks (CIESIN Thematic Guide, 2007; Epstein et al., 1998; Gubler, 1998). Workshop participants considered both weather and climate effects on vector-borne diseases; they also discussed the development of models for outbreak prediction based on weather patterns and debated the usefulness of modeling the potential effects of climate change on disease transmission and spatial distribution.

[14]Popular music provides an indicator of the impact of Lyme disease and its vector on the American public. Around the time this workshop was held, Brad Paisley's song, "Ticks," topped the Country and Western charts and monopolized airwaves with its (dare we say infectious?) chorus: "I'd like to see you out in the moonlight/ I'd like to kiss you way back in the sticks/ I'd like to walk you through a field of wildflowers/ And I'd like to check you for ticks." Source: http://www.azlyrics.com/lyrics/bradpaisley/ticks.html.

[15]Since naming conventions for family (class) names are inconsistent, we have chosen to italicize them throughout this report.

TABLE SA-2 Studies Suggesting Links Between ENSO-Driven Variations in Temperature and Precipitation and Arthropod-Borne Infectious Diseases

Disease	Vector
Murray Valley encephalitis[a]	mosquito
Bluetongue[b]	midge
Rift Valley fever[c]	mosquito
African horse sickness[d]	midges and mosquitoes
Ross River fever[e]	mosquito
Dengue[f]	mosquito
Malaria[g*]	mosquito
Chikungunya[h]	mosquito

[a]Nicholls (1986); [b]Baylis et al. (1999); [c]Linthicum et al. (1999); [d]Baylis et al. (1999); [e]Woodruff et al. (2002); [f]Linthicum et al. (2008); [g]Bouma et al. (1996); [h]Chretien et al. (2007).
[*]For malaria, links with ENSO may be noted only in certain locations.
SOURCE: Linthicum (2007).

Ocean Temperatures and Outbreaks

Other than the seasons, the El Niño/Southern Oscillation (ENSO)[16] is the primary source of global variation in temperature and rainfall (Patz et al., 2005; Ropelewski and Halpert, 1987). Decades of observation indicate that ENSO-associated weather anomalies influence outbreaks of a variety of vector-borne diseases (see Table SA-2, and also Linthicum et al. in Chapter 1) (Anyamba et al., 2006).

Upon recognizing, some 25 years ago, that RVF outbreaks were associated with periods of heavy rainfall, speaker Kenneth Linthicum and colleagues discovered through a series of field and laboratory studies that *Aedes* mosquito vectors of RVF lay virus-infected eggs in moist soil after heavy rains and flooding. These eggs can remain viable and infected in dry soil for extended periods of time, allowing the virus to persist for years in an area during dry years. When the next heavy rainfall event produces flooding of egg habitats infected *Aedes* mosquito populations are produced and can infect domestic animals. If immature mosquito habitats remain flooded for a month or more secondary *Culex* mosquito vector populations will surge and become infected after feeding on viremic domestic animals, and potentially cause an epizootic and/or epidemic. With this information, the researchers developed an operational model capable of predicting RVF outbreaks based on ocean temperatures, rainfall anomalies, and vegetation characteristics.

[16]El Niño refers to the large-scale ocean-atmosphere phenomenon linked to a periodic warming in sea surface temperatures across the central and east-central equatorial Pacific Ocean. ENSO also includes a cooling phase, known as La Niña. Changes in sea surface temperature patterns across the large area of the Pacific influence atmospheric circulation, and thereby precipitation and temperature patterns, throughout the global tropics (Anyamba et al., 2006).

After the U.S. National Oceanic and Atmospheric Administration (NOAA) issued an unscheduled El Niño advisory in September 2006, Linthicum's team monitored the developing temperature and rainfall anomalies and soon issued alerts for a variety of diseases, including RVF in East Africa, based on its operational model. When RVF activity was detected in Kenya in December 2006, a broad range of governmental, nongovernmental, and international agencies responded to the imminent epidemic that included a ban on animal slaughter, distribution of mosquito nets, insecticidal spraying of vector habitats, and domestic animal vaccination (CDC, 2007b). While the application of these measures limited the spread and severity of RVF in Kenya—compared to the 1997-1998 outbreak—they did not prevent the recurrence of this disease. Speaker C. J. Peters of the University of Texas Medical Branch in Galveston observed, however, that had the many organizations responding to the 2006-2007 outbreak been better coordinated, their efforts would have been more effective.

These events illustrate the potential uses of vector-borne disease forecasting in reducing the impact and limiting the spread of disease. Environmental models may one day be used to identify imminent outbreaks of specific vector-borne diseases by tracking and integrating factors critical to disease transmission, Linthicum said. "It's important for prevention and preparation to know that we can forecast," he concluded, "and then when we do forecast, it's important that we mobilize."

Climate and the European Emergence of Bluetongue

That many infectious diseases are strongly influenced by seasonal or anomalous changes in weather suggests that they would also be influenced by longer-term climatic changes (Patz et al., 2000). Climate can affect disease transmission through its influence on the replication and movement (and perhaps, the evolution) of disease microbes and vectors; less directly, climate shapes ecology and human behavior, which in turn control pathogen behavior.

Climatic warming appears to have precipitated the emergence of bluetongue in northern Europe, where it was identified for the first time in 2006 (see Osburn in Chapter 2) (Institute for Animal Health, 2007a). There it caused a series of localized outbreaks, infecting more than 2,000 sheep and cattle, of which 30 percent and 10 percent of cases, respectively, proved fatal. While the source of bluetongue introduction into Europe remains unknown, recent increases in regional temperatures appear to favor its establishment and transmission (European Food Safety Authority, 2007). The summer of 2006 was the warmest on record in northern Europe, where temperatures have been logged since the late 17th century. As speaker Bennie Osburn of the University of California, Davis, pointed out, temperatures in northern Europe remained warm into early November in 2006, rendering the season not only unusually hot, but abnormally long as well.

On June 13, 2007, a sentinel animal in Germany was announced to have

displayed evidence of bluetongue infection during April. This was the first indication that the virus strain responsible for the outbreak in northern Europe last year might have successfully overwintered in the region. As of late August 2007, clinical and subclinical cases of bluetongue have been reported in sheep and cattle on hundreds of farms in Germany, Belgium, France, the Netherlands, and Luxembourg (Institute for Animal Health, 2007b). According to the European Commission (2007), bluetongue has now been found in the United Kingdom, where hundreds of thousands of sheep and tens of thousands of cattle—all immunologically naïve to the virus—will present a vulnerable target for arriving midges (Institute for Animal Health, 2007a). Since April 2007, bluetongue has made its way across the English Channel to threaten livestock in the UK and most of northern Europe (see Figure SA-6).

Because the few species of the midge *Culicoides* known to transmit bluetongue lived in habitats with narrow temperature ranges, Osburn noted that the disease was long thought to be restricted to a band between 40º north and 35º south of the equator; any *Culicoides* blown north of this zone by the wind were not expected to reproduce, or perhaps even to survive. However, with the onset of a span of warm years stretching from 1998 to the present, the bluetongue vector *Culicoides imicola* staged a surprising incursion into Greece (1999) and Italy (2002) and continued to move north; it became established as far north as 45º by 2005, and found at 52º in 2006. "Bluetongue is emerging only . . . where expansion of the virus's range appears to be the consequence of spread of competent insect vectors as the result of climate change," conclude Osburn and co-author N. James MacLachlan (MacLachlan and Osburn, 2006).

Global Climate Change and Vector-Borne Disease Emergence

In their April 2007 report, the Intergovernmental Panel on Climate Change (IPCC) states that "observational evidence from all continents and most oceans shows that many natural systems are being affected by regional climate changes, particularly temperature increases" (IPCC, 2007). The rate of warming of the earth's surface over the past 50 years is nearly twice that over the past 100 years, and global average temperatures are projected to increase between 1.4 and 5.5°C by the end of this century (Solomon et al., 2007). Temperature increases are in turn associated with rising sea levels and increased extremes of the hydrologic cycle (e.g., floods and droughts). The future effects of climate change and extreme weather events on disease emergence and resurgence, a subject of debate among researchers, was raised by workshop participants in a discussion that anticipated a detailed exploration of this topic at a December 2007 Forum public workshop entitled *Global Climate Change and Extreme Weather Events: Understanding the Potential Contributions to the Emergence, Reemergence, and Spread of Infectious Disease.*

Because transmission patterns of arthropod-borne diseases are strongly influ-

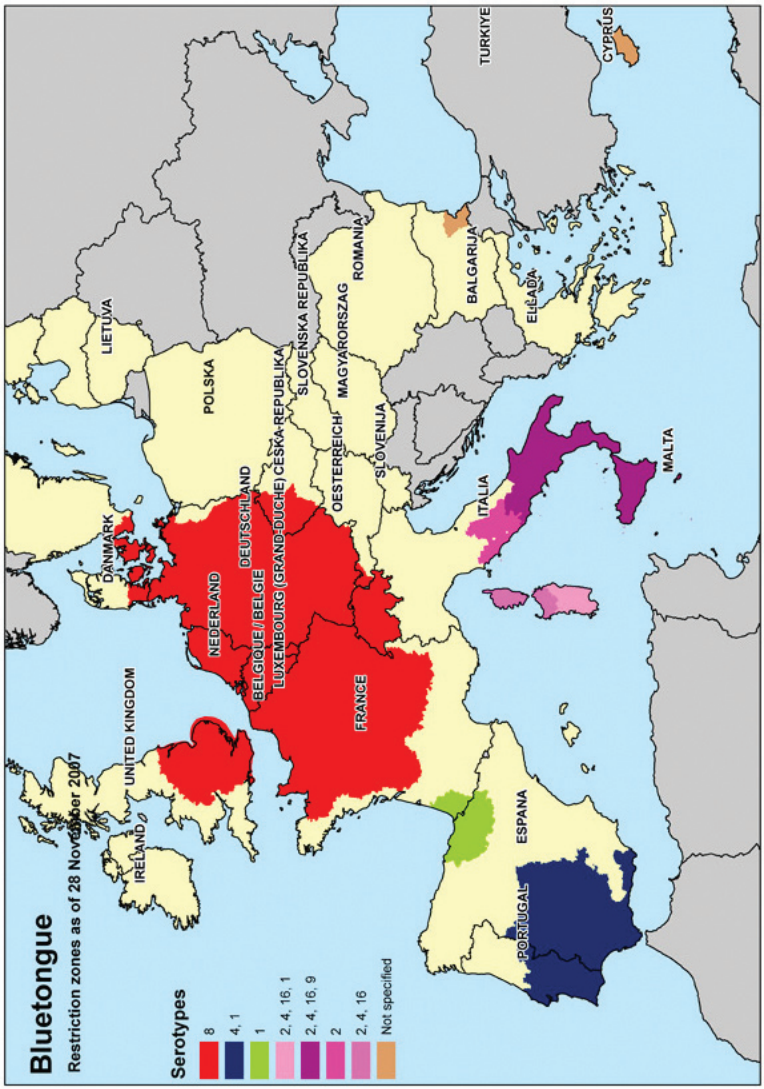

FIGURE SA-6 Map of the distribution of bluetongue throughout Europe as of November 28, 2007.
SOURCE: Copyright European Communities (2007).

enced by changes in ambient temperature, some researchers predict that certain vector-borne diseases, including malaria, yellow fever, and dengue, will expand their range to higher elevations and latitudes in response to global warming (Harrus and Baneth, 2005). Brownstein et al. (2003) state that, based on their observations of the importance of climatic factors in the distribution of the black-legged tick, "climate change may be involved in controlling the future distribution of the Lyme disease vector" (Brownstein et al., 2003). Of course, it is also possible for hot weather to have a detrimental effect on vector populations and pathogen survival, which could result in a reduction of certain vector-borne diseases in some regions (Sutherst, 2004).

Patz remarked that biological systems can amplify the effects of small changes in temperature to dramatic effect, a relationship that has inspired the creation of climate-based models to predict disease range such as those described by Patz and Olson in Chapter 1. However, as several workshop participants argued, these models are severely limited by the fact that climate is not always the most important factor in defining the range of a vector-borne disease. In many cases, anthropogenic impacts on local ecology, such as deforestation and water use and storage, represent far more significant influences on the prevalence and range of vector-borne diseases (Reiter, 2001); in addition, human behavior can significantly limit disease prevalence (Reiter et al., 2003).

"We need to avoid the knee-jerk reaction that because bugs like warm temperatures, as temperatures go up, we'll have more bugs," Hayes contended. He instead advocated the careful examination of the complex ecological relationships involved in vector-borne disease transmission dynamics (including those discussed by Patz and Uejio in Chapter 1). Toward that goal, Patz and coworkers are developing models that incorporate climate, geography, land use, and socioeconomic factors to predict malaria risk.

LESSONS LEARNED: CASE STUDIES OF VECTOR-BORNE DISEASES

Presentations of case studies of vector-borne diseases enabled workshop participants to explore the diverse and unique epidemiological challenges offered by dengue, WNV encephalitis, RVF, HPS, malaria, SOD, and bluetongue; these narratives are collected in Chapter 2. The following summary highlights examples of lessons learned from these cases that may be applicable to the surveillance, detection, prediction, control, and management of other vector-borne diseases.

Surveillance and Detection

As is true for all infectious diseases, the early detection of vector-borne disease outbreaks is essential to their control. In Mexico, for example, the detection

of initial cases of dengue fever by syndromic surveillance[17] alerts health workers to impose vector control measures immediately in order to mitigate an outbreak that will arrive within days, Beaty reported. Surveillance of pesticide resistance in vector populations informs the choice of control strategies; this is particularly true for malaria-carrying mosquitoes, which are rapidly developing resistance to existing insecticides (see Coleman and Hemingway in Chapter 2). In order to improve surveillance for insecticide resistance and pathogen infection, and thereby malaria and dengue control, the IVCC is developing survey kits for vector testing in the field (see Eisen and Beaty in Chapter 2). Results from field surveys should greatly enhance the IVCC's aforementioned DSSs for malaria and dengue.

Even as field surveillance methods become faster, more accurate, and less costly, "laboratory-based surveillance must be improved and maintained, not only in the United States but especially in developing countries where a lot of vector-borne diseases will reemerge," Gubler observed. Ultimately, surveillance systems will enable global tracking of vector-borne and other infectious diseases.

An example of such a surveillance system, called ArboNET, was created in response to the introduction of WNV to the United States in 1999 (see Petersen in Chapter 2 and Nasci in Chapter 3). It was the first national integrated human-animal disease surveillance system (there are now similar national [HHS, 2007] and international [WHO, 2007b] systems for influenza surveillance in birds and humans), according to speaker Lyle Petersen of the CDC, which administers the network. ArboNET is a real-time electronic reporting system that captures data on WNV in humans, dead birds, mosquitoes, horses, and live captive sentinel animals (chickens) (Gubler et al., 2000).

ArboNET analyses of data—which are collected and reported to CDC by health departments across the country—have revealed a number of significant trends; among them, that WNV activity moved across the country with migrating birds, a finding that anticipated an enzootic[18] WNV outbreak that occurred in the southeastern United States in 2001 (CDC, 2001). Because human WNV epidemics have arisen rapidly under such conditions, a key goal of ArboNET is to better predict when human outbreaks will occur, Petersen said. Ecological surveillance offers some promise in this regard, he added, since outbreaks in birds and sometimes other species (e.g., horses) tend to precede those in humans—but only by a few weeks, so response must be rapid to prevent or mitigate human disease.

An important, and under-recognized, impact of the emergence of WNV in the United States is the threat it poses to the nation's blood supply. Within 3 years of its arrival, Petersen said, WNV had become the most common transfusion-

[17]For a discussion of the strengths and challenges of infectious disease detection and surveillance, see the summary report of the Forum's recent workshop, *Global Infectious Disease Surveillance and Detection: Assessing the Challenges—Finding Solutions* (2007).

[18]An enzootic disease is endemic (constantly present) in an animal population but usually affects only a small number of animals at a given time (MedicineNet.com, 2007).

transmissible viral agent[19] due to its high incidence of infection in donor populations (Biggerstaff and Petersen, 2002; Pealer et al., 2003; Petersen, 2008). The cost of screening donated blood for WNV is approximately three times the current CDC budget for surveillance, prevention, and control of the virus (Custer et al., 2005; Korves et al., 2006; Petersen, 2008). By late July 2007—weeks away from the annual disease peak, in which 90 percent of cases typically occur—nearly four times as many WNV cases had been reported as compared with the previous year (Grady, 2007), suggesting a need for increased vigilance on the part of the health care community.

Outbreak Prediction

Weather patterns and anomalies, and ENSO events in particular, are associated with outbreaks of several arthropod-borne diseases, as previously noted (see "Factors in Emergence," as well as Linthicum et al. in Chapter 1). Speaker Charles Calisher of Colorado State University discussed findings that suggest ENSO influences outbreaks of HPS, a rodent-borne viral disease of which the first human epidemic was reported in the spring of 1993 (see Calisher in Chapter 2). This outbreak, and a subsequent one in 1998, occurred in the Four Corners region of the continental United States, where the borders of Utah, Colorado, New Mexico, and Arizona meet.

Prior to each HPS outbreak, ENSO had brought a warm, wet winter to the region, which in turn prompted an abrupt rise in local populations of the deer mouse *Peromyscus maniculatus*, the vertebrate host of the Sin Nombre virus (SNV) that causes HPS (Calisher et al., 2005). Humans can always become infected with hantavirus, but risk of human exposure increases (and human cases increase) with the expansion of the deer mouse population, Calisher explained; thus, in order to understand the dynamics of SNV and thereby predict HPS outbreaks, he and colleagues monitored populations of deer mice—as well as of other rodents that share their environment, and which also carry other types of hantaviruses—at three ecologically diverse locations in the Four Corners region over nearly 6 years.

The researchers identified both seasonal and interannual meteorological influences on the population dynamics of these diverse rodent species, but these factors did not entirely explain variations in rodent populations (Calisher et al., 2005). "Much longer-term studies will be required to discern the effects of truly rare phenomena or to identify trends or cycles that have a multiyear periodicity,

[19]The ranking of WNV as the most common transfusion-transmissible virus is not universally accepted. Hepatitis B and C, for example, are chronic infections, and thus pose an ongoing risk for transmission by all infected persons. WNV—although contracted by more people than hepatitis on an annual basis—is an acute infection, and thus poses only a relatively short-term transmission risk in a given individual.

such as the El Niño southern oscillation," Calisher and colleagues wrote. The results of these studies, they observed, "have important implications for those attempting to model population dynamics of rodent populations for purposes of predicting disease risk."

Vector Control

The control of disease vector populations by habitat modification, a mainstay of early 20th century public health, was replaced by chemical methods when they became relatively inexpensive and widely available. Pesticides remain the primary means to prevent or mitigate most vector-borne diseases, but resistance has increasingly limited the effectiveness of this strategy. Because insecticide resistance poses an especially significant barrier to controlling malaria and dengue, and because vector control measures could potentially reduce the incidence of additional vector-borne diseases, IVCC supports the development of novel insecticides and deployment methods as one of its foremost goals (see Eisen and Beaty in Chapter 2).

Profits drive manufacturers to produce more innovative insecticides for golf courses than to protect people from vector-borne diseases, just as they encourage pharmaceutical companies to develop more drugs to combat aging and obesity than malaria. Thus, Beaty explained, IVCC attempts to help for-profit companies market insecticides that they have already discovered that show promise for public health applications, but which may have been dropped from development due to their unsuitability for commercial purposes. An insecticide that breaks down in ultraviolet light would not be effective for spraying fields, for example, but if incorporated into bed-nets and curtains, it might control mosquitoes inside houses and other buildings. Several such novel products in IVCC's pipeline will be made available to developing countries upon their approval, Beaty said.

"Our focus [at IVCC] is the control of vectors in and around the house," he explained, because most dengue virus mosquito-borne human disease transmissions occur indoors. In addition to supporting the development of inexpensive domestic products such as pyrethroid-impregnated bamboo curtains and mats, IVCC encourages their combined use in an approach known as *casa segura* ("safe house"). Scott also advocated the *casa segura* strategy for vector control and advised that market analyses of both households and ministries of health be conducted in order to guide product development.

Emphasis on controlling mosquitoes indoors was one of several targeted vector control strategies discussed by workshop participants. As previously mentioned, Scott and coworkers took advantage of spatial and temporal heterogeneities in dengue-carrying mosquito populations in order to increase the efficiency of control efforts (see "Hallmarks of Vector-Borne Disease," as well as Chapter 2). Based on a simulation model designed to predict the effect of dengue vaccine in various outbreak scenarios, he suggested that combining immunization (should

an effective vaccine be developed) with vector control would be advantageous. By contrast, controlling dengue solely through immunization could cause significant problems, such as more severe disease following infection with heterotypic strains of dengue, or perhaps greater rates of morbidity among older persons with waning immunity.

"Vector control, in essence, slows the force of infection and makes the delivery of vaccine more effective," Scott concluded. "Therefore an integrated program with vector reduction and immunization will more effectively prevent epidemic dengue and is more sustainable than either strategy alone." However, he noted, implementing such programs will take "a change in mind set to start to get people who are working on vaccines to think about working together with people who are working on vector control."

Multidisciplinary Research and Management

Research on infectious diseases must often be conducted in the midst of epidemics and in concert with management efforts. This challenging process was described by speaker David Rizzo of the University of California, Davis, who has worked to understand and mitigate the effects of SOD in California since shortly after its emergence there in the mid-1990s (see also Chapter 2 Overview). Caused by the fungus-like water mold *Phytopthora ramorum*, SOD kills several oak species and causes nonfatal leaf disease in many other plants, including rhododendrons and California bay laurel (California Oak Mortality Task Force, 2004; Faden, 2004). *P. ramorum* thrives in the cool, wet climate of California coastal forests—where it has caused substantial mortality in tanoak and several oak species—and has also been detected in the United Kingdom and a number of other European countries. SOD is not, strictly speaking, a vector-borne disease because it is not transmitted by arthropods; instead, humans (in the form of hikers, mountain bikers, and equestrians, who unknowingly carry *P. ramorum* spores on their clothes, shoes, equipment, and companion animals) appear to be the main vehicle for spreading this pathogen over long distances.

Because the SOD pathogen was only identified in 2000, researchers are still learning about its disease cycle and transmission dynamics. As they probe the ecological context of SOD and refine epidemiological models, Rizzo and colleagues are also working to manage the disease in natural ecosystems as well as in the nursery trade. To target monitoring efforts, they developed risk models based on findings from laboratory studies of the pathogen's sporulation behavior, combined with data on the distribution of host species and climate. Areas identified by the models are investigated by various methods, including aerial imaging, plot-based monitoring, and sampling streams to determine whether the pathogen is present within a watershed. If the pathogen is detected at a sufficiently early stage, the affected vegetation may be clear-cut and burned in hopes of eradicating the disease. While this approach has not yet proven completely successful, Rizzo

observed, it has significantly limited the spread of SOD. For areas where the pathogen is established, the researchers attempt to develop management schemes that avoid deleterious ecological consequences.

In all of their efforts, Rizzo and colleagues collaborate with a multidisciplinary team, the California Oak Mortality Task Force.[20] This group brings together plant biologists, anthropologists, entomologists, and ecologists from research and educational institutions, as well as representatives from interested public agencies, nonprofit organizations, and private interests (e.g., the nursery trade). The task force coordinates research, management, monitoring, and public policy efforts with regard to oak mortality and, as Rizzo noted, educates its broad constituency on developments in the understanding and management of SOD.

NEEDS AND OPPORTUNITIES

Insofar as vector-borne diseases represent the more general class of emerging infectious diseases, they entail a host of needs and opportunities all too familiar to workshop participants, and well characterized in numerous reviews and reports (Karesh and Cook, 2005; NRC, 2005), including the founding documents of the Forum on Microbial Threats, *Emerging Infections: Microbial Threats to Health in the United States* (1992) and *Microbial Threats to Health: Emergence, Detection, and Response* (2003). Briefly, these challenges include the following:

- Integration of research efforts and findings on infectious diseases in humans, livestock, and wild animals, as well as in crop and wild plants
- Training, research, and laboratory- and field-based surveillance in countries where diseases are likely to emerge (and especially in Asia, the source of many recently emerged zoonoses)
- More and better trained personnel, capacity, and tools for disease detection, diagnosis, and response
- Need for improved vaccines, drugs, and diagnostics
- Outbreak response plans that feature well-defined triggers for implementation
- Containment of outbreaks as local public health events
- Measures to limit the movement of pathogens and vectors via global transportation
- Risk communication that provides timely, reliable information to the public in the event of an outbreak, thereby preventing panic
- Political will sufficient to deliver economic support for these measures

Vector-borne diseases cast a singular emphasis on some of the aforementioned issues and present unique considerations for research and control (see Beaty and Eisen in Chapter 3). The following summary of a very wide-ranging

[20]See http://nature.berkeley.edu/comtf.

discussion therefore highlights specific challenges that originate in the definitive role of the vector in the ecology and epidemiology of this important class of human, animal, and plant infectious diseases.

Integrating Disciplines and Systems

In the course of a panel discussion on integrating strategies for surveillance, diagnosis, and response, the four discussants—who represented the CDC, the National Institute of Allergy and Infectious Disease of the National Institutes of Health (NIAID/NIH), and the U.S. Department of Agriculture (USDA)—emphasized the importance of multidisciplinary efforts toward understanding and addressing individual vector-borne diseases, as well as groups of diseases that share a common vector (see Chapter 3). Roger Nasci, chief of the Arboviral Diseases Branch at CDC's Division of Vector-Borne Infectious Diseases, described multidisciplinary teams as "essential" to addressing international health problems, but also noted the difficulties in coordinating such teams (e.g., the previously discussed response to RVF in Kenya).

Panelists described existing multidisciplinary programs of limited scope, such as CDC field teams that respond to vector-borne outbreaks and research groups that address West Nile encephalitis and plague (see Nasci in Chapter 3), and advocated a wider adoption of this approach. "We have to provide an environment to foster [multidisciplinarity] in training, as well as in research," said David Morens of NIAID; for example, by changing the current paradigm of highly compartmentalized Ph.D. programs and instead emphasizing interdisciplinary studies in global health (see Chapter 3) (Hotez, 2004). Similarly, Forum member Lonnie King observed that working at the interface of different scientific cultures is a learned skill that needs to be taught. Panelist Sherrilyn Wainwright (see Chapter 3), a veterinary epidemiologist with the USDA currently working at Colorado State University, suggested that involvement in multidisciplinary research trains scientists to better integrate their distinct cultures in other circumstances, such as outbreak response.

Participants in the ensuing open discussion urged the expansion of multidisciplinary research and response and encouraged the development of "transdisciplinary" programs that integrate diverse disciplines in a meaningful fashion, rather than simply involving representatives of different fields. Some also advocated expanding the range of disciplines brought to bear on vector-borne diseases beyond public health, ecology, and the biomedical sciences, to include professionals such as urban planners, hydrologists, ecologists, and engineers.

ArboNET, a pioneer among integration disease surveillance systems, provides a model for the collection and organization of information on zoonotic diseases, according to Nasci (see Chapter 3, Petersen in Chapter 2, and previous discussion in "Lessons Learned: Case Studies of Vector-Borne Diseases"). This environmental surveillance program could be harnessed for broader use, as is

currently being explored in an experimental ArboNET/plague surveillance system designed to test models that could provide early warning of plague outbreaks. In addition to gathering surveillance on vector-borne diseases, it would be useful to integrate and disseminate data that have already been accumulated, King observed, because to a large extent, "we don't know what we know." For example, as Nasci pointed out, data from the USDA's equine arbovirus monitoring program could be integrated into ArboNET.

Knowledge Gaps

The need to understand better the ecology of vector-borne diseases, a central theme of workshop discussions (see Fish in Chapter 1), was identified as critical to a host of purposes:

- Targeting surveillance and control efforts
- Minimizing surveillance costs over large areas
- Forecasting risk and anticipating expansion of disease range (including globalization)
- Designing containment or exclusion strategies

In addition, basic questions remain to be answered about most important vector-borne diseases (see Chapter 2 and Fish in Chapter 1). The following information was deemed essential by workshop presenters:

- Quantitative descriptions of endemic and epidemic disease cycles in all hosts
- Measurements of disease transmission potential by known and potential vectors
- Timing, distribution, and abundance of disease-competent vectors
- Mechanisms of host infection
- Mechanisms of pathogenesis
- Mechanisms of transovarial transmission
- Spatial and temporal distributions of vectors and environmental conditions in settings at risk for disease emergence

Field studies of vectors are crucial to answering many of these questions; however, as several participants who engage in such research attested, this work is not well funded. For example, Fish has written, "Some research is being done on methods for reducing the risk of Lyme disease through tick population suppression and other field intervention strategies, but this effort has been meager compared to that already invested in vaccines [that were withdrawn from the market]. One can only imagine what impact [the money invested in developing the discontinued Lyme vaccine, conservatively estimated at $200 million] would have

[had] upon research to answer some basic questions about tick ecology, such as what limits the geographic distribution of Lyme disease vectors" (Fish, 2001a).

Obstacles to Scientific Education and Training

The introduction of WNV into the United States resulted in an unprecedented demand for expertise in mosquito surveillance and control operations throughout most of the country, Fish observed in a 2001 editorial (Fish, 2001b). However, there is a strong perception among those in the field that—after three decades of decline in mosquito-borne disease in the United States, the dismantling of training programs, and a loss of employment opportunities for vector biologists and medical entomologists—positions went unfilled, and few academic institutions were capable of providing such training. The CDC briefly financed training in medical entomology at four institutions with the new funds provided to it for WNV, but that funding has since been cut, and the programs are slated for termination (Fish, 2007).

Panelist Adriana Costero, Vector Biology Program Officer at NIAID/NIH, described the Institute's programs, which fund basic and translational research and training in the United States and in disease-endemic countries (see Chapter 3). However, several participants expressed discouragement at the lack of research funding targeted specifically for vector ecology and the resulting dearth of expertise—as well as the persistence of knowledge gaps—in this field. Various causes were postulated for this deficit, from the broad (funding trends that favor solutions to well-defined problems, preferably posed by the "disease du jour," over descriptive studies of infectious diseases) to the specific (the organization of NIH study sections [Spielman, 2003]). However, as Forum member Stephen Morse observed, every scientific specialty complains of insufficient funding, a symptom of a scientific establishment focused on specialized research programs that compete for limited funds.

Multidisciplinary approaches offer a solution to this dilemma by creating unified communities, synergies of expertise, and economies of scale commensurate with problems as complex and wide-ranging as the prevention and mitigation of vector-borne disease. Such efforts, it was suggested, might be most expediently funded if they capitalized on the "disease du jour," and also if they offered near-term benefits for public health (e.g., how best to use existing pesticides in disease control and prevention).

Barriers to Implementation

There is a general lack of infrastructure for implementing vector-borne disease interventions in most settings, Morens observed, whether they are cities in the United States—as revealed by the introduction of Lyme disease—or impoverished countries where vector-borne diseases cause major morbidity and

mortality. "Many folks were shocked to discover [upon the arrival of WNV] that there were state health departments in the United States that had no vector people anymore," he said. The domestic situation has improved somewhat, he added, but the same cannot be said for developing countries, where infrastructures for infectious disease control lack far more than vector biologists. Moreover, legal and bureaucratic barriers increasingly impede international research on and response to vector-borne disease. Because many vector-borne infectious agents have been classified as "Select Agents," they are subject to rules associated with the USA Patriot Act[21] that substantially limit the ability of foreign scientists to work on U.S.-funded research efforts even within their own countries. In addition, U.S. air transportation regulations and bans on the international transport of biological specimens by nations experiencing disease outbreaks slow and sometimes stop the vital exchange of biological materials (see Morens in Chapter 3).

Meanwhile, 8 years after the introduction of WNV, the U.S. response to the threat of vector-borne disease is fading, as illustrated by recent funding reductions that will shrink the CDC's WNV program by nearly 50 percent over the next 2 years (Fish, 2007). "These cuts will force big reductions in federal support for the surveillance and control of WNV in 57 state and local jurisdictions," Fish noted in an editorial in the May 27, 2007, *New York Times*: "While federal financing for biosecurity and public health preparedness has . . . become a priority, in fact little has been learned from the WNV experience," he continued. WNV is certainly not the last mosquito-borne virus that will invade the United States, Fish predicted, but without sustained federal support for surveillance and control of such diseases, "we will again be vulnerable to threats, accidental or not, and incapable of prompt action that could curb or prevent epidemics."

Reflecting on this situation, Forum member George Korch wondered aloud how governments and industry might be convinced to invest in addressing vector-borne diseases. "What is the product that medical entomology and infectious disease studies provide?" he inquired. A major common goal for countries, or cultures, is to have a productive and healthy workforce that translates into the well-being of the entire community, he suggested. Thus, in order to convince the pharmaceutical industry, as well as governments, that vector-borne diseases are worth solving, researchers will need to provide evidence of economic benefit and opportunities for strategic investment. Even training is a short-term solution unless it fits into a grand matrix of vector-borne disease control, Korch said.

[21]"Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism (USA PATRIOT ACT) Act of 2001." The USA PATRIOT Act (Patriot Act), Public Law 107-56, enacted by Congress and signed by the President on October 26, 2001, provides expanded law enforcement authorities to enhance the federal government's efforts to detect and deter acts of terrorism in the United States or against United States' interests abroad (DoJ/OIG, 2003).

Conclusions

While acknowledging the global burden of vector-borne diseases, as well as the daunting obstacles to much-needed research on their control, prevention, and treatment, Forum chairman Fred Sparling also expressed optimism and excitement in the pursuit of solutions. Recalling that the final recommendation in the 2003 report *Microbial Threats to Health* advocated the creation of interdisciplinary centers for infectious disease research, he applauded the development of such a center—albeit a "virtual" one—at Colorado State University, in close association with the nearby CDC Division of Vector-Borne Infectious Diseases.[22]

Other universities (e.g., Vanderbilt, Duke, Johns Hopkins, and the University of Washington, Seattle[23]) are creating centers for global health. These initiatives are driven, in large part, by the promise of funding from the Bill and Melinda Gates Foundation and other public and private sources, Sparling said. In such a climate, and in such interdisciplinary venues, he encouraged vector biologists to look for opportunities and synergies and, thereby, support for their field. Like vector-borne diseases themselves, he concluded, research in this area is rife with thorny problems, but also abundant with opportunity.

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[22]Included in this consortium are U.S. Department of Agriculture/Agriculture Research Service, U.S. Department of the Interior, and the National Wildlife Research Center, all of which are co-located in and around Ft. Collins, Colorado, for the study of vector-borne diseases.

[23]Although only a few are listed, there are many universities with, or in the process of creating, such centers.

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1

Vector-Borne Disease Emergence and Resurgence

OVERVIEW

The once limited geographic and host ranges of many vector-borne diseases are expanding, spurred largely by anthropogenic factors. Epidemics of malaria, dengue, and other formerly contained vector-borne diseases are on the rise in the developing world, and in recent years the United States has witnessed the introduction of West Nile virus (WNV) in New York City and the emergence of previously unknown Lyme disease. Contributors to this chapter examine global, regional, and local phenomena associated with the emergence and resurgence of these and other vector-borne diseases, and explore the use of such information to predict future outbreaks and anticipate the geographic spread of vectors and pathogens.

The chapter begins with a summary of the workshop's keynote address, which was presented by Duane Gubler of the University of Hawai'i. Gubler describes the "dramatic global reemergence of epidemic vector-borne diseases" of the past three decades, in parallel with influential demographic, economic, and societal trends. He considers the changing epidemiology of malaria, plague, dengue, yellow fever, and WNV, identifies key factors in the emergence and spread of vector-borne disease, and discusses the implications of these trends for public health. In particular, he notes that advances in transportation, which centuries ago removed infectious disease barriers between the Old and New Worlds (that is, the eastern and western hemispheres), now drive the rapid, global dispersion of pathogens and their vectors. "If we hope to reverse the trend of emerging and reemerging infectious diseases," Gubler insists, "the movement of pathogens and arthropod vectors via modern transportation must be addressed."

In his presentation on anthropogenic factors in tick-borne pathogen emergence, Durland Fish of Yale University focused on the "steadily increasing" presence of tick-borne disease in the northeastern United States associated with the reversal of deforestation in that region (see Summary and Assessment subsection entitled "Reforestation and Tick-Borne Disease"). In addition to Lyme disease, which rose from obscurity to become the country's most common vector-borne disease within the span of two decades, black-legged deer ticks (*Ixodes scapularis*) serve as the vector for *Anaplasma phagocytophilum*—a bacterium that causes a flu-like illness called human granulocytic anaplasmosis—and the protozoan *Babesia microti* can be spread by transfused blood from an infected human.

The adults of this tick species feed exclusively on white-tailed deer; only the nymphs feed on and transmit pathogens to humans. The decline of agriculture in the northeastern United States and the subsequent reforestation of this region over the past several decades have provided an ideal habitat for increasing numbers of white-tailed deer, their attendant ticks, and the pathogens they bear. This trend may well continue and gain momentum, Fish noted, since various non-native tick-borne arboviruses could infect any of several hundred human-feeding species of ticks present in the United States.

Although vector-borne plant diseases share many ecological and epidemiological features with their animal and human counterparts, they tend to be studied in isolation. In his contribution to this chapter, presenter Rodrigo Almeida of the University of California, Berkeley, argues that new insights on the nature of vector-borne diseases could be gained through the exchange of tools and ideas among disparate research communities. Plant systems, for example, "allow large experiments to be conducted, with multiple hosts, vector species and pathogen strains, which could be used to experimentally address ecological and evolutionary hypotheses on pathogen range and transmission efficiency," he explains. In describing the rise of Pierce's disease of grapevines in California following the recent introduction of a highly efficient insect vector for a local bacterial pathogen, Almeida explores a common pattern of vector-borne disease emergence from an agricultural perspective.

The final essays in this chapter address the profound influence of climate on vector-borne disease distribution and transmission. The first, by presenter Kenneth Linthicum of the U.S. Department of Agriculture's (USDA's) Agricultural Research Service (ARS) Center for Medical, Agricultural, and Veterinary Entomology and co-authors, focuses on the effects of regional variations in temperature and rainfall on vector-borne disease transmission. The primary driver of global climate variability, the periodic warming of the Pacific Ocean surface known as the El Niño/Southern Oscillation (ENSO), has been linked with outbreaks of a variety of arthropod-borne diseases, the authors note. In the case of Rift Valley fever (RVF), this association was sufficiently strong to permit them to develop risk maps that successfully predicted a major outbreak in Africa in

2006-2007, providing an early warning that reduced the impact and spread of the disease. Such forecasts, they conclude, may potentially predict risk for the spread of diseases on a global scale and offer health and agricultural authorities the possibility of targeting disease surveillance and control efforts, and thereby improve their cost-effectiveness.

Two consecutive contributions, from workshop speaker Jonathan Patz, of the University of Wisconsin, Madison, and co-authors, discuss the possible effects of global climate change on vector-borne disease emergence. The first paper, by Patz and S. H. Olson, comprises an overview of the effects of climate change on disease risk at both global and local levels. It is followed by an update, by Patz and C. K. Uejio, which presents detailed evidence for the effects of climate change on Lyme disease and WNV, the two most prevalent vector-borne diseases in North America.

Vector-borne pathogens are particularly sensitive to climatic conditions due to their influence on vector survival and reproduction, biting and feeding patterns, pathogen incubation and replication, and the efficiency of pathogen transmission among multiple hosts. The authors discuss evidence that an overall rise in global temperatures could enlarge the geographic range of malaria in Africa and increase the frequency of dengue outbreaks worldwide, but they place greater emphasis on opportunities for disease emergence in local environments driven by land use practices such as deforestation, cultivation, and dam construction. Given these influences, risk assessments for vector-borne diseases should incorporate appropriately scaled analyses of the effects of land use on microclimate and weather, habitat, and biodiversity, the authors conclude. The need for such considerations is clearly illustrated in their discussion of WNV distribution and transmission dynamics, which appear to be influenced by a broad and complex range of environmental factors.

THE GLOBAL THREAT OF EMERGENT/REEMERGENT VECTOR-BORNE DISEASES

Duane J. Gubler, Sc.D.[1]
University of Hawai‘i, Honolulu, Hawai‘i

Introduction

At the beginning of the 20th century, epidemic vector-borne diseases were among the most important global public health problems (Gubler, 1998, 2002a).

[1]Director, Asia-Pacific Institute for Tropical Medicine and Infectious Diseases; Professor and Chair, Department of Tropical Medicine, Medical Microbiology and Pharmacology, John A. Burns School of Medicine.

Diseases such as yellow fever (YF), dengue fever (DF), plague, louse-borne Typhus, malaria, etc., caused explosive epidemics affecting thousands of people. Subsequently, other vector-borne diseases were identified as major causes of disease in both humans and domestic animals. As the natural history of these diseases became better understood, prevention and control measures, primarily directed at the arthropod vectors, were highly successful in controlling disease transmission. Effective prevention and control accelerated in the post-World War II years with the advent of new insecticides, drugs, and vaccines. By the 1960s, the majority of important vector-borne diseases had been effectively controlled in most parts of the world, and those that were not yet controlled were targeted for more intensive programs using new vaccines, drugs, and insecticides.

Unfortunately, "success led to failure"; some of the successful programs, such as the *Aedes aegypti* eradication program that effectively controlled epidemic YF and DF throughout the American tropics for over 40 years, and the global malaria eradication program that effectively controlled malaria in Asian and American countries, were disbanded in the 1970s because the diseases were no longer major public health problems (Gubler, 1989, 2004; Gubler and Wilson, 2005; IOM, 1992). Additionally, residual insecticides were replaced with less effective chemicals used as space sprays to control adult mosquitoes. The 1970s ushered in a 25-year period characterized by decreasing resources for infectious diseases, decay of the public health infrastructure to control vector-borne diseases, and a general perception that vector-borne diseases were no longer important public health problems. Coincident with this period of complacency, however, was the development of global trends that have contributed to the reemergence of epidemic infectious diseases in general, and vector-borne diseases in particular, in the past 25 years. In addition to the emergence of newly recognized diseases, there was increased incidence and geographic expansion of well-known diseases that were once effectively controlled (Gubler, 1989, 1998; IOM, 1992, 2003; Mahy and Murphy, 2005). This paper will briefly review the changing epidemiology of several of the most important vector-borne diseases and discuss the lessons learned from this global reemergence.

The Reemergence of Epidemic Vector-Borne Diseases as Public Health Problems

The earliest indications that epidemic vector-borne diseases might reemerge came in the early 1970s. Subsequent warnings were ignored by public health officials and policy makers because of competing priorities for limited resources (Gubler, 1980, 1987, 1989; IOM, 1992). The 1980s ushered in a period with increased epidemic vector-borne disease activity associated with expanding geographic distribution of both the vectors and the pathogens via modern transportation and globalization. It was not until the Institute of Medicine (IOM) report on emerging infectious diseases that policy makers took notice (IOM, 1992), and not

until after the 1994 plague epidemic in India that new resources were allocated to emerging infectious diseases (Fritz et al., 1996; WHO, 1994).

Parasitic, bacterial, and viral pathogens may be transmitted by blood-sucking arthropods. Mosquitoes, which primarily transmit parasitic and viral diseases, are the most important arthropod vectors; ticks, which primarily transmit bacteria and viruses, are next in importance.

Parasitic Diseases

Of the parasitic infections transmitted by arthropods, malaria is by far the most important, although there has also been a reemergence of leishmaniasis and African trypanosomiasis. The principal problem area for malaria is Africa, where 95 percent of all global cases occur, most of them in children under 5 years of age (Gubler and Wilson, 2005). This disease is dealt with elsewhere and will not be considered further here.

Bacterial Diseases

Two newly recognized vector-borne bacterial diseases, Lyme disease, caused by *Borrelia burgdorferi,* and ehrlichiosis, caused by *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum,* and *Ehrlichia ewingui,* have emerged as important public health problems in the past three decades (Dumler et al., 2007; Steere et al., 2004). Both have small rodents as their natural vertebrate reservoir host, with hard ticks as their principal vectors. Both diseases are found primarily in temperate regions of the world, where emergence has been associated with environmental change. Figure 1-1 shows the dramatic increase in reported cases of Lyme disease in the United States since the Centers for Disease Control and Prevention (CDC) began surveillance in 1982. The increased transmission in the United States is directly related to reforestation of the northeastern United States, allowing the mouse and deer populations to increase unchecked, which in turn has allowed the tick population to increase. A final factor has been the trend in recent decades to build houses in woodlots where humans share the ecology with deer, mice, and ticks; thus most transmission to humans in the northeastern United States where the majority of cases of Lyme disease occur, is residential (Steere et al., 2004).

Plague, caused by *Yersinia pestis*, is the most important reemergent bacterial vector-borne disease. The current global increase in case reports of plague is primarily due to outbreaks in Africa. However, it is the potential of plague to cause explosive epidemics of pneumonic disease, transmitted person-to-person and with high mortality, that makes it important as a reemergent infectious disease and as a potential bioterrorist threat. This was illustrated in 1994 when an outbreak of plague occurred in Surat, Gujarat, India (WHO, 1994). Although this was a small outbreak (most likely less than 50 cases) that should have been

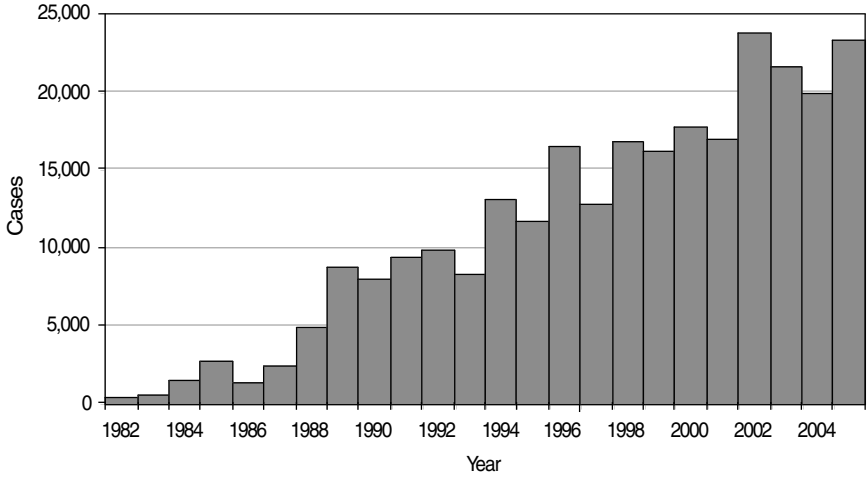

FIGURE 1-1 Reported Lyme disease cases by year, United States, 1982-2005.
SOURCE: Adapted from Gubler (1998) and CDC (2006), courtesy, Division of Vector-Borne Infectious Diseases, CDC, Fort Collins, CO.

a relatively unimportant local public health event, it became a global public health emergency. The reasons for this are complicated and beyond the scope of this article, but it is a classic case of "success breeding failure." Briefly, because the Indian Health Service had successfully controlled epidemic plague in India for over 30 years (the last confirmed human plague case prior to 1994 was in 1966), laboratory, clinical, and epidemiologic capacity to diagnose and control plague had deteriorated. Thus, when the Surat outbreak occurred, the clinical and laboratory diagnosis was confused, creating lack of confidence in public health agencies and ultimately panic when it was finally announced that the disease was pneumonic plague. Within a few weeks in early October 1994, an estimated 500,000 people fled Surat, a city of about 2 million people at that time. Many of these people traveled to other urban areas in India, and within days, newspapers were reporting plague cases in other cities. The World Health Organization implemented Article 11 of the International Health Regulations (WHO, 1983) for the first time in 33 years because it was thought that people with pneumonic plague might board airplanes in India and transport the disease to other urban centers around the world (Figure 1-2). Many countries stopped air travel and trade with India and most implemented enhanced surveillance for imported plague cases via airplane travel. This was the first global emerging infectious disease epidemic that impacted the global economy since infectious diseases were controlled in the 1950s. It is estimated that this small outbreak cost India US$3 billion (John, 1999) and the global economy US$5 to $6 billion. Fortunately, there were no

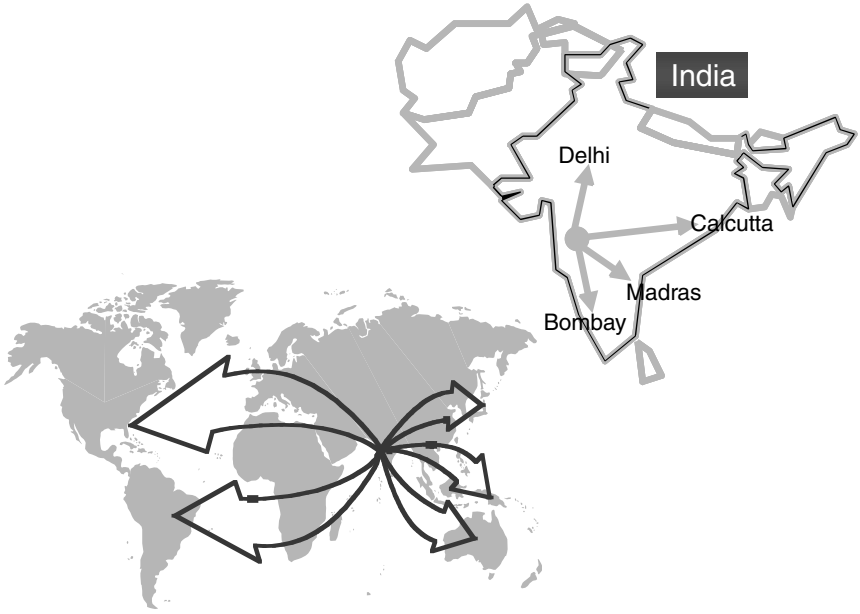

FIGURE 1-2 Suspected spread of pneumonic plague from India, 1994.
SOURCE: Courtesy, Division of Vector-Borne Infectious Diseases, CDC, Fort Collins, CO.

cases of plague exported from India (Fritz et al., 1996), but this epidemic was the "wake-up call" that modern transportation and globalization were major drivers of pandemic infectious diseases. It was this epidemic that helped stimulate in the first funding of CDC's Emerging Infectious Disease Program.

Arboviral Diseases

Of the vector-borne diseases, it is the arboviruses that have become the most important causes of reemergent epidemic disease (Gubler, 1996, 2002a). In 2007, there are few places on Earth where there is no risk of infection with one or more of these viral diseases, most of which are transmitted by mosquitoes. The more important reemergent epidemic arboviral diseases are presented in Table 1-1. They include members of three families (*Togaviridae*, *Flaviviridae*, and *Bunyaviridae*). Three diseases—dengue fever, West Nile, and yellow fever—will be discussed as case studies to illustrate the changing epidemiology of arboviral diseases.

TABLE 1-1 Emergent/Reemergent Arboviral Diseases of Humans

- Dengue hemorrhagic fever
- Yellow fever
- West Nile fever
- Japanese encephalitis
- Chikungunya
- Rift Valley fever
- Alkumra fever (Kyasanui Forest disease)
- Venezuelan equine encephalitis
- Epidemic polyarthritis
- Barmah Forest
- Oropouche
- California encephalitis
- Crimean-Congo hemorrhagic fever

West Nile Virus[2]

West Nile virus (WNV) (*Flaviviridae,* genus *Flavivirus*), an African virus, belongs to the Japanese encephalitis virus (JEV) sero-group, which includes a number of closely related viruses, including JEV in Asia, St. Louis encephalitis virus in the Americas, and Murray Valley encephalitis virus in Australia. All have a similar transmission cycle involving birds as the natural vertebrate hosts and *Culex* species mosquitoes as the enzootic/epizootic vectors, and all cause severe and fatal neurologic disease in humans and domestic animals, which are generally thought to be incidental hosts, as well as in birds.

The clinical illness associated with WNV in humans ranges from asymptomatic infection to viral syndrome to neurologic disease (Hayes and Gubler, 2006), but historically it has been considered among the least virulent of the Japanese encephalitis sero-group viruses (Hayes, 1988); recent epidemics, however, have changed that perception.

From the time WNV was first isolated from the blood of a febrile patient in the West Nile province of Uganda in 1937 (Smithburn, 1940) until the fall of 1999, it was considered relatively unimportant as a human and animal pathogen. The virus was enzootic throughout Africa, West and Central Asia, the Middle East, and the Mediterranean, with occasional extension into Europe (Hayes, 1988). A subtype of WNV (Kunjin) is also found in Australia (Hall et al., 2002). A characteristic of WNV epidemiology during this 62-year history (1937-1999) was that it caused epidemics only occasionally, and the illness in humans, horses,

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and birds was generally either asymptomatic or mild; neurologic disease and death were rare (Marfin and Gubler, 2001; Murgue et al., 2001, 2002).

In late August 1999, an astute physician in Queens, New York, identified a cluster of elderly patients with viral encephalitis (Asnis et al., 2000). Because of the age group involved and the clinical presentation, these cases were initially thought to be St. Louis encephalitis, but subsequent serologic and virologic investigation showed them to be caused by WNV (Lanciotti et al., 1999). The epidemic investigation, which focused only on neurologic disease, identified 62 cases with 7 (11 percent) deaths, all of them in New York City (Nash et al., 2001). Epidemiologic studies, however, showed widespread transmission throughout New York City, with thousands of infections (Montashari et al., 2001; Nash et al., 2001). The virus caused a high fatality rate in birds, especially those in the family *Corvidae* (Komar, 2003). Genetic sequence of the infecting virus suggested it was imported from the Middle East, most likely from Israel (Lanciotti et al., 1999). Although it will never be known for sure, epidemiologic and virologic evidence suggests the virus was introduced in the spring or early summer of 1999, most likely via infected humans arriving from Israel, which was experiencing an epidemic of WNV in Tel Aviv at the time (Giladi et al., 2001; Marfin and Gubler, 2001).

Over the next 5 years, WNV rapidly moved westward across the United States to the west coast (Figure 1-3), north into Canada, and south into Mexico, the Caribbean, and Central America. In 2002, it caused the largest epidemic of meningoencephalitis in U.S. history with nearly 3,000 cases of neurologic disease and 284 deaths. That same year, there was a large epizootic in equines with over 14,500 cases of neurologic disease and a case fatality rate of nearly 30 percent (Campbell et al., 2002). The epidemic curve for human cases in the United States is shown in Figure 1-4. In 2003, another large epidemic occurred, but the epicenter of transmission was in the plains states and the majority of the reported cases were not neurologic disease (Hayes and Gubler, 2006). Since 2003, the virus has persisted with seasonal transmission during the summer months, but at a lower level; the majority of cases have been in the plains and western states.

WNV was first detected south of the U.S. border in 2001 when a human case of neuro-invasive disease was reported in the Cayman Islands (Campbell et al., 2002), and birds collected in Jamaica in early 2002 were positive for WNV-neutralizing antibodies (Komar and Clark, 2006). In 2002, WNV activity was reported in birds and/or equines in Mexico (in six states) and on the Caribbean islands of Hispaniola (Greater Antilles) and Guadeloupe (Lesser Antilles). Most likely, the virus was also present in Mexico in 2001, since a cow with WNV-neutralizing antibody was detected in the southern state of Chiapas in July of 2001 (Ulloa et al., 2003). In 2003, the virus was detected in 22 states of Mexico; in Belize, Guatemala, and El Salvador in Central America; and in Cuba, Puerto Rico, and the Bahamas in the Caribbean. In 2004, WNV activity was reported from northern Colombia, Trinidad, and Venezuela, the first reported activity in

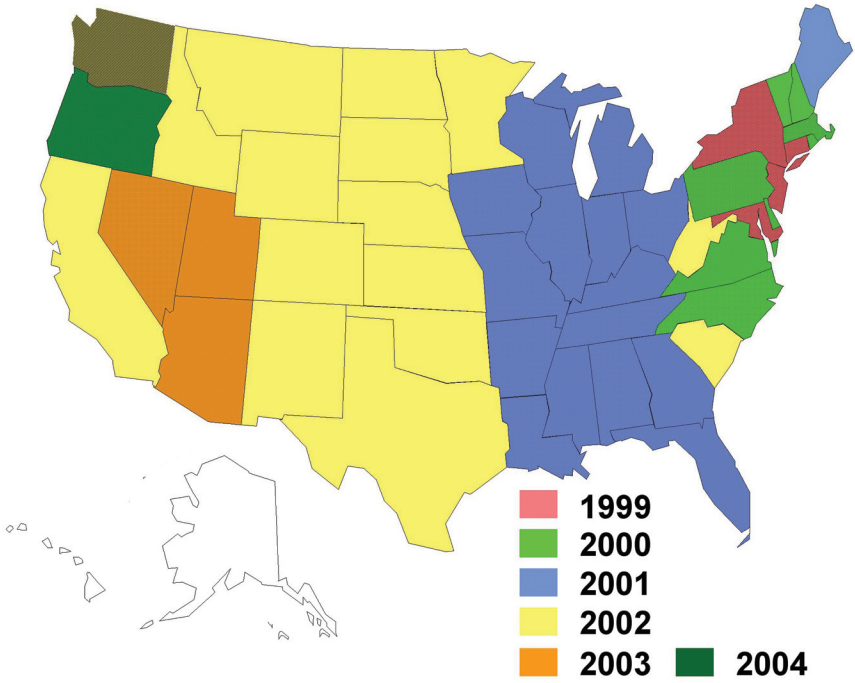

FIGURE 1-3 The sequential westward movement of West Nile virus in the United States by year, reported to CDC as of January 31, 2006. Human infection was found in all states in the continental United States with the exception of Maine.
SOURCE: Reprinted from Gubler (2007).

South America; in 2006, Argentina reported WNV transmission (Komar and Clark, 2006; Morales et al., 2006).

Migratory birds have likely played an important role in the spread of WNV in the western hemisphere (Owen et al., 2006; Rappole et al., 2000). This conclusion is supported by data on the movement of WNV in migratory birds in the Old World (Malkinson et al., 2002). Moreover, the westward movement of WNV across the United States and Canada can best be explained by introduction via migratory birds that fly south to Central and South America in the fall and north from those areas in the spring. Thus, the yearly movement westward in 2000, 2001, 2002, 2003, and 2004 shows very good correlation with the Atlantic, Mississippi, Central, and Pacific flyways of migratory birds (Figures 1-3 and 1-5). After introduction to an area, local dispersion of WNV likely occurred via movement of resident birds, which often fly significant distances. Interestingly, the major epidemic in each region of the country occurred the following year after introduction, with the exception of the 1999 New York outbreak.

The emergence of a WNV strain with greater epidemic potential and viru-

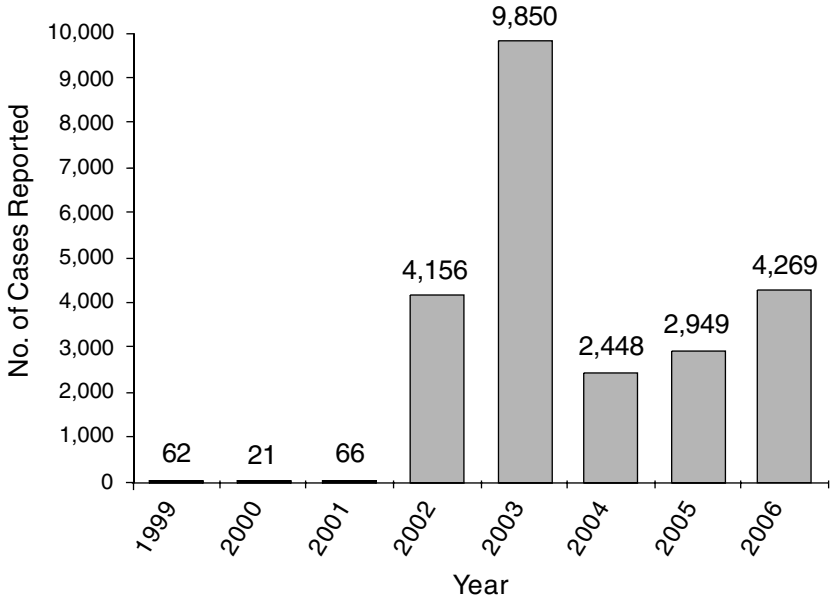

FIGURE 1-4 Epidemic West Nile virus in the United States, 1999-2006, reported to CDC as of May 2, 2007.
SOURCE: CDC (2007).

lence was likely a major factor in the spread of WNV in both the Old and the New Worlds (Marfin and Gubler, 2001). The first evidence of this new strain of WNV was in North Africa in 1994, when an epidemic/epizootic of serologically confirmed WNV occurred in Algeria; of 50 cases with neurologic disease 20 (40 percent) were diagnosed as encephalitis and 8 (16 percent) died (Murgue et al., 2002). Over the next 5 years, epidemics/epizootics occurred in Morocco, Romania, Tunisia, Israel, Italy, and Russia, as well as jumping the Atlantic and causing the epidemic in Queens, New York (Figure 1-6). All of these epidemics/epizootics were unique from earlier epidemics in that they were associated with a much higher rate of severe and fatal neurologic disease in humans, equines, and/or birds. This virus most likely had better fitness and caused higher viremias in susceptible hosts, allowing it to take advantage of modern transportation and globalization to spread, first in the Mediterranean region and Europe, and then to the western hemisphere. This speculation is supported by sequence data documenting that the viruses isolated from these recent epidemics/epizootics are closely related genetically, most likely having a common origin; all belonged to the same clade (Lanciotti et al., 1999, 2002) (Figure 1-7). Moreover, experimental infection of birds has documented that viruses in this clade, represented by the

FIGURE 1-5 Migratory bird flyways in the western hemisphere. In the fall birds fly south to areas in tropical America where they spend the winter. In the spring, they fly north again, potentially carrying the virus with them each way.
SOURCE: Reprinted from Gubler (2007).

New York 1999 isolate, have greater virulence than virus strains isolated earlier (Brault et al., 2004; Langevin et al., 2005).

The broad vertebrate host and vector range of WNV was another important factor in the successful spread of epidemic/epizootic WNV transmission. The virus has been isolated from 62 species of mosquitoes, 317 species of birds, and more than 30 species of non-avian hosts since it entered the U.S. in 1999 (CDC, 2007, unpublished data). The non-avian vertebrate hosts include rodents, bats, canines, felines, ungulates, and reptiles, in addition to equines and humans. It is unknown what role any of these non-avian species play in the transmission cycle of WNV, but the fact that so many mammal and opportunistic blood-feeding mosquitoes have been found infected suggests that there may be secondary transmission cycles involving mammals and mammal-feeding mosquitoes, putting humans and domestic animals at higher risk for infection.

FIGURE 1-6 Epidemics caused by West Nile virus, 1937-2007. The red stars indicate epidemics that have occurred since 1994 and have been associated with severe and fatal neurologic disease in humans, birds, and/or equines.
SOURCE: Reprinted from Gubler (2007).

Dengue/Dengue Hemorrhagic Fever[3]

The dengue viruses (DENVs) are also members of the family *Flaviviridae*; there are four dengue serotypes (DENV-1, DENV-2, DENV-3, DENV-4), which make up the dengue complex within the genus *Flavivirus*. While the DENVs have a primitive sylvatic maintenance cycle involving lower primates and canopy-dwelling mosquitoes in Asia and Africa, they have also established an endemic/epidemic cycle involving the highly domesticated *Ae. aegypti* mosquito and humans in the large urban centers of the tropics. They have become completely adapted to humans and current evidence suggests that the sylvatic cycle is not a major factor in the current emergence of epidemic disease (Gubler, 1997; Rico-Hesse, 1990).

The DENVs cause a spectrum of illness in humans ranging from inapparent infection and mild febrile illness to classic DF to severe and fatal hemorrhagic disease (WHO, 1997). All age groups are affected, but in endemic areas, most illness is seen in children, who tend to have either a mild viral syndrome or the more severe dengue hemorrhagic fever (DHF), a vascular leak syndrome. DENV infection has also been associated with severe and fatal neurologic disease and massive hemorrhaging with organ failure (Sumarmo et al., 1983).

Dengue is an old disease; the principal urban vector, *Aedes aegypti*, and the

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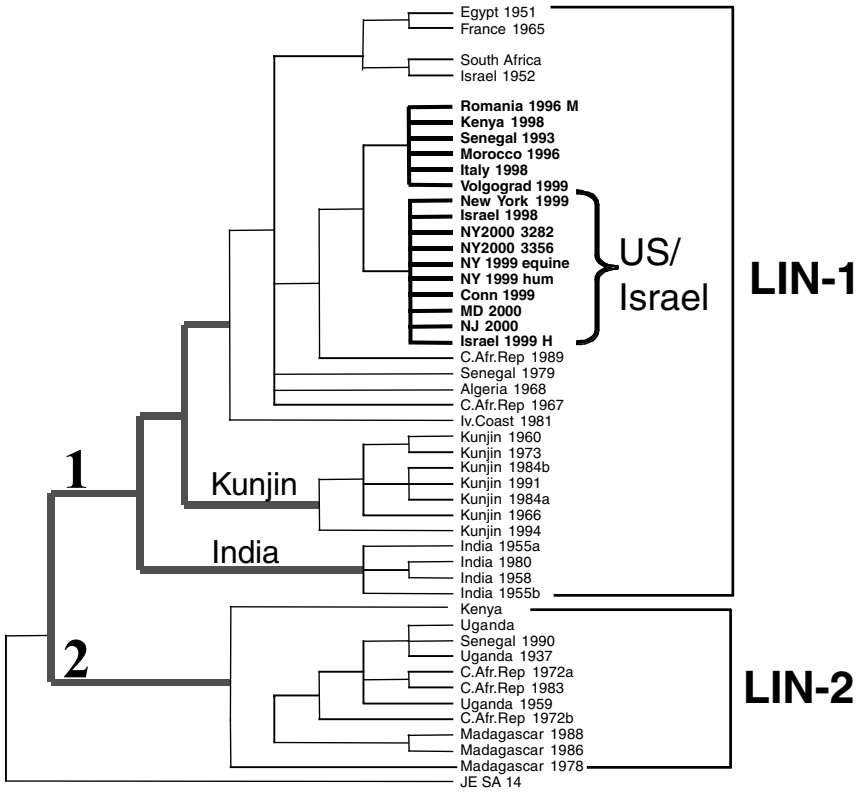

FIGURE 1-7 Phylogenetic tree of West Nile viruses based on sequence of the envelope gene. Viruses isolated during recent epidemics all belong to the same clade, suggesting a common origin.
SOURCE: Reprinted from Gubler (2007).

viruses were spread around the world as commerce and the shipping industry expanded in the 17th, 18th, and 19th centuries. Major epidemics of DF occurred as port cities were urbanized and became infested with *Ae. aegypti*. Because the viruses depended on the shipping industry for spread, however, epidemics in different geographic regions were sporadic, occurring at 10- to 40-year intervals. The disease pattern changed with the ecological disruption in Southeast Asia during and after World War II. The economic development, population growth and uncontrolled urbanization in the post-war years created ideal conditions for increased transmission and spread of urban mosquito-borne diseases, initiating a global pandemic of dengue. With increased epidemic transmission, and the movement of people within and between countries, hyperendemicity (the co-circulation

of multiple DENV serotypes) developed in Southeast Asian cities, and epidemic DHF, a newly described disease, emerged (Gubler, 1997; Halstead, 1980; WHO, 1997). By the mid-1970s, DHF had become a leading cause of hospitalization and death among children in the region (WHO, 1997, 2000). In the 1980s and 1990s, dengue transmission in Asia further intensified; epidemic DHF increased in frequency and expanded geographically west into India, Pakistan, Sri Lanka, and the Maldives, and east into China (Gubler, 1997). At the same time, the geographic distribution of epidemic DHF was expanding into the Pacific islands in the 1970s and 1980s and to the American tropics in the 1980s and 1990s (Gubler, 1989, 1993, 1997; Gubler and Trent, 1994; Halstead, 1992).

Epidemiologic changes in the Americas have been the most dramatic. In the 1950s, 1960s, and most of the 1970s, epidemic dengue was rare in the American region because the principal mosquito vector, *Aedes aegypti*, had been eradicated from most of Central and South America (Gubler, 1989; Gubler and Trent, 1994; Schliessman and Calheiros, 1974). The eradication program was discontinued in the early 1970s, and the mosquito then began to reinvade those countries from which it had been eliminated. By the 1990s, *Aedes aegypti* had regained the geographic distribution it had before eradication was initiated (Figure 1-8). This was another classic case of "success breeding failure."

Epidemic dengue invariably followed after reinfestation of a country by *Aedes aegypti*. By the 1980s, the American region was experiencing major epidemics of DF in countries that had been free of the disease for more than 35 years (Gubler, 1989, 1993; Gubler and Trent, 1994; Pinheiro, 1989). With the introduction of new viruses and increased epidemic activity came the development of hyperendemicity in American countries and the emergence of epidemic DHF, much as had occurred in Southeast Asia 25 years earlier (Gubler, 1989). From 1981 to 2006, 28 American countries reported laboratory-confirmed DHF (Gubler, 2002b) (Figure 1-9).

While Africa has not yet had a major epidemic of DHF, sporadic cases of severe disease have occurred as epidemic DF has increased in the past 25 years. Before the 1980s, little was known of the distribution of DENVs in Africa (Carey et al., 1971). Since then, however, major epidemics caused by all four serotypes have occurred in both East and West Africa (Gubler, 1997; Monath, 1994).

In 2007, dengue viruses and *Ae. aegypti* mosquitoes have a worldwide distribution in the tropics with 2.5 to 3.0 billion people living in dengue-endemic areas. Currently, DF causes more illness and death than any other arboviral disease of humans. The number of cases of DF/DHF reported to the World Health Organization (WHO) has increased dramatically in the past 3 decades (Figure 1-10). Each year, an estimated 100 million dengue infections and several hundred thousand cases of DHF occur, depending on epidemic activity (Gubler, 1997, 2002b, 2004; WHO, 2000).

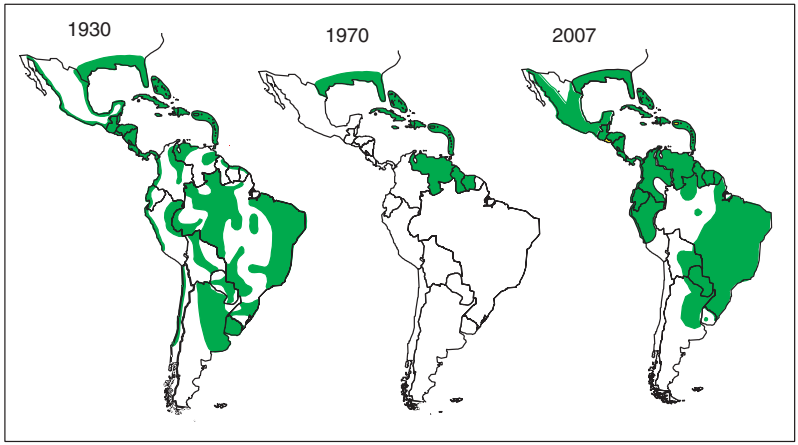

FIGURE 1-8 Distribution of *Aedes aegypti* in American countries in 1930, 1970, and 2007.
SOURCE: Courtesy, Division of Vector-Borne Infectious Diseases, CDC, Fort Collins, CO; adapted from Gubler (1998).

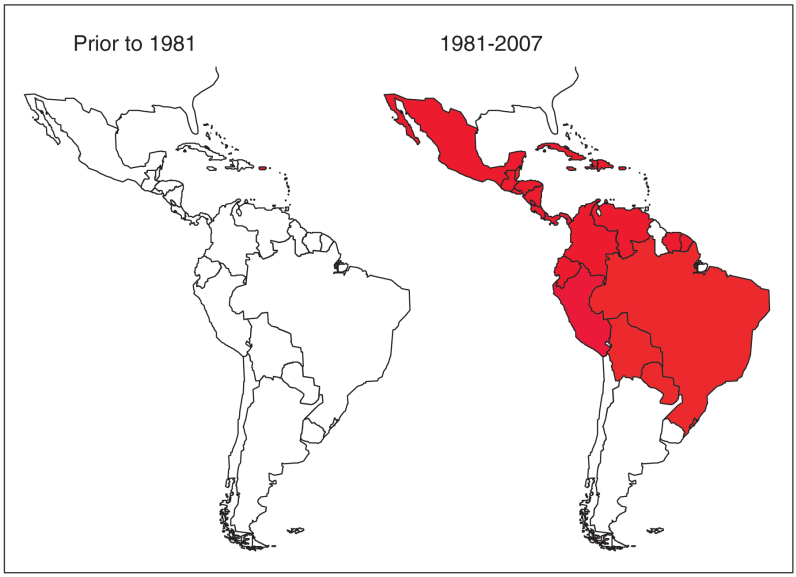

FIGURE 1-9 Countries reporting confirmed DHF prior to 1981 and 1981 to 2007.
SOURCE: Courtesy, Division of Vector-Borne Infectious Diseases, CDC, Fort Collins, CO; adapted from Gubler (1998).

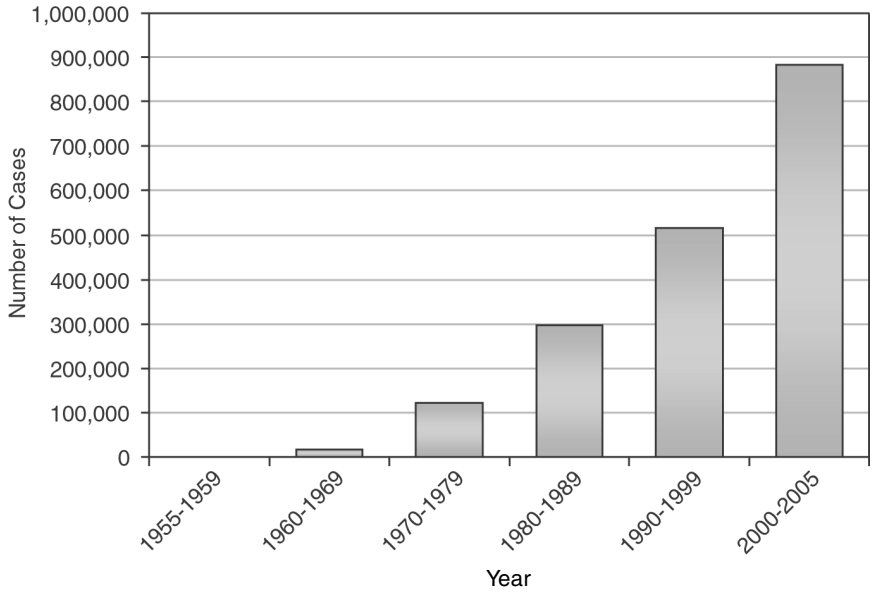

FIGURE 1-10 Mean annual global reported cases of DEN/DHF to the World Health Organization, by decade, 1955-2005.
SOURCE: Adapted from MacKenzie et al. (2004).

Yellow Fever[4]

Yellow fever virus (YFV) was the first arbovirus to be isolated and the first shown to be transmitted by an arthropod. It is the type species of the family (*Flaviviridae*: genus *Flavivirus*) (Gubler et al., 2007). Its natural home is the rainforests of sub-Saharan Africa where it is maintained in a cycle involving lower primates and canopy-dwelling mosquitoes (Monath, 1988). It was transported to the western hemisphere with the slave trade in the 1600s and became adapted to an urban cycle involving humans and *Aedes aegypti* mosquitoes, similar to dengue. It also established a sylvatic monkey cycle in the rain forests of the Amazon basin similar to the one in Africa.

The first recorded epidemic of YF occurred in 1648 and was followed by numerous epidemics in port cities of the New World, as far north as Boston (Monath, 1988). Urban epidemic transmission was effectively controlled in the Americas in the 1950s, 1960s, and 1970s by the *Aedes aegypti* eradication program (see earlier discussion) (Gubler, 1989; Schliessman and Calheiros, 1974) (Figure 1-8). The last known urban epidemic occurred in Brazil in 1942 (Monath,

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1988). In Francophone countries of West Africa, YF was controlled by mass vaccination programs. The result was the disappearance of major urban epidemics of YF in both Africa and the Americas. In the mid-1980s, however, the urban disease reemerged in West Africa, with major epidemics in Nigeria and increased transmission in other countries (Gubler, 2004; Monath, 1988; Nasidi et al., 1989; Robertson et al., 1996). Kenya experienced its first epidemic in history in 1993 (Sanders et al., 1998). In the Americas, the reinfestion of most Central and South American countries by *Aedes aegypti* has put the urban centers of the American tropics at the highest risk for epidemic urban YF in more than 60 years (Gubler, 1989, in press). Thus, the disease continues to be an important public health problem in both Africa and the Americas.

The reemergence of epidemic YF in the past 30 years has not been as dramatic as that of DF/DHF. While there has been increased epidemic activity in both Africa and the Americas, the outbreaks have been limited and mostly associated with sylvatic cycles. Of concern is that several of the outbreaks in the Americas have occurred in or in close proximity to urban areas where *Aedes aegypti* occurs, greatly increasing the risk of urban transmission (Gubler, 2004; Van der Stuyft et al., 1999). Additionally, the recent increase in ecotourism without proper immunization has increased the risk of YF being introduced to urban areas where *Aedes aegypti* occurs (CDC, 2000).

Currently, the threat is that YFV will become urbanized in the American tropics and spread geographically much as DENVs have done over the past 25 years. The biggest concern is that it will be introduced to the Asia-Pacific region, where there are approximately 1.8 billion people living in large urban centers under crowded conditions in intimate association with large populations of *Aedes aegypti* mosquitoes, thus creating ideal conditions for increased urban transmission. While there is an effective, safe, and economical vaccine for YF, its supply is limited and it would take months to increase production to the point where adequate doses could be produced. By then YFV would likely be widely distributed in the region.

If YF was introduced to the Asia-Pacific, the initial cases would most likely be misdiagnosed as DHF, leptospirosis, rickettsiosis, hantavirus disease, or malaria, thus potentially allowing it to spread and become established in widespread areas before it was identified. Thus, YF virus could be introduced and become established in Asia-Pacific countries weeks to months before it was recognized. Even after it is diagnosed, it is not likely that an effective control program could be mounted because most countries in the region do not have effective *Aedes aegypti* control programs. Once recognized as YF, it would likely cause overreaction and panic on the part of the press, the public, and health officials. Regardless of whether YF virus caused a major epidemic in this region, there would be a major public health emergency, creating social disruption and great economic loss to all countries of the region, making the Indian plague epidemic of 1994 (Fritz et

al., 1996; John, 1999; WHO, 1994) and the 2003 SARS epidemic (Drosten et al., 2003) pale by comparison.

It is not known whether YFV would become established in Asia (Downs and Shope, 1974; Gubler, 2004; Monath, 1989). YFV was most likely introduced sporadically to the Pacific and Asia in the past (Usinger, 1944), but secondary transmission has never been documented. There are several possible explanations why there have not been YF epidemics in the Asia-Pacific region (Monath, 1989). First, logistics: during the time when major YF epidemics were occurring in the Americas, the virus and the mosquitoes depended on ocean vessels to be transported to new geographical locations. The probabilities of the virus being introduced to Asia were low because the Panama Canal had not been built, and there was not as much commerce between Caribbean, Central and South American counties and Asia, as there was with the United States and Europe. Moreover, YF epidemics were not common in East Africa, thus decreasing the probability of introduction to India. Second, the high heterotypic flavivirus antibody (DENV-1, DENV-2, DENV-3, DENV-4, JEV, and many other flaviviruses of lesser importance) rates in Asian populations, while not protecting against YF infection, could possibly modulate the infection and down-regulate viremia and clinical expression, as has been shown in monkeys (Theiler and Anderson, 1975), thus decreasing the likelihood of secondary transmission by mosquitoes. Third, there has been some suggestion that Asian strains of *Aedes aegypti* mosquitoes are less susceptible to YFV than American strains (Gubler et al., 1982). Finally, it is possible that evolutionary exclusion may prevent YFV from becoming established in areas where closely related flaviviruses are endemic. Most likely, a combination of these factors has contributed to preventing YF from becoming established in Asia in the past.

The reason why urban YF has not occurred in the American tropics, despite the high risk in recent years, is not known. As noted for Asia, the high seroprevalance rates for the DENVs and other flaviviruses in most Central and South American countries could down-regulate viremia and illness, thus decreasing the risk of secondary transmission and clinical diagnosis. Additionally, the enzootic YFV may require adaptation to *Aedes aegypti* and humans, before becoming highly transmissible in the urban environment. If it does become adapted, however, it is important to remember that the logistic and demographic factors that influence arbovirus spread at the beginning of the 21st century are very different from past centuries. First, tens of millions of people travel by jet airplane between the cities of tropical America and the Asia-Pacific region every year; this provides the ideal mechanism for people incubating YFV to transport it to new geographic locations. There has been an increase in ecotourism in recent years, and since 1996, at least six tourists have died in the United States and Europe as a result of infection with YFV acquired during travel to YF endemic countries without vaccination (CDC, 2000; Gubler, 2004; Gubler and Wilson, 2005). If urban epidemic transmission of YF begins in the Americas, there could be thousands

of YFV infected people traveling to Asia-Pacific countries where *Aedes aegypti* exposure is high, thus dramatically increasing the probability that epidemic YF transmission will occur in Asia.

Why Has There Been Such a Dramatic Resurgence of Vector-Borne Diseases?[5]

The dramatic global reemergence of epidemic vector-borne diseases in the past 25 years is closely tied to global demographic, economic, and societal trends that have been evolving over the past 50 years. Complacency and deemphasis of infectious diseases as public health problems in the 1970s and 1980s resulted in a redirection of resources and ultimately to a decay of the public health infrastructure required to control these diseases. Coincident with this trend, unprecedented population growth, primarily in the cities of the developing world, facilitated transmission and geographic spread. This uncontrolled urbanization and crowding resulted in a deterioration in housing accompanied by a lack of basic services (e.g., water, sewer, and waste management). Population growth has been a major driver of environmental change in rural areas as well (e.g., deforestation, agriculture land use, and animal husbandry practice changes). All of these changes contributed to increased incidence of vector-borne infectious diseases.

Many urban agglomerations (population >5 million) have emerged in the past 50 years, and most have an international airport through which millions of passengers pass every year (Wilcox et al., 2007). In addition, globalization has insured an equally dramatic increase in the movement of animals and commodities between population centers. The jet airplane provides the ideal mechanism by which pathogens of all kinds move around the world in infected humans, vertebrate host animals, and vectors. A classic example of how urbanization combined with globalization has influenced the geographic expansion of disease is illustrated by the DENVs (Figure 1-11). In 1970, only Southeast Asian countries were hyperendemic with multiple virus serotypes co-circulating, as a result of World War II. The rest of the tropical world was hypoendemic with only a single DENV serotype circulating, or nonendemic (Figure 1-11A). In 2007, the whole of the tropical world is hyperendemic as a direct result of urbanization, lack of mosquito control, and increased movement of viruses in people via modern transportation (Figure 1-11B). The result has been increased frequency of larger epidemics, and the emergence of the severe and fatal form of disease, DHF, in most tropical areas of the world. Globalizaton and modern transportation were also responsible for the recent spread of WNV to and throughout the western hemisphere (Figure 1-6). Increased transmission is a major driver of genetic change in all of these viruses, which can result in virus strains with greater virulence or epidemic potential being spread around the globe. The concern is that YF

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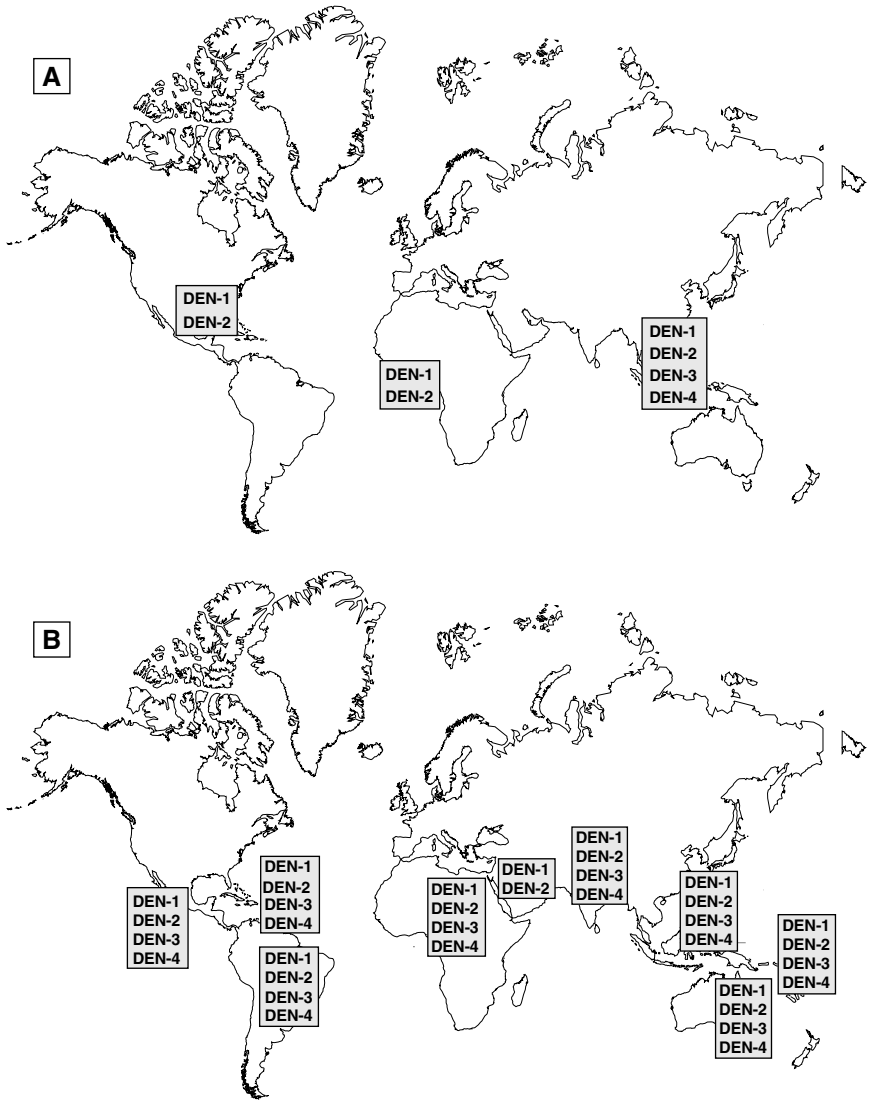

FIGURE 1-11 The global distribution of dengue virus serotypes, (A) 1970 and (B) 2007.
SOURCE: Adapted from Mackenzie et al. (2004).

TABLE 1-2 Exotic Infectious Diseases That Have Recently Been Introduced to the United States

Diseases	Autochthonous Transmission
• West Nile fever	Yes
• Yellow fever	No
• Mayaro fever	No
• Dengue fever	Yes
• Chikungunya	No
• SARS	No
• Monkeypox	Yes
• CJD/BSE	No
• HIV/AIDS	Yes
• Lassa fever	No
• Malaria	Yes
• Leishmaniasis	Yes
• Chagas disease	Yes
• Cyclospora	Yes
• Cholera	No

or RVF will be the next vector-borne diseases to spread because of globalization and modern transportation.

There are many other vector-borne diseases that have the potential for geographic spread. As an illustration of movement of infectious disease pathogens, Table 1-2 lists some of the exotic diseases introduced into the United States in recent years. It should be noted that the majority of these pathogens are vector-borne, zoonotic, and viruses. In addition, five species of exotic mosquitoes have been introduced and have become established in the country in the past 25 years. Some of the more important epidemic vector-borne diseases affecting humans at the beginning of the new millennium and which have the potential to spread via modern transportation are shown in Table 1-3. Again, it should be noted that most are zoonotic viral diseases. There is reason to believe that, sooner or later, one or more known or unknown pathogens will cause devastating epidemic disease.

Lessons Learned and Challenges to Reverse the Trend[6]

At the dawn of the 21st century, epidemic infectious diseases have come "full circle" in that many of the diseases that caused epidemics in the early 1900s, and which were effectively controlled in the middle part of the 20th century, have reemerged to become major public health problems. Complacency and competing priorities for limited resources have resulted in inadequate resources to continue

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TABLE 1-3 Principal Epidemic Vector-Borne Diseases Affecting Humans at the Beginning of the 21st Century

- Malaria
- Plague
- Leishmaniasis
- African trypanosomiasis
- Relapsing fever
- Yellow fever
- Dengue fever and dengue hemorrhagic fever
- West Nile encephalitis
- Japanese endephalitis
- Rift Valley fever
- Venezuelan equine encephalitis
- Chikungunya
- Epidemic polyarthritis
- Other arboviruses
- Zoonose

prevention and control programs when there is no apparent disease problem. Only when an epidemic occurs do policy makers respond by implementing emergency response plans, but by then it is usually too late to have any impact on transmission.

In today's world of modern transportation and globalization, we have learned to expect the unexpected: that old diseases will reemerge and new diseases will emerge, and that modern transportation and globalization will disperse them around the world. Once introduced and established, it is unlikely that zoonotic disease agents can be eliminated from an area.

We have learned that international cooperation and collaboration are critical to developing and maintaining effective early warning disease detection and emergency response systems. Unfortunately, while elaborate epidemic preparedness and response plans are often drawn up, these plans are most often not implemented until it is too late to impact disease transmission because the decision to declare an emergency is one that often has important political and economic implications. As a result, public health problems that should remain localized have the potential to become more widespread because of modern transportation and the mobility of people.

We have learned that we must emphasize prevention. Local public health infrastructure must be rebuilt and maintained in order to contain disease outbreaks as local public health events instead of letting them spread around the world via modern transportation. The public and the press require accurate and reliable information in order to prevent panic and overreaction.

TABLE 1-4 Pathogens of Tomorrow: From Whence They Will Come?

From Asia and Animals
• Human population growth
• Urbanization
• Environmental change
• Animal husbandry
• Agricultural practices
• Human behavior
• Cultural practices
• Economic growth
• Trade

We have learned that most newly emergent infectious diseases will likely be caused by zoonotic pathogens, and those that cause major regional or global epidemics that impact the global economy will likely originate in Asia. This has been the case for the past 25 years, and demographic, societal, and economic trends suggest this trend will continue for the indefinite future (Table 1-4). Thus, it is projected that most of the world's population growth will occur in the cities of Asia in the next 25 years, and most of the world's economic growth will occur in Asian countries. Changes in animal husbandry and agricultural practices, combined with regional human behavior and cultural practices, and increased trade, will all facilitate the emergence of exotic zoonotic pathogens in a region where people from rural areas continue to migrate to large urban centers, and from which the movement of people, animals, and commodities increase the risk of dispersal via modern transportation and globalization.

Finally, if we hope to reverse the trend of emerging and reemerging infectious diseases, the movement of pathogens and arthropod vectors via modern transportation must be addressed. This problem has important political and economic implications, but if it is not dealt with, the long-term costs will far exceed those required to proactively address the problem. Local public health infrastructure, including laboratory and epidemiologic capacity, must be developed in all countries, but especially in those tropical developing countries where new diseases may emerge. Effective laboratory-based, active disease surveillance systems are needed in every country, as are public health personnel that can respond rapidly and effectively to control epidemic transmission before it spreads. We need new tools (vaccines, drugs, insecticides, diagnostic tests, etc.), and finally, we need to better understand the ecology of newly emerging diseases in order to develop effective prevention strategies; drugs or vaccines will likely not be developed for most of these pathogens.

WHY WE DO NOT UNDERSTAND THE ECOLOGICAL CONNECTIONS BETWEEN THE ENVIRONMENT AND HUMAN HEALTH: THE CASE FOR VECTOR-BORNE DISEASE

Durland Fish, Ph.D.[7]
Yale University

New challenges in addressing the global rise of human disease burden due to emerging and reemerging infectious diseases have resulted in increased interest in the environmental determinants of disease risk and the underlying ecological processes that are involved (Guernier et al., 2004; Morens et al., 2004). Vector-borne diseases are exquisitely sensitive to environmental change because of the complex ecological processes that regulate the distribution and abundance of vectors in the environment, their contact with humans, and often also nonhuman reservoir hosts of infection for vectors (Sutherst, 2004). No other infectious disease threats of humans exhibit such extensive dependence upon ecological complexity. Progress in successfully addressing the problem of global vector-borne disease will rely upon our willingness and ability to understand this complexity to the extent that intelligent mitigation measures can be planned and implemented. Such progress has been hampered by an imbalance of research disciplines and allocated resources that have been applied to the problem, which favors reductionistic disciplines over holistic or organismic disciplines. A new interdisciplinary approach to the understanding of vector-borne diseases is long overdue.

The science of understanding how organisms, including human pathogens, interact with the environment lies squarely within the discipline of ecology. Yet, in the United States, the formal discipline of ecology is divorced from the realm of biomedical sciences, both in academia and in government agencies. Evidence for this is supported by the absence of formal training programs in ecology within medical schools and schools of public health, the exclusion by MEDLINE of all five journals published by the Ecological Society of America from its database (only two are just now indexed from 2006), and the absence of a specific study section within the National Institute of Allergy and Infectious Diseases (NIAID) to peer review extramural research proposals in ecology. These, as well as other intellectual and cultural barriers, have effectively alienated the discipline of ecology from the mainstream of biomedical science.

Historically, successful vector-borne disease prevention has relied upon the management or elimination of vector populations within the environment. Early concrete examples include louse-borne epidemic typhus during World War II (Raoult et al., 2004), mosquito-borne malaria in the Tennessee Valley (Patterson, 2004), and tick-borne encephalitis in Siberia (Uspensky, 1999). Prior to our

[7]Yale School of Public Health; Yale School of Forestry and Environmental Studies; Yale Center for EcoEpidemiology.

dependence on insecticides for vector population control, an emphasis was placed on ecological studies of vectors as well as their parasites and predators for biological control. Wetlands and water management for mosquito control and malaria prevention depended on knowledge of habitat specificity for egg laying and larval development (Herms and Gray, 1944). The use of larvivorus fish for mosquito-borne arbovirus control depended on ecological knowledge of both predator and prey species (Geiger and Purdy, 1919). Host-specific hymenopterous parasitoids[8] were discovered and deployed against ticks for prevention of Rocky Mountain spotted fever (Smith and Cole, 1943). The rapid success of chemical insecticides for reducing a broad range of vector populations virtually eliminated the need for continued ecological studies. Consequently, the emphasis on ecological studies of vectors, which dominated vector-borne disease research activities in the early 20th century, has yet to be restored despite the serious limitations of insecticide dependence resulting from vector resistance and adverse environmental impact (Busvine, 1978; Patterson, 2004).

Rather than returning to ecological studies that would provide a better understanding of the complex relationships among vectors, reservoir hosts and pathogens, and the environment that could potentially reveal alternative intervention strategies for vector-borne diseases, research emphasis was placed instead on reductionistic disciplines that promised to develop novel approaches for vector population suppression or elimination, such as genetic manipulation (sterility, translocation, conditional lethal genes, etc.) (Baker et al., 1978; Busvine, 1978; Seawright et al., 1978) and interruption of the physiological processes involved in the conversion of host blood into egg production (Borovsky et al., 1993; Hagedorn, 1974; Shapiro, 1980). These basic genetic and biochemical studies dominated vector biology research for more than two decades (1970s and 1980s). The extensive research on reproductive physiology has yet to produce a product or strategy that would impact vector-borne disease and the only apparent outcome of genetic manipulation studies so far has been the controversial use of sterile insect releases (Molyneux, 2001; Enserink, 2007), a technology developed in the 1950s (Bushland et al., 1955).

Throughout the most recent decade, research in vector biology has been dominated by the discipline of molecular biology with the ultimate goal of manipulating vector populations through the introduction of genes that will reduce vector competence for specific pathogens, thereby eliminating the need for population suppression (Aldhous, 1993; Alphey et al., 2002; Kramer, 2004; Speranca and Capurro, 2007; Nene et al., 2007). This approach has received wide acceptance as a promising area of research and has benefited from generous support from the World Health Organization (WHO), the National Institutes of Health (NIH), and the Bill and Melinda Gates Foundation. While novel and extremely productive in understanding the molecular mechanisms of vector/pathogen interactions, this

[8]Parasitic wasps such as those commonly used for biological control of insect pests.

purely reductionistic approach is generally not viewed as having an immediate impact on vector-borne disease prevention (Spielman, 1994; Aultman et al., 2001; Enserink, 2002; Knols and Scott, 2002; Scott et al., 2002; Tabachnick, 2003; Toure and Manga, 2004). The many technical and logistic barriers to the practical implementation of transgenic vectors for disease control will likely delay the use of this technology for several more decades.

Such reductionistic and narrowly focused research agendas have contributed little to a broader understanding of the interactions between vectors and their physical or biological environment(s), which is essential for a complete understanding of vector-borne disease epidemiology and the development of other novel approaches for vector-borne disease prevention. Consequently, progress in our understanding of basic vector ecology has seriously lagged over many decades compared to that in fields of genetics, biochemistry, and molecular biology, which are the more traditional biomedical disciplines. Evidence for this lies in the relative paucity of vector-related publications in top-ranked ecology journals compared to top journals in traditional biomedical disciplines, and the progressive decline in the academically trained professional workforce specializing in vector ecology (see later discussion).

The scope of basic ecological processes that are poorly understood about vectors is extraordinary considering their importance in human disease transmission. Far more is known about how parasites, predators, and pathogens influence the abundance of insect species of agricultural importance than for most vectors of human disease (Service, 1983). The processes by which larval mosquitoes acquire nutrients in aquatic environments lag behind our knowledge of nutrient procurement for common aquatic stream insects (Merritt et al., 1992, 1996). Nutrient procurement is critical to the understanding of animal (and plant) ecology, yet significant studies have been conducted on only a very few of the more than 3,000 known mosquito species (Fish and Carpenter, 1982; Walker et al., 1988, 1991; Smith et al., 1998; Kaufman et al., 2006). Manipulation of the aquatic microfauna upon which mosquito larvae depend would seem to have tremendous potential for exploitation. However, this essential aspect of mosquito ecology is tragically understudied compared to the ongoing effort on transgenic vectors.

Natural mechanisms of animal population regulation were a prime topic in ecology during the 1950s and 1960s, but such studies applied to vector species are exceedingly rare (Evans and Smith, 1952; Southwood et al., 1972). Consequently, we know very little about the natural limits of population growth for vector populations and efforts to reduce population density of vectors are not based on knowledge of the regulatory processes already operative in nature. For holometabolous[9] insect vectors, such knowledge would direct intervention efforts to either larval or adult populations (Herms and Gray, 1944). For tick populations, knowledge of the relative importance of on-host versus off-host mortality

[9]Insects that undergo complete metamorphosis (larva, pupa, and adult stages).

would provide intelligent choices for host reduction or habitat modification in population suppression efforts (Fish, 1993). Ignorance concerning the procurement of carbohydrate resources by adult mosquitoes, an essential daily requirement compared to the few life-time blood meals a female needs for reproduction (Foster, 1995), prevents its exploitation for control or surveillance applications. The fact that larval habitats for most species of sand fly vectors of leishmaniasis, Carrion's disease, and phleboviruses are totally unknown to science (Tesh and Guzman, 1996; Feliciangeli, 2004) adds to the long list of astounding gaps in our basic knowledge of vector ecology.

In contrast, recent advances in genomic sciences have resulted in the ability to do complete genome sequencing for vectors and vector-borne pathogens (Gardner et al., 2002; Holt et al., 2002). These expensive projects are generally considered to be landmark accomplishments in the effort against global vector-borne diseases. While much basic research on vectors and pathogens is certain to ensue at the molecular level, there is no clear path to applications and its future impact upon vector-borne disease is uncertain (Enserink, 2002; Tabachnick, 2003). Basic research in all biological disciplines is essential for progress and innovation, but the disciplines of environmental science and ecology have not received a fair share of research support or recognition in biomedical science. This short-sightedness has limited our understanding of important connections between the environment and vector-borne disease and has weakened our overall effort to combat global vector-borne disease.

Imbalance in the total research effort among biological disciplines participating in vector-borne diseases is likely to continue for some time until a workforce is trained in interdisciplinary sciences that include ecology and environmental sciences. Concerns about this imbalance were articulated in a previous report published by the National Research Council in 1983 (NRC, 1983). Many subsequent articles and editorials on this subject have since appeared (Edman, 1993; Fish, 2001b; Gubler, 2001; Spielman, 2003, 2006), but with no apparent impact upon the status quo. Consequently, the workforce of academic professionals trained in the field aspects of vector biology and vector-borne disease has diminished to such a critical point that the capacity for such training is now endangered.

The recent epidemics of Lyme disease and West Nile virus in the United States have demonstrated our inability to effectively respond to vector-borne disease threats in our own backyard (literally). The traditional biomedical response of supporting basic research on diagnostics, therapeutics, and vaccines (Fauci et al., 2005) has had little, if any, impact on the natural courses of these epidemics (Fish, 2001a; Edman, 2005). Precise measures of environmental surveillance that identify populations at risk are inadequate for both diseases and prevention measures for both still depend primarily upon the controversial use of broad spectrum insecticides. Efforts to contain these epidemics through novel intervention directed at vectors or their reservoir hosts have been hampered by decades of inadequate basic research support on the environmental determinants of vector-

borne disease risk coupled with an inadequate workforce with interdisciplinary training. A recent effort by the Centers for Disease Control and Prevention (CDC) to support academic training specifically in response to these recent vector-borne disease threats has not been sustained (Fish, 2007).

New technologies that have tremendous potential for improving our understanding of relationships between the environment and vector-borne disease risk include remote sensing by Earth-orbiting satellites, geographic information systems, and spatial statistics (Fish, 1996). A constellation of satellites continuously acquires a broad range of environmental data on vegetation, water, atmosphere, land use, and weather on a global scale that are archived and available for research and applications in vector-borne diseases (Beck et al., 2000). Geographic information systems provide powerful tools for capturing and analyzing spatially explicit data (Ostfeld et al., 2005). New statistical methods are being developed to determine spatial patterns in environmental data that reveal relationships between cause and effect. These powerful new tools are just beginning to be applied to vector-borne diseases and other human health problems (Hay et al., 2000, 2007). Courses in these topics are now being taught in schools of public health as well as in the environmental sciences.

The bridging of environmental sciences and infectious disease epidemiology through this common technology offers some immediate hope for broadening the realm of scientific disciplines participating in vector-borne disease research (Fish, 2002). Such new technologies combined with the wealth of existing basic knowledge and theories of contemporary ecology will do much to improve our understanding of the complex relationships among the environment and vectors, pathogens, reservoir hosts, and, consequently, human health.

While other emerging disease threats, such as directly transmitted zoonotic pathogens and, to a lesser extent, directly transmitted human pathogens, also are dependent upon the environment, vector-borne diseases have the greatest potential for advancing the integration of ecology and environmental science into the mainstream of infectious disease epidemiology. Such integration is long overdue, and it will fill a significant void in the spectrum of biological disciplines currently contributing to human health.

ECOLOGY OF EMERGING VECTOR-BORNE PLANT DISEASES

Rodrigo P. P. Almeida, Ph.D.[10]
University of California, Berkeley

Individuals, populations, communities, and ecosystems are impacted by pathogenic organisms at different levels. During epidemics, high mortality may result in temporary or permanent perturbations of ecological networks within communities (Daszak et al., 2000). Alterations in community structure can significantly impact habitats driving ecosystem change. On the other hand, anthropogenic environmental changes may have catastrophic consequences to natural communities and populations, in some cases resulting in pathogen spill over to humans (e.g., Daszak et al., 2000; Patz et al., 2004; Power and Mitchell, 2004). Therefore, reducing the social, economic, and environmental impacts of diseases requires in-depth knowledge of pathogen, host, and vector biology and ecology.

The increasing number of emerging diseases and epidemics in recent decades has stimulated interest in understanding how new diseases arise and previously rare diseases increase in incidence. However, most of the research linking diseases with environmental change has been limited to human and animal pathogens (e.g., Daszak et al., 2000; Patz et al., 2004). In this essay I will argue that there are important connections and similarities between human diseases and plant diseases, focusing on those occurring in agricultural systems. I will also discuss similarities among vector-borne diseases and present an example of how the introduction of an invasive vector species has dramatically modified the ecology of a bacterial pathogen of previous limited importance. One of my main goals is to emphasize that much could be gained in our understanding of the ecology of vector-borne human and animal diseases from work done with agricultural systems, and vice versa. Unfortunately, to this date researchers in these two domains remain largely unaware of each other.

Emerging Vector-Borne Diseases

The number of disease epidemics has dramatically increased in recent years, as have the threat of emerging new diseases and the reemergence of other diseases. Although biological factors such as pathogen mutations have been demonstrated to be associated with recent epidemics (Anishchenko et al., 2006), surveys have suggested that most diseases can be linked to anthropogenic activities (Woolhouse and Gowtage-Sequeria, 2005). A growing body of literature exists on pathogens disseminated without the aid of vectors, such as primate viruses "jumping" to human hosts primarily due to bush meat hunting activities (Wolfe et al., 2005).

[10]Department of Environmental Science, Policy and Management.

Commerce, frequency and speed of transportation, invasive species, pesticide resistance, urbanization, climate change, and many other factors have been linked to emerging human diseases (Woolhouse and Gowtage-Sequeria, 2005). Anderson et al. (2004) conducted the only survey that systematically studied factors driving emerging plant diseases. Although introductions (56 percent) and weather (25 percent) were determined to be responsible for most emerging plant diseases, other factors were also found to be of importance. Interestingly, it was observed that viruses composed 47 percent of all emerging plant diseases. A similar trend was found in human emerging diseases (Woolhouse and Gowtage-Sequeria, 2005). Therefore, emerging human and plant diseases share driving factors, and approaches to control either one might be instructive to researchers working with both groups of pathogens.

Human Health, Environmental Change, and Plant Diseases

One of the challenges for this century will be to sustainably produce enough food for an exponentially growing world population. In 2006, 6.5 billion people inhabited the planet; the World Health Organization estimates that number will increase to 9 billion by 2050 (UN, 2007). Increasing crop yield with sustainable agricultural approaches that are not detrimental to the environment will be challenging. Approximately 40 percent of the world's yield is currently lost due to pests (pre- and post-harvest) (Agrios, 1997). Because malnutrition and poverty are directly linked to human health, sustainably producing increased quantities of food to populations around the world will be a global challenge for future generations.

The increased technological inputs for agriculture and the expanding scale of monocultures provide continual change in challenges for producing food. The expansion of agricultural land and increased pesticide, irrigation, and fertilizer use have been the major controllable inputs to increase crop yield. These alternatives have various detrimental effects on the environment and human and animal health. Furthermore, the long-term sustainability of these strategies is questionable due to the environmental impact of current agricultural technology (Altieri and Nichols, 2005). To increase farm land one must explore new regions, infiltrating into forest, grassland, or other habitats that may provide important ecosystem services. An increased human-natural vegetation interface may also result in new human and plant diseases, as pathogens may spill over from natural environments into new host organisms (Power and Mitchell, 2004). To reduce losses and increase yield per unit area, pesticides and fertilizers must be applied in increasing quantities. The environmental and health impacts of pesticides have been highly publicized. Fertilizers have a similar reputation, for example their role in driving toxic algal blooms caused by agricultural runoff in waters throughout the world (Gilbert et al., 2006). Because food production is tightly connected to human health, promoting sustainable agricultural practices

may reduce the impact of human pathogens from individual to population levels. Quantitatively determining the importance of plant health in the maintenance of a healthy human population and a sustainable environment would certainly be an interesting exercise.

Contrasting Plant and Animal Vector-Borne Diseases

A large diversity of organisms transmits plant pathogens. The most common vectors are insects, but mites, nematodes, and fungi are also important (Agrios, 1997). Insects transmit plant-pathogenic viruses, bacteria, fungi, nematodes, and protozoa. Among insects, sap-sucking hemipterans such as aphids, leafhoppers, planthoppers, and whiteflies are the major vectors. Of those, aphids are the most important group, as they are responsible for disseminating 70 percent of vector-borne plant viruses (Nault, 1997). Like vector-borne animal pathogens, vector-plant pathogen interactions can be classified based on several characteristics, such as requirement for circulation and/or propagation within vector and temporal characteristics of transmission and pathogen retention (Gray and Banerjee, 1999; Ng and Perry, 2004). Molecular determinants of vector transmission have been well explored for only a few plant disease systems compared to numerous animal disease systems (e.g., Gray and Gildow, 2003).

In addition to commonalities in transmission biology, the ecology of vector-borne diseases of plant and humans also share important similarities. Human vector-borne pathogens are generally categorized as the etiological agents of anthroponotic (human-centered) diseases such as malaria or zoonotic (having an animal reservoir) diseases such as Lyme disease, in relation to their ecology (Eldrige and Edman, 2000). This is an important distinction with epidemiological implications, as the involvement of animal hosts in addition to humans in zoonotic diseases must be well understood to devise control strategies to reduce pathogen spread. A similar scenario occurs with plant pathogens. Some insect vectors are host-specific (e.g., certain aphid species), whereas others can have broad host ranges (e.g., sharpshooter leafhoppers). The host range of plant pathogens is largely dependent on the degree of vector specificity required for efficient dissemination and on the host range of the vectors, as usually there are no other means of spread. Pathogens transmitted by species with narrow host ranges tend to be plant specific, whereas those transmitted by polyphagous insects may infect many plants and cause disease in several crops or weeds. Some phloem-limited bacteria (mollicutes) of maize, for instance, only colonize species in the plant genus *Zea* (maize and teosintes) and are spread by a few oligophagous leafhopper vectors that have co-evolved with those host plants (Nault, 1990). In contrast, insect transmission of the bacterium *Xylella fastidiosa* has low vector specificity, being transmitted by several sharpshooter leafhoppers and the more distantly related spittlebugs. Both of these insect groups tend to be polyphagous (Redak et al., 2004). In consequence, this pathogen could colonize hosts in at

least 94 species tested in 28 different plant families (Hill and Purcell, 1995a). Therefore, plant pathogens with a very narrow host range behave ecologically as anthroponotic diseases, whereas those with a wide host range behave more similarly to zoonotic ones.

Nevertheless, several relevant differences must be kept in mind when extrapolating concepts from animal to plant systems or vice versa. Host movement is significantly different in these systems. The host immune response of plants is very different from that of animals. Host genetic diversity may be high in animal systems, but is usually extremely low in crops. Moreover, the spatial, age structure, and population densities of crop plants differ dramatically from those of animals. In addition, plant disease epidemics often are not categorized as such unless at least thousands of individuals are infected. Therefore, host social networks, movement, immune response, and recovery are not considered of importance in plant epidemiology. Conversely, other approaches that incorporate the availability of large numbers of static susceptible hosts are more useful for plant systems.

The Plant Pathogenic Bacterium *Xylella fastidiosa* as a Case Study

The xylem-limited bacterium *X. fastidiosa* is present throughout the Americas and causes disease in many crops of economic importance, including Pierce's disease of grapevines (PD), almond leaf scorch (ALS), and citrus variegated chlorosis (CVC) (Purcell, 1997). *X. fastidiosa* is disseminated among plants by sharpshooter leafhoppers (Hemiptera: *Cicadellidae*) and spittlebugs (Hemiptera: *Cercopidae*), both of which specialize in feeding on the sap in plant xylem (water-conducting tissue) (Severin, 1949, 1950). Sharpshooter leafhoppers are considered the most important vectors in epidemics examined so far. Transmission is not specific, as different strains of *X. fastidiosa* are transmitted by different vector species. There is no transmission of *X. fastidiosa* from parent to offspring and no required latent period (Freitag, 1951; Purcell and Finlay, 1979). However, the bacterium multiplies in the foregut of vectors and is persistent in adult insects but is lost when immature insects molt (Hill and Purcell, 1995b; Purcell and Finlay, 1979). The inoculum of *X. fastidiosa* for plant inoculation is located in the canals leading to the sucking pump (cibarium) of the foregut of vectors (Almeida and Purcell, 2006; Purcell et al., 1979). Transmission efficiency, however, varies dramatically depending on the combination of host plant, bacterial strain, and vector species. The factor most clearly associated with transmission efficiency is bacterial densities within plants, with higher cell numbers resulting in increased transmission rates (Hill and Purcell, 1997). The ecology of *X. fastidiosa* shares similarities with complex zoonotic diseases with multiple host species. *X. fastidiosa* has a very wide host range (Hill and Purcell, 1995a), with colonization patterns varying from systemic pathogenic plant-strain associations to infections that die out over time (Purcell and Saunders, 1999). The host range of sharpshooter vectors can also be very large, with up to a few hundred plants

listed for certain species (Redak et al., 2004). Because *X. fastidiosa* has such a wide host range and is vectored without specificity by a group of insects that tends to be polyphagous, the resulting diseases have complex epidemiology.

Although *X. fastidiosa* has been present in California for over 100 years, only three large epidemics have occurred in that period of time, all of which were associated with grapevine hosts (PD) (reviewed by Hopkins and Purcell, 2002). The first one occurred in the late 1800s in Southern California, which decimated the incipient grape industry in the region. In the 1930s to 1940s an epidemic in the Central Valley associated with infected sharpshooters migrating from alfalfa fields was also of importance and resulted in several breakthroughs in our understanding of *X. fastidiosa* diseases by researchers at the time. In recent decades, however, the disease has been constantly present at low incidence in the wine grape growing coastal valleys of Napa and Sonoma. The third, and current, epidemic emerged after the introduction of a polyphagous invasive vector species, *Homalodisca vitripennis* (glassy-winged sharpshooter; Hemiptera: *Cicadellidae*) (Sorensen and Gill, 1996), into Southern California in 1989 (Blua et al., 1999). This invasive species is the driving factor of PD epidemics in Southern California and the southernmost region of the Central Valley. It is also responsible for several emerging *X. fastidiosa* diseases in California, such as oleander leaf scorch. I will discuss the current hypothesis on how *H. vitripennis* has increased the incidence of PD and how it may be responsible for the emergence of new diseases.

An Invasive Vector Driving the Emergence of a Rare Disease

PD epidemics have occurred in different regions of California, although much of Southern California and the Central Valley have been largely disease free in the last decades. The introduction of *H. vitripennis* into the state dramatically changed this scenario. In 1999, reports of PD outbreaks in the small wine region of Temecula Valley resulted in very high infection rates in just a few years after the epidemic began (Purcell and Feil, 2001); a similar situation occurred in Kern County, the southernmost area of the Central Valley, starting in 2000 (Hopkins and Purcell, 2002). A large area-wide monitoring, control, and research project is in place to address this problem and temporarily limit the distribution of *H. vitripennis*. The driving factor associated with the outbreak was the presence of extremely large numbers of *H. vitripennis* in vineyards. This vector overwinters in large number on citrus, up to thousands per plant, and has a larger dispersal range than that of typical sharpshooters. Therefore, it has been suggested that sheer numbers of an invasive species, not under biological control by native parasitoids, predators, or parasites, was the main factor driving the epidemic. Two cycles of pathogen spread could occur in this scenario, one of primary spread by infective vectors migrating from citrus to grape in early spring, and a second cycle with a new generation of vectors on grape that could acquire the pathogen from plants infected earlier in the year and transmit it to new plants during the

summer and fall. Because citrus does not serve as a host of *X. fastidiosa* strains causing disease in grape in the United States, it has been suggested that secondary spread is responsible for the outbreak, a hypothesis dubbed "vine-to-vine spread" (Hopkins and Purcell, 2002).

Although the ecological factors responsible for these outbreaks are not well understood, it is clear that large vector populations are an important component of this system. *H. vitripennis* is a poor vector of *X. fastidiosa* to grape when compared to other species (Almeida and Purcell, 2003). Therefore, its ecology and behavior seem to offset low transmission rates. In addition, *H. vitripennis* can infect dormant vines under field conditions, opening a new window of time for new infections, when infective insects on citrus may migrate to vines in warm days during the winter (Almeida et al., 2005). That may be important because *H. vitripennis* overwinters on citrus and moves to vines in early spring when young shoots are present, remaining in vineyards until the winter (Park et al., 2006). Furthermore, *H. vitripennis* can also inoculate the woody tissue of vines, which are closer to tissues of the plant that are not pruned off during the winter, possibly resulting in a larger number of infections late in the growing season that persist through to the next year (Almeida and Purcell, 2003). On the other hand, evidence demonstrated that some late infections recover by a yet to be determined plant physiological mechanism during dormancy (Feil et al., 2003). In summary, PD epidemics in the presence of *H. vitripennis* in California seem to be driven primarily by an invasive vector species that compensates for poor transmission efficiency by having large populations in and near citrus, and behavioral and ecological characteristics that promote pathogen spread within vineyards.

Emergence of New X. fastidiosa *Diseases*

There are many strains, or genetic clusters, of *X. fastidiosa* isolates (Schuenzel et al., 2005). Like other bacterial pathogens, the difficulty in defining species boundaries, or what a bacterial species is, has plagued the taxonomy of *X. fastidiosa*. Nevertheless, this is a pathogen primarily limited to the Americas, with only one exception in Asia (pear disease) and a report from Europe (Purcell, 1997). Diversity studies have focused on diseased crops, biasing sample collection towards pathogenic isolates occurring in a limited number of host plants (e.g., Hendson et al., 2001; Schuenzel et al., 2005). Pathogenicity studies, linking genetic diversity to host species susceptibility, have not been widely conducted, limiting the interpretation of molecular diversity results. Studies in the United States have provided an idea of *X. fastidiosa*'s diversity, primarily because it causes disease in many host plants in the country compared to Brazil, for example, where it is documented to cause disease in only three crops. If environmental samples from alternative, nonsymptomatic hosts were included in such surveys, it is reasonable to assume that a much larger number of genetic clusters could be identified. As previously mentioned, this is a pathogen transmitted by several

polyphagous sharpshooters with very wide plant host ranges. Thus, this pathogen has the potential to diverge and maybe have a high rate of genetic recombination among isolates in different environments and host plants.

Oleander leaf scorch (OLS) emerged in the mid-1990s in Southern California, and was tightly associated with the presence of *H. vitripennis* (Purcell et al., 1999). OLS is caused by what at the time was a new strain of *X. fastidiosa*. It is possible that this strain of *X. fastidiosa* was present in alternative host plants in the region, with limited dispersal by native vector species occurring in low numbers and without feeding preference for oleander; an alternative hypothesis is that this strain was an introduction into California. It can be hypothesized that *H. vitripennis*, present in high numbers and with feeding preference for oleander, could have acquired this strain from an alternative host and transferred it to oleander where it was maintained by the presence of susceptible hosts by a vector occurring in high number on the same host. A similar mechanism may be responsible for the emergence of *X. fastidiosa* diseases in many host plants in the presence of *H. vitripennis* in recent years, including mulberry, sweet gum, and olive (Wong et al., 2006).

A model for the emergence of new diseases after the introduction of a new vector into a region could be valid for vector-borne diseases in which pathogens are maintained in the environment in hosts of marginal epidemiological importance by vector species with little or no preference for feeding on humans or animals of interest. In this situation, pathogens have the opportunity to not only be maintained in endemic cycles, but also diverge and evolve into new strains, as different vector species may have associations with hosts of variable degrees of specificity. The introduction of a new vector species may result in pathogen acquisition from such cycles and its transfer to new disease cycles where it may be self-maintained (Figure 1-12).

Concluding Remarks

Human, animal, and plant vector-borne pathogens share several biological, ecological, and epidemiological similarities, but important differences exist. Unfortunately, scientists studying these systems rarely exchange ideas or are aware of each other's research contributions. Plant scientists, for example, could incorporate tools and concepts from studies on human diseases that integrate pathogen spatial and temporal distribution and molecular population genetics to develop disease spread and evolution models. On the other hand, plant systems allow large experiments to be conducted, with multiple hosts, vector species, and pathogen strains, which could be used to experimentally address ecological and evolutionary hypotheses on pathogen range and transmission efficiency. Finally, ecological hypotheses based on either system may be useful in building models that can be tested for the development of disease control strategies.

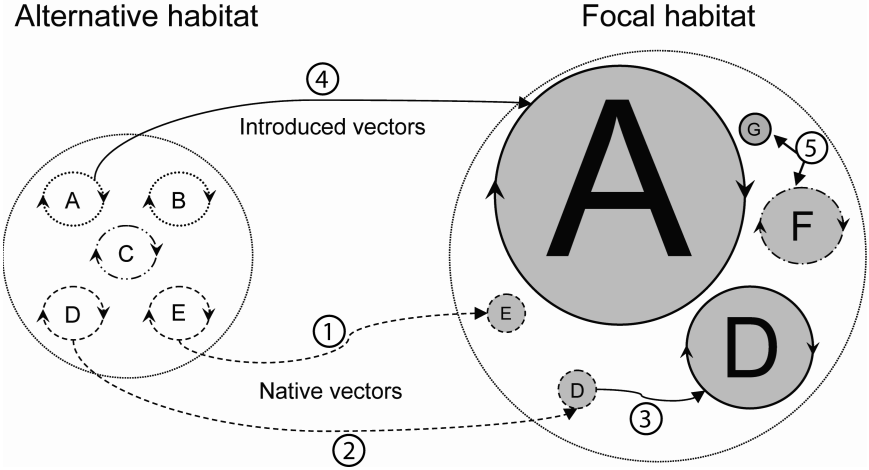

FIGURE 1-12 Model illustrating a hypothesis on how newly introduced vectors may drive new disease epidemics. On the left, different strains of a pathogen (labeled with different letters) are maintained in endemic disease cycles in alternative habitats by different vector species (different dashed-line circle borders). An introduced vector species is indicated by solid lines. On the right, shaded disease cycles occur on hosts of interest (e.g., humans, animals, plants), with circle size representing the dimensions of the epidemic. In this scenario, several pathogen strains are kept in alternative hosts indefinitely by native vectors, with occasional infection of a host of interest with epidemiological consequences (dead-end hosts; spread events [numbered circles] 1 and 2). However, an invasive vector could acquire the pathogen from otherwise dead-end hosts and establish a new epidemic disease cycle (event 3). An alternative may occur when introduced vectors acquire a pathogen from an endemic cycle and establish a new epidemic cycle in a new host, as illustrated with isolate A (event 4). An invasive vector may also introduce novel pathogens (event 5) to focal habitat which may (F) or may not (G) spread. It may also be possible for vectors to move pathogens from epidemic cycles to endemic ones, which would function as pathogen reservoirs for future epidemics.

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ECOLOGY OF DISEASE: THE INTERSECTION OF HUMAN AND ANIMAL HEALTH

Kenneth J. Linthicum, Ph.D.[11, 12]
USDA-ARS Center for Medical, Agricultural, and Veterinary Entomology

Seth C. Britch, Ph.D.[12]
USDA-ARS Center for Medical, Agricultural, and Veterinary Entomology

Assaf Anyamba, Ph.D.[13]
NASA Goddard Space Flight Center

Jennifer Small[13]
NASA Goddard Space Flight Center

Compton J. Tucker, Ph.D.[13]
NASA Goddard Space Flight Center

Jean-Paul Chretien, M.D., Ph.D.[14]
Department of Defense-Global Emerging Infections System

Ratana Sithiprasasna, Ph.D.[15]
Armed Forces Research Institute of Medical Sciences

Introduction

President John F. Kennedy stated in the early 1960s in reference to the world community, "For in the final analysis, our most basic common link, is that we all inhabit this small planet, we all breathe the same air, we all cherish our children's futures, and we are all mortal." More than 40 years later it is evident that on this small planet we also share the same animal and human vector-borne infectious diseases, as evidenced by the global spread of emerging diseases such as West Nile virus (Hayes et al., 2005).

Population growth, frontier agricultural expansion, and urbanization transform the landscape and the surrounding ecosystem, affecting climate, diseases,

[11]Corresponding author. Agricultural and Veterinary Entomology, 1600 S.W. 23rd Drive, Gainesville, FL 32608. Phone: (352) 374-5700; Fax: (352) 374-5850; E-mail: Kenneth.Linthicum@ars.usda.gov.
[12]Mosquito and Fly Research Unit.
[13]Biospheric Sciences Branch.
[14]Division of Preventive Medicine, Walter Reed Army Institute of Research.
[15]Department of Entomology.

and interactions between animals and humans. Additionally, the earth's oceans serve as the engine of the earth's climate and ecosystems, and they are closely linked (NASA, 1999). Epstein (2002) described how climate variability has a direct impact on infectious diseases, and increased disease transmission has been linked to the El Niño/Southern Oscillation (ENSO)-driven global climate anomalies (Checkley et al., 2000; Pascual et al., 2000). Outbreaks of vector-transmitted diseases such as Murray Valley encephalitis, bluetongue, Rift Valley fever (RVF), African horse sickness, Ross River virus disease, and malaria also have been associated with ENSO phenomena (Anyamba et al., 2006). In this work we briefly address (1) the effect of ecology on vector-borne disease, (2) the role of ecology and global climate in disease forecasting, and (3) the potential use of forecasting to reduce impact and limit spread of vector-borne disease.

Effect of Ecology on Vector-Borne Diseases

Several examples will be used to demonstrate that we share a global environment that strongly influences vector-borne disease transmission. First, we will describe how temperature plays a major role in the ability of *Aedes aegypti* to transmit dengue virus in Southeast Asia and possibly chikungunya virus in Africa. Second, we will describe how rainfall affects the ability of *Aedes* and *Culex* species to transmit RVF in sub-Saharan Africa. Third, we will describe how modifications to environment such as the construction of a dam and development of rice irrigation projects affect the ability of *Culex* species to transmit RVF in Mauritania and Senegal. During periods of elevated transmission there is a significantly increased risk of globalization of these and other arboviruses. The ability to predict periods of high risk might permit us to design better prevention, containment, or exclusion strategies to limit globalization of these and other pathogens.

Temperature

The *Ae. aegypti* mosquito is the principal vector of dengue viruses in Southeast Asia and most of the world's tropics. Dengue virus infection in humans can produce classical dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), and these diseases are endemic in Southeast Asia. DHF and DSS cases are reported to the Ministry of Health in Thailand by health care professionals, clinics, and hospitals; however, classic dengue fever is so common that it is not reported to the Ministry of Health. Cases of DHF represent approximately 1 percent of the total dengue infections (Gubler, 1988). The spatial distribution of DHF between years is highly variable and not well understood. The incidence of DHF is affected by temperature-induced variation in the vectorial capacity of mosquitoes (Watts et al., 1987) and other factors including the virus and human hosts. Vectorial capacity is dependent upon the extrinsic incubation

period of the virus in the mosquito vector the time from virus ingestion to the time that virus infects the salivary glands of the mosquito.

Global climate is significantly affected by the variability of sea surface temperatures (SSTs). Due to its location, the climate in Southeast Asia is influenced by the variability in both the Pacific and Indian Ocean temperatures. The impacts of the interannual variability in SSTs in these oceans is revealed in atmospheric circulation through outgoing longwave radiation (OLR) measurements. These satellite-derived measurements are a proxy indicator of cloudiness and hence rainfall. When expressed as anomalies with respect to reference long-term means, negative OLR anomalies in the tropics represent regions of precipitating clouds, whereas positive OLR anomalies are associated with dry conditions. Through such measurements the impacts of such phenomena as ENSO on global cloudiness and rainfall patterns can be observed. Various climate indicators, such as SST and OLR, can be measured with instruments on Earth-orbiting satellites (Anyamba et al., 2006). Large-scale variability in the climate regime producing either floods or droughts has the effect of enhancing the emergence and propagation of various disease vectors.

DHF incidence data, calculated per 100,000 population, were examined for all provinces in Myanmar (1981-1988) and Thailand (1979-1998) and compared to OLR anomalies over those two countries, respectively. There was a positive correlation, with a several-month lag, between OLR anomalies and reported DHF cases in 1987 and 1990-1991 in Myanmar, and in 1980, 1984-1985, 1987, 1988-1989, and 1997-1998 in Thailand. This indicates that hot and dry conditions, which characterize warm ENSO episodes in this region, preceded increased DHF occurrence (Linthicum, unpublished observations). Drought conditions in Southeast Asia are associated with the occurrence of warm ENSO episodes. The relationship between dengue incidence in Thailand and OLR anomalies is depicted in Figure 1-13. Dengue incidence data were obtained from Nisalak et al. (2003). Recently, warm dry conditions associated with a warm ENSO event in 2006-2007 led to elevated transmission, and the government of Indonesia reported that it considered the DHF outbreak in April 2007 to be "an extraordinary situation" (ProMed-Mail, 2007).

Chikungunya virus, which causes febrile illness and joint pain, is also transmitted by *Ae. aegypti* and other *Aedes* species in Africa. Epidemics of chikungunya fever affected hundreds of thousands of people in the Indian Ocean basin from 2005 to 2007, and the initial outbreak occurred in coastal Kenya in 2004 (Chretien et al., 2007). They demonstrated, analyzing satellite-derived normalized difference vegetation index (NDVI) data anomalies and rainfall measurements, that the chikungunya outbreak began in June 2004 following unusually dry and warm conditions, especially in May 2004 (Figure 1-14). Widespread water storage and elevated temperatures, thus increasing habitat for container-breeding *Ae. aegypti*, were thought to have contributed to this outbreak along the coast to Kenya.

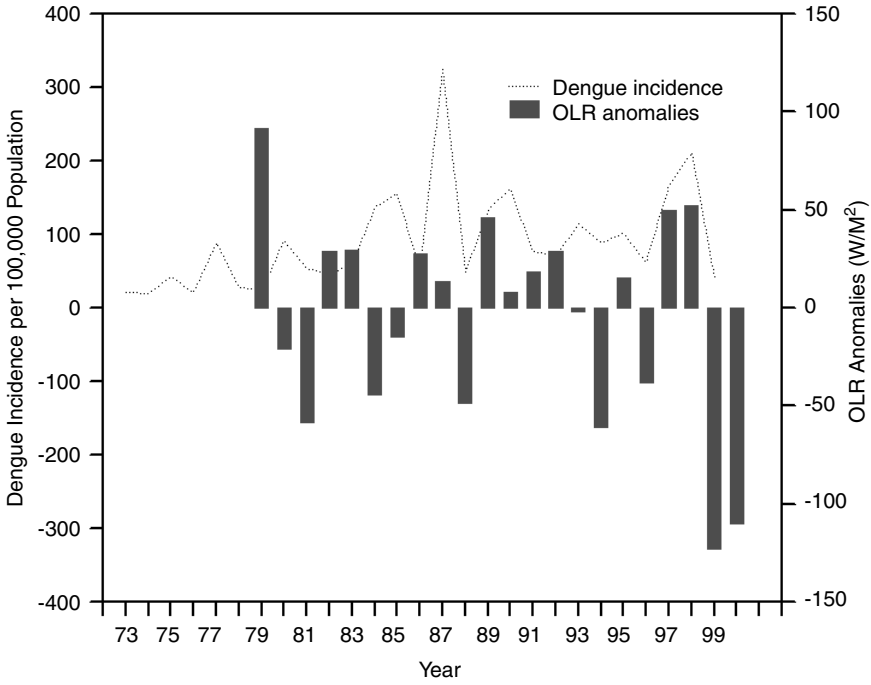

FIGURE 1-13 Dengue incidence calculated per 100,000 population for Thailand from 1973 to 1999 plotted against OLR anomalies from 1979 to 2000. Increase and peaks in dengue incidence is preceded by hot and dry periods indicated by positive OLR anomalies. Drought conditions in Southeast Asia are associated with the occurrence of warm ENSO episodes.

Rainfall

Outbreaks of RVF are known to follow periods of widespread and heavy rainfall associated with the development of a strong intertropical convergence zone over East Africa (Davies et al., 1985). Rainfall has a significant effect on the ability of various *Aedes* and *Culex* species to transmit RVF in sub-Saharan Africa. Excessive rainfall is thought to precipitate RVF virus outbreaks by flooding mosquito breeding habitats and producing a hatch of primary (RVF-vertically-infected *Aedes spp.*) and increase in secondary (*Culex spp.*) vectors (Linthicum et al., 1985). Additionally, there are strong linkages between ENSO events and outbreaks of RVF as depicted in Figure 1-15 (Linthicum et al., 1999). These linkages have permitted us to develop a monitoring and risk mapping system using a suite of satellite-derived measurements including SST, OLR, rainfall, and NDVI to map areas with potential for an RVF outbreak (Anyamba et al., 2002).

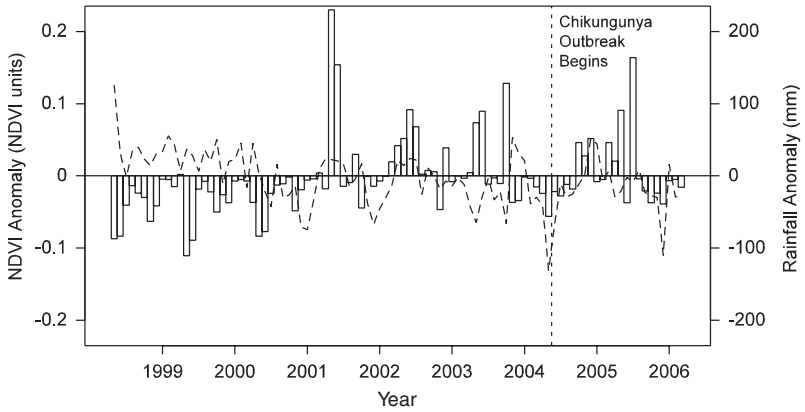

FIGURE 1-14 NDVI (dashed line) and rainfall anomalies (bars) for Lamu, Kenya, between 1998 and 2006. Negative NDVI and rainfall anomalies indicate unusually dry conditions.
SOURCE: Chretien et al. (2007).

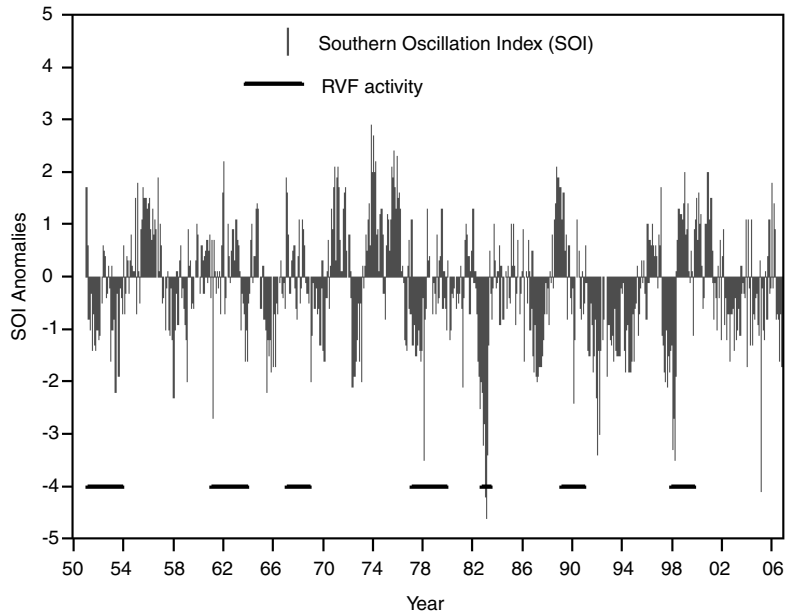

FIGURE 1-15 Southern Oscillation Index (SOI) anomalies between January 1950 and 2006. Periods of RVF activity in Kenya are depicted by black bars. Monthly SOI values are shown as standardized deviations based on the 1951-1980 mean. Outbreaks of RVF coincide with the negative phase of the SOI.

Environmental Modifications

An RVF virus epizootic/epidemic occurred in West Africa in the Senegal River basin in October and November 1987 (Jouan et al., 1988). Severe hemorrhagic disease was observed in the human population of the area, accompanied by a high incidence of abortion and disease in their livestock (Ksiazek et al., 1989). More than 200 strains of RVF virus were isolated from patients in the local hospital in Rooso, Mauritania.

Unlike other sub-Saharan RVF epizootics, which occurred during periods of very heavy rainfall, this outbreak occurred during a period of only average rainfall. Immediately prior to the outbreak, however, a series of ecological modifications to the Senegal River were instituted by the Mauritanian and Senegalese governments in cooperation with internationally sponsored programs. These modifications included the construction of two dams on the Senegal River (one at Diama in the delta region and one 1,200 km up river at Manantelli in Mali). Dams and dikes were also constructed along the river to control the natural flooding.

The controlled management of the river resulted in several dramatic changes in the ecology of the river basin. Although not designed to impound water, the Diama dam caused extensive flooding and vegetation growth in Senegal and Mauritania (Figure 1-16). This flooding peaked in October 1987, coinciding with the RVF outbreak (Linthicum et al., 1994). New areas of increased rice agricultural development were identified in satellite data along the river where we observed intense *Culex* species mosquito immature development as late as January 1988. Subsequent RVF activity in this region has tended to cluster along the Senegal River, indicating that landscape modification can contribute to endemism of diseases.

The association between RVF activity and alterations in the ecology of the region suggests that the development of new ecological habitats for potential *Culex* species mosquito vectors may have caused and/or enhanced the epidemic. Just as new technological developments, like irrigation projects, can enhance or in some cases cause disease outbreaks, new technologies, like satellite remote

FIGURE 1-16 Diama Dam on Senegal River (left), and resulting flooding (center) and vegetation development (right) in Mauritania in January 1988 after the closure of dam.

sensing, can now help in the prediction and possible control of these same outbreaks.

Knowledge of Global Climate and Ecology to Forecast Disease

ENSO is the most well-known phenomenon influencing global climate variability. Important aspects of interannual variability in global weather patterns are linked to ENSO. El Niño refers to a large-scale ocean-atmosphere climate phenomenon that is linked to periodic warming of SSTs across the central equatorial Pacific. Because of the large size of the Pacific Ocean, changes in SST patterns and gradients across the basin influence global atmospheric circulation.

There is building evidence suggesting links between ENSO-driven climate anomalies and infectious disease, particularly those transmitted by arthropods, such as Murray Valley encephalitis (Nicholls, 1986), bluetongue (Baylis et al., 1999), RVF (Linthicum et al., 1999), Ross River virus (Woodruff et al., 2002), dengue (Linthicum et al., unpublished), malaria (Bouma and Dye, 1997; Bouma et al., 1996), and chikungunya (Chretien et al., 2007).

The link established between ENSO and RVF, based on ecological studies (Anyamba et al., 2002), was used to establish in 2000 an operational RVF risk mapping system for sub-Saharan Africa, the Nile Valley, and the Arabian Peninsula.[16] The convergence of a Pacific El Niño event and the warming of the western Indian Ocean led to widespread and persistent rainfall in semiarid lands of East Africa. As described earlier under "Rainfall," flooding of mosquito habitats introduce RVF-infected *Aedes* mosquitoes into the environment and vegetation develops providing ecological microhabitats conducive for mosquito survival and propagation. Ocean temperatures, rainfall, and vegetation development are monitored and this information is used to produce RVF risk maps monthly.

In July to October 2006, anomalous positive SSTs in the equatorial east Pacific, indicative of the typical development of El Niño conditions, were observed. In October 2006, SSTs 2°C and 1°C above normal developed in the equatorial eastern Pacific Ocean and equatorial western Indian Ocean, respectively, suggesting the development of heavy rainfall in East Africa (Figure 1-17). Additionally, negative OLR anomalies were observed over the equatorial Indian Ocean and East Africa indicating elevated convective activity and heavy rainfall. The persistence of these conditions eventually produced extremes in global-scale climate anomalies similar to those observed in previous years, and RVF risk maps predicted the outbreak that occurred in December 2006 and continued until May 2007 (Anyamba et al., 2006).

[16]See http://www.geis.ha.osd.mil/RVFWeb/index.htm.

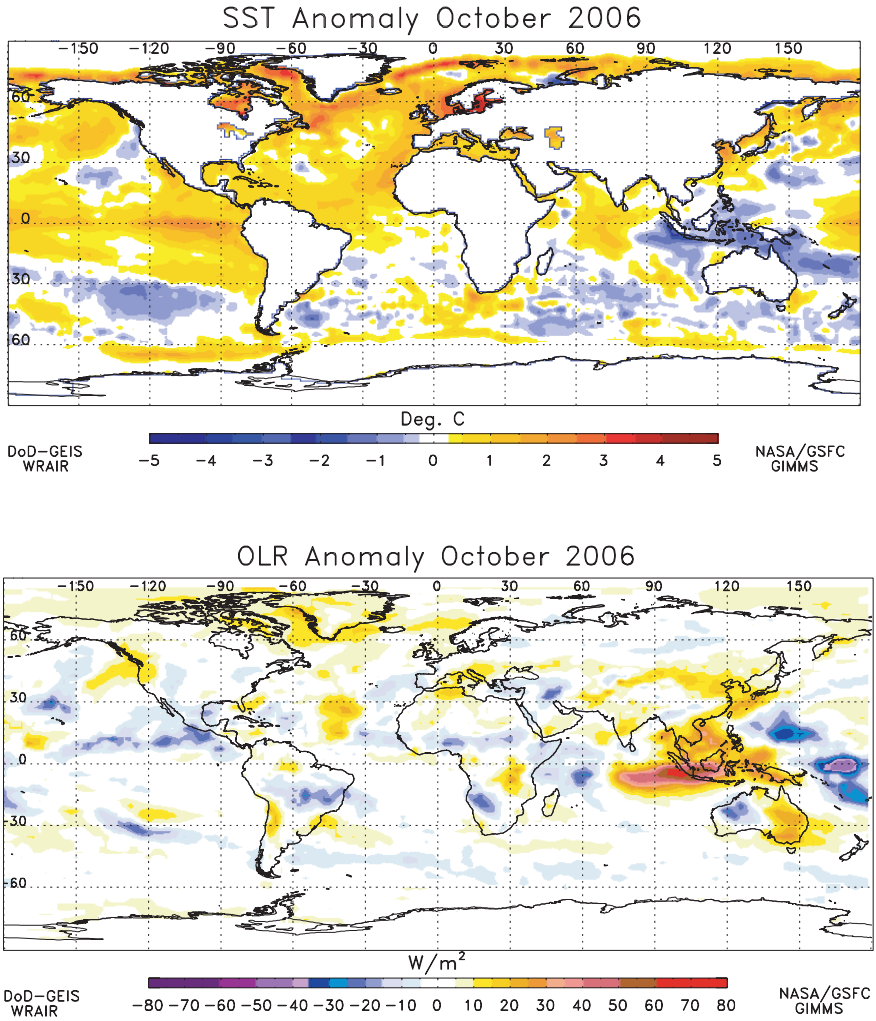

FIGURE 1-17 SST anomalies for October 2006 (top) and OLR anomalies for October 2006 (bottom). SSTs are shown in degrees Celsius, and OLR is shown as watts per square meter. Positive (negative) SST anomalies in the western equatorial Indian Ocean are associated with negative (positive) OLR anomalies in East Africa. The opposite patterns occur over Southeast Asia.
SOURCE: Anyamba et al. (2006).

Disease Forecasting to Reduce Impact and Limit Spread

The prediction of the 2006-2007 RVF in East Africa and subsequent observations of response activities can give us an insight about how disease forecasting based on ecological conditions might help reduce the impact and spread of vector-borne diseases. Between September and November 2006, several alerts were provided to the international public health and agricultural communities, presentations were made in scientific forums, and news media were notified. The World Health Organization (WHO) notified appropriate representatives and officials in East African countries, and the Food and Agriculture Organization (FAO) issued an Emergency Prevention System for the Transboundary Animal Diseases (EMPRES) Watch in November 2006 (FAO, 2006). The EMPRES program provides, at an international level, an overall initiative for coordination of the RVF-Early Warning System, where data integration and analysis are performed before being disseminated to recipient countries, international organizations, and key stakeholders in the form of RVF bulletins and risk assessments. Regional task forces in Kenya were alerted, and field assessment was promoted in flooded areas.

The U.S. Army Research Unit based in Nairobi, Kenya (USAMRU-K) and the Kenya Medical Research Institute were alerted and started mosquito surveillance of mosquitoes in northeastern Kenya in flooded areas in November. RVF was isolated in December in conjunction with the first report of human cases. WHO, FAO, the government of Kenya, USAMRU-K, and the U.S. Centers for Disease Control and Prevention (CDC) mobilized response teams and resources in an attempt to identify the extent of the outbreak and provide control and containment operations. The government of Kenya banned slaughter of livestock in eastern and northeastern Kenya and started a public education campaign, and various organizations became involved in distribution of mosquito nets and personal protection measures, application of insecticides to mosquito habitats, domestic animal vaccination, and other control measures. The response to the 2006-2007 RVF outbreak was 1 to 1.5 months earlier than that which occurred in the 1997-1998 outbreak in the same part of Africa. It appears likely that the early warning contributed to a reduced impact of the disease and limited its geographical spread.

Advance knowledge of an RVF, dengue, or chikungunya outbreak in their endemic areas might be used to prevent globalization of the disease by assessing favorable conditions in other parts of the world where suitable mosquito vectors, potential domestic animal hosts, and likely habitats for disease exist. Knowledge of vector-borne disease activity in endemic areas can be used to trigger monitoring of trade, and movement of people and mosquitoes on aircraft between sites of disease outbreaks and other places in the world where introduction might occur. For example, early planning and active monitoring of ships and containers arriving from endemic ports and dispersed into the wide network of inland

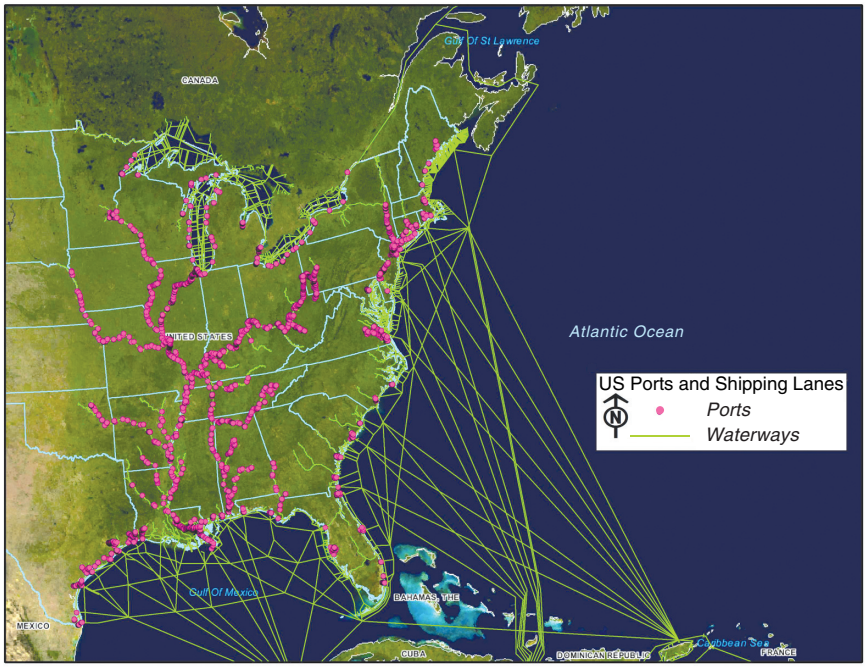

FIGURE 1-18 Shipping lanes entering eastern U.S. ports and inland container facilities from offshore destinations. The figure is based on data from the U.S. Bureau of Transportation Statistics.

container facilities in the United States could potentially detect and eliminate introduced RVF threats before these threats reach suitable human, animal, or mosquito hosts (Figure 1-18). Early detection of RVF in human or mosquito hosts could provide early warning in the United States or other nonendemic regions or countries before ecological conditions become optimal for elevated mosquito populations, thus permitting targeted implementation of mosquito control, animal quarantine, and vaccine strategies in time to reduce or prevent animal and human diseases (Linthicum et al., 2007). Additionally, the RVF risk mapping system in operation in Africa could be adapted for use in the United States and neighboring countries.

Conclusions

Understanding the ecology of vector-borne viral disease transmission is critical and can provide linkages between the environment, including climate, and mosquito densities. These linkages can be evaluated with spatial and temporal

statistics, generating risk maps to inform the community at risk. This information can provide a powerful tool to public health and agricultural authorities, enabling them to target disease surveillance/control efforts, minimize cost of surveillance over large areas, design better containment or exclusion strategies to limit disease spread, and predict risk and permit anticipation of globalization of vector-borne diseases.

CLIMATE CHANGE AND HEALTH: GLOBAL TO LOCAL INFLUENCES ON DISEASE RISK[17]

Jonathan A. Patz, M.D., M.P.H. [18]
University of Wisconsin

Sarah H. Olson[18]
University of Wisconsin

The World Health Organization has concluded that the climatic changes that have occurred since the mid 1970s could already be causing annually over 150,000 deaths and five million disability-adjusted life-years (DALY), mainly in developing countries. The less developed countries are, ironically, those least responsible for causing global warming. Many health outcomes and diseases are sensitive to climate, including: heat-related mortality or morbidity; air pollution-related illnesses; infectious diseases, particularly those transmitted, indirectly, via water or by insect or rodent vectors; and refugee health issues linked to forced population migration. Yet, changing landscapes can significantly affect local weather more acutely than long-term climate change. Land-cover change can influence micro-climatic conditions, including temperature, evapo-transpiration and surface run-off, which are key determinants in the emergence of many infectious diseases. To improve risk assessment and risk management of these synergistic processes (climate and land-use change), more collaborative efforts in research, training and policy-decision support, across the fields of health, environment, sociology and economics, are required.

In the past half-century, global mean temperature has risen by 0.6°C, sea level has risen by a mean of 1-2 cm/decade, and ocean heat content has also measurably increased (Figure 1-19). The rate of change in climate is faster now than in any period in the last 1,000 years. Between 1990 and 2100, according to

[17]Reprinted with permission from Maney Publishing. Copyright Liverpool School of Tropical Medicine, 2006. This article was originally published in *Annals of Tropical Medicine and Parasitology* 100(5-6):535-549 (2006). See http://www.maney.co.uk/journals/atmp and http://www.ingentaconnect.com/content/maney/atmp.

[18]Center for Sustainability and the Global Environment (SAGE), the Nelson Institute and Department of Population Health Sciences.

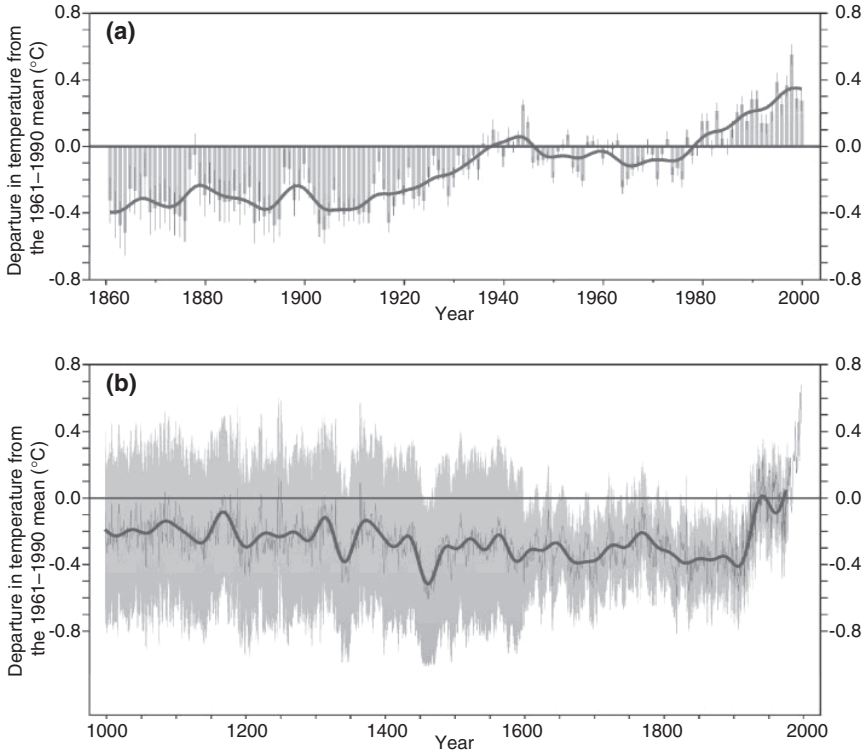

FIGURE 1-19 Variations in the mean surface temperatures recorded (using thermometers) across the planet in the past 140 years (a) and (using a combination of tree-ring, coral, and ice-core analysis and, for recent decades, thermometers) in the northern hemisphere over the past 10,000 years (b). These graphs are reprinted here with permission of the Intergovernmental Panel on Climate Change (IPCC, 2001a).

the United Nations Intergovernmental Panel on Climate Change (IPPC), mean global temperatures will increase by 1.4-5.8°C and sea level will rise by 9-88 cm, with mid-range estimates of 3°C and 45 cm, respectively (Houghton et al., 2001). However, additional greenhouse-gas releases from warmer oceans (CO_2) and warmer soils (CO_2 and methane) will increase the estimated warming from human-induced emission another 2°C by the end of the century (Torn and Harte, 2006). Extremes of the hydrological cycle (e.g., floods and droughts) are expected to accompany the global warming.

Non-Infectious Diseases

Heat Waves

Extremes in air temperature, both hot and cold, are associated with higher levels of human morbidity and mortality than seen within an intermediate or 'comfortable' range of temperatures. The relationship between temperature and mortality is typically 'J-shaped,' indicating asymmetry, with a steeper slope at higher temperatures (Curriero et al., 2002). In the U.S.A., heat waves are more deadly than hurricanes, floods and tornadoes combined.

The extreme heat wave that hit much of Europe in 2003 is estimated to have killed up to 45,000 people in just 2 weeks (Walker, 2004; Kosatsky, 2005). The summer of 2003 was probably Europe's hottest summer in >500 years, with mean temperatures 3.5°C above normal (Beniston, 2004; Luterbacher et al., 2004; Schar et al., 2004). Although the level of temperature-related mortality seems to vary with geographical location, the temperature-mortality relationship found in European and North-American cities appears similar to that in São Paulo, a developing Brazilian city with sub-tropical conditions (Gouveia et al., 2003). The results of the relevant studies conducted so far indicate a clear vulnerability to heat in the relatively cool, temperate regions, and tropical regions may show similar sensitivity as location-specific temperatures rise.

Built environments markedly modify the intensity of ambient temperatures, in a phenomenon known as the 'urban heat island effect.' Black asphalt and other dark surfaces (on roads, parking lots or roofs) reduce albedo (reflectivity) and consequently increase the heat retention of the surface. In addition, the loss of trees in urban areas diminishes the cooling effect of evapotranspiration. During heat waves, when stagnant atmospheric conditions may persist, air pollution often compounds the effects of the elevated air temperatures (Frumkin, 2002). Urban areas may therefore suffer from both global and localized warming.

Severe Storms and Rise in Sea Level

Floods, droughts and extreme storms have claimed millions of lives during the recent past, and have adversely affected the lives of many more people. On average, disasters killed 123,000 people world-wide each year between 1972 and 1996. Africa suffers the highest rate of disaster-related deaths, even though 80 percent of the people affected by natural disasters are in Asia (Loretti and Tegegn, 1996). Disaster-related mental disorders, such as post-traumatic-stress disorder (PTSD), may substantially affect population well-being, depending upon the unexpectedness of the impact, the intensity of the experience, the degree of personal and community disruption, and the long-term exposure to the visual signs of the disaster.

Hurricanes only form in regions where sea surface temperatures exceed

26°C, and sea-surface warming by slightly more than 2°C intensifies hurricane wind speeds by 3-7 m/s (or 5 percent-12 percent) (Knutson et al., 1998). Records indicate that sea-surface temperatures

have steadily increased over the last 100 years, and more sharply over the last 35 years. The highest mean sea-surface temperatures ever recorded occurred between 1995 and 2004 (Trenberth, 2005). During the first half of this period, there was a doubling in the overall hurricane activity in the North Atlantic and a five-fold increase in such activity in the Caribbean (Goldenberg et al., 2001). The North Atlantic Oscillation (NAO) was in its warm phase at this time, making it difficult to attribute the extra hurricanes to the long-term trends in warming. Sea-surface temperature is, however, correlated with hurricane intensity, and the frequency of higher-category storms has increased in many other parts of the world (Figure 1-20).

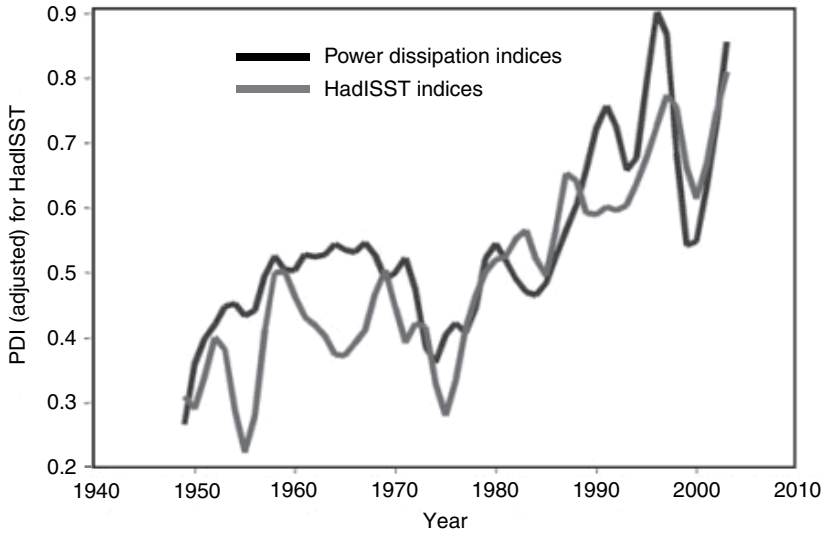

FIGURE 1-20 The increasing trend in strong tropical storms seen over the last 50 years. For the plot, the power dissipation indices (PDI) for the Atlantic Ocean and Western Pacific were adjusted (by multiplying them by a factor of 5.8610213) so that they could be plotted on the same y-axis as the HadISST. The annual HadISST indices—combined measures of sea-surface temperatures and sea-ice concentrations—were averaged between 30ºS and 30ºN, and the lines for both variables were smoothed (Emanuel, 2005). The PDI has nearly doubled over the past 30 years. Reproduced from a figure created by Emanuel (2005), with the permission of Nature Publishing.

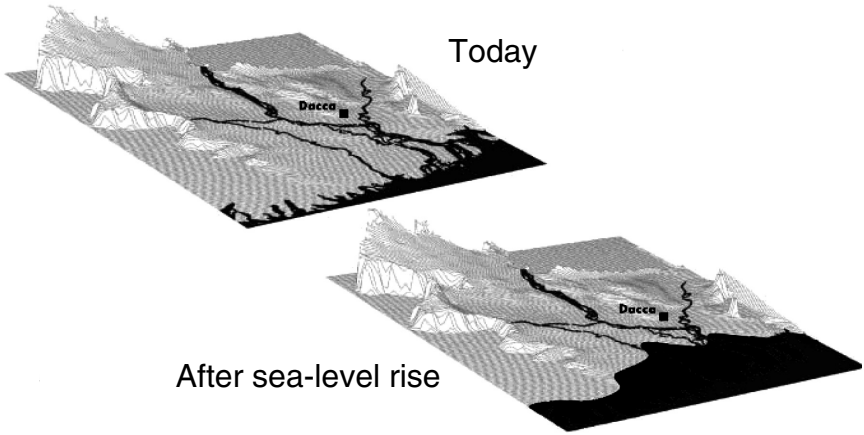

FIGURE 1-21 The potential impact of sea-level rise on Bangladesh. If sea levels rose by 1.5 m, 17 million people (15 percent of the population) and an area of 22,000 km^2 would be affected. This figure is adapted from one produced by the United Nations Environment Programme (Patz, 2005) and is reprinted here with the permission of John Wiley and Sons.

Rise in sea level Warmer oceans also cause sea levels to increase, primarily as the result of the thermal expansion of salt water. Even if the mid-range predictions of climate change are correct and sea levels in the 2080s are, on average, 'only' 40 cm higher than the current values, the coastal regions at risk of storm surges will become much greater and the population at risk will increase from the current 75 million to 200 million (McCarthy et al., 2001). Rising sea levels will result in the salination of coastal freshwater aquifers and the disruption of stormwater drainage and sewage disposal. A case study for Bangladesh (Nicholls and Leatherman, 1995) indicates that >15 percent of the total population would be adversely affected by a 1.5-m rise in sea level (Figure 1-21).

Droughts That droughts cause famines is well recognized. Malnutrition remains one of the largest health crises world-wide, with approximately 800 million people—close to half residing in Africa—currently undernourished (WHO, 2002). Droughts and other climate extremes not only have direct impacts on food crops but can also indirectly influence food supply by altering the ecology of plant pathogens. While projections of the effect of climate change on global food-crop production appear to be broadly neutral, such change will probably exacerbate regional inequalities in the food supply (Parry et al., 2004). As there is a breakdown in sanitation as water resources become depleted, droughts can also increase the incidence of diarrhoea and diseases, such as scabies, conjunctivitis and trachoma, associated with poor hygiene (Patz and Kovats, 2002).

Air Quality and Climate

Air temperature affects the problems posed by air pollutants. Ground-level ozone smog tends to become worse with increasing air temperature but the relationship is nonlinear, with a strong correlation only seen at temperatures above 32°C. In their recent study, Bell et al. (2006) predicted that, because of global warming, the mean number of days exceeding the health-based "8-h ozone standard" will increase by 60 percent in the eastern U.S.A.—from 12 to almost 20 days per summer—by the 2050s.

Pollen levels in the air may also increase with global warming, as higher levels of CO_2 promote growth and reproduction by many plants. When, for example, ragweed (*Ambrosia artemisiifolia*) plants were experimentally exposed to high levels of CO_2 they increased their pollen production several-fold; this response is perhaps part of the reason for rising levels of ragweed pollen observed in recent decades (Ziska and Caulfield, 2000; Wayne et al., 2002). Ziska et al. (2003) found that ragweed grew faster, flowered earlier and produced more pollen in urban locations than in rural locations, presumably because of the relatively high air temperatures and CO_2 levels in the urban areas.

Finally, if the frequency of flooding increases, significant exposure to moulds may also pose respiratory health risks during the post-flood clean-ups (Patz et al., 2001).

Infectious Diseases

Water- and Food-Borne Diseases

Water shortages, as mentioned above, contribute to diarrhoeal disease through poor hygiene, especially in poor countries. On the other hand, flooding can contaminate drinking water with run-off from sewage lines, containment lagoons (such as at animal-feeding operations), or conventional (non-point-source) pollution from across watersheds.

The parasites in the genus *Cryptosporidium* are usually associated with domestic livestock but can contaminate water intended for human consumption, especially during periods of heavy precipitation. In 1993 a cryptosporidiosis outbreak in Milwaukee, which killed more than 50 people and potentially exposed over 400,000 more to *Cryptosporidium*, coincided with unusually heavy spring rains and run-off from melting snow (Mac Kenzie et al., 1994). A review of outbreaks of any water-borne disease in the U.S.A. over a 50-year period demonstrated a distinct seasonality, a spatial clustering in the key watersheds, and a strong association with heavy precipitation (Curriero et al., 2001).

Certain food-borne diseases are also affected by fluctuations in temperature. Across much of continental Europe, for example, an estimated 30 percent of reported cases of salmonellosis occur when air temperatures are 6°C above the

mean (Kovats et al., 2004). In the U.K., the monthly incidence of food poisoning is strongly correlated with air temperatures in the previous 2-5 weeks (Bentham and Langford, 1995).

Coastal waters One type of phytoplankton, the dinoflagellates, thrive in warm waters with adequate nitrogen, and they are the primary component of toxic "red tides." They can cause acute paralytic, diarrhoeic, and amnesiac poisoning in humans, as well as extensive die-offs of fish and shellfish and the marine mammals and birds that depend on the marine food-web. The frequency and global distribution of toxic algal incidents and the incidence of human intoxication from algal sources appear to be increasing (Van Dolah, 2000).

Vibrio species also proliferate in warm marine waters. Zooplankton that feed on algae can serve as reservoirs for *Vibrio cholerae* and other enteric pathogens of humans. In Bangladesh, cholera follows the seasonal increase in sea-surface temperatures that can enhance plankton blooms (Colwell, 1996). During the El Niño event in 1997-1998, winter temperatures in Lima increased to >5°C above normal, and the number of daily admissions for diarrhoea rose to levels that were twice as high as recorded, over the same months, in the previous 5 years (Checkley et al., 2000). Although long-term studies of the El Niño Southern Oscillation (ENSO) have shown a consistent association with cholera and other diarrhoeal diseases, the oscillation appears to have played an increasing role in cholera outbreaks in recent years, perhaps because of concurrent climate change (Rodo et al., 2002). A detailed understanding of the inter-annual cycles of cholera and other infectious diseases, however, requires the combined analyses of both environmental exposure and the host's intrinsic immunity to a disease. When they considered these factors together, Koelle et al. (2005) found that the inter-annual variability seen in cholera in Bangladesh was strongly correlated, across periods of <7 years, with sea-surface temperatures in the Bay of Bengal, ENSO and the extent of flooding in Bangladesh, and, across longer periods, with the monsoon rains and the discharge of the Brahmaputra river.

Vector-Borne Diseases

As the human pathogens transmitted indirectly by insect or rodent vectors spend considerable time outside of their vertebrate hosts, they may easily be affected by environmental conditions. The range of suitable climatic conditions within which each vector-borne pathogen and its vector can survive and reproduce is limited. The incubation time of a vector-borne infective agent within its vector is typically very sensitive to changes in temperature and humidity (Gubler et al., 2001). Table 1-5 shows some examples of temperature thresholds.

Malaria Between 700,000 and 2.7 million people—mostly children in sub-Saharan Africa—die each year of malaria (www.cdc.gov/malaria), and, thanks

TABLE 1-5 Temperature Thresholds of Some Human Pathogens and Their Vectors[a]

	Pathogen			Vector	
Disease	Name	Threshold (ºC) Minimum for Transmission	Maximum for Survival	Name	Lower Threshold (ºC)
Malaria	*Plasmodium falciparum*	16-19	33-39	*Anopheles* mosquitoes	8-10 for biological activity
	P. vivax	14.5-15	33-39	*Anopheles* mosquitoes	8-10 for biological activity
Chagas disease	*Trypanosoma cruzi*	18	38	Triatomine bugs	2-6 for survival, 20 for biological activity
Schistosomiasis	*Schistosoma spp.*	14.2	>37	Snails (*Bulinus* and others)	5 for biological activity, 25±2 as optimum
Dengue fever	Dengue virus	11.9	NYD	*Aedes* mosquitoes	6-10 for biological activity
Lyme disease	*Borrelia borgdorferi*	NYD	NYD	*Ixodes* ticks	5-8 for biological activity

[a]The thresholds shown assume optimum humidity (vector survival tends to decrease rapidly as dryness increases) and differ considerably within and between species. This table is based on one drawn up by the Intergovernmental Panel on Climate Change (Anon., 2001), using data from various studies (Purnell, 1966; Pfluger, 1980; Curto de Casas and Carcavallo, 1984; Molineaux, 1988; Rueda et al., 1990), and is published here with permission of the Cambridge University Press. NYD, Not yet determined.
SOURCE: Reprinted from IPCC (2001b).

to climate and land-use change, drug resistance, ineffective control efforts, and various socio-demographic factors, there is no evidence that malaria-attributable mortality is falling. Malaria is an extremely climate-sensitive tropical disease, making the assessment of the potential change in malarial risk, caused by past or projected global warming, one of the most important topics in the field of climate change and health (Patz et al., 2005). The incidence of malaria varies seasonally in highly endemic areas, and malaria transmission has been associated with temperature anomalies in some African highlands (Zhou et al., 2005). In the Punjab region of India, excessive monsoon rainfall and the resultant high humidity have been recognized for years as major factors in the occurrence of malaria epidemics. More recently in the region, the frequency of malaria epidemics was observed to increase approximately five-fold during the year following an El Niño event (Bouma and van der Kaay, 1996). In Botswana, Thomson et al. (2006) recently

showed that indices of El Niño-related climate variability can serve as the basis of malaria-risk prediction and early warning.

Highland malaria Air temperatures decrease by a mean of 6°C for every 1,000 m gained in elevation. In areas where human malaria is endemic, this effect usually precludes the transmission of malarial parasites at high altitudes, partly because the parasites cannot produce sporozoites in mosquitoes living at low temperatures. The minimum temperatures for the sporogony of *Plasmodium falciparum* and *P. vivax*, for example, are approximately 18°C and 15°C, respectively (Figure 1-22). As seen in the African highlands (Bodker et al., 2003), mosquito abundance tends to decrease with increasing altitude. Global warming is likely to result in an increase in the altitudes at which no malaria transmission occurs. In Africa, Tanser et al. (2003) estimated that the risk of exposure to malaria, measured in person months, will be 16 percent–28 percent higher in 2100 than at present. Having compared climate suitability maps for malaria in the topographically diverse country of Zimbabwe, Ebi et al. (2005) concluded that the warming predicted from global-climate models could make the country's entire highland area climatologically suitable for malarial transmission by 2050. The highland areas of Africa that are not currently endemic for malaria but are, as the result of global warming, at high risk of becoming areas where transmission occurs are shown in Figure 1-23. Pascual et al. (2006) recently reported that the East African highlands had generally become warmer since 1950, over a period in which malaria incidence had also increased. There are well-recognized non-linear and threshold responses of malaria to the effect of regional temperature changes. In a form of biological 'amplification,' the response of mosquito populations to warming can be more than an order of magnitude larger than the measured change in temperature, an increase of just 0.5°C translating into a 30 percent–100 percent increase in mosquito abundance (Pascual et al., 2006). In the African highlands, where mosquito populations are relatively small compared with those in lowland areas (Minakawa et al., 2002), such biological responses may be especially significant in determining the risk of malaria.

Malaria and local effects on climate from land-use change Changing landscapes can significantly affect local climate more acutely than long-term global warming. Land-cover change, for example, can influence the micro-climatic conditions, including temperature, evapo-transpiration and surface run-off (Foley et al., 2005), that are key to determining mosquito abundance and survivorship. In Kenya, Afrane et al. (2005) observed that open treeless habitats had warmer mean midday temperatures than forested habitats, and that deforestation also affected indoor hut temperatures (Figure 1-24). As a result, the gonotrophic cycle of female *Anopheles gambiae* s.l. during the dry and rainy seasons was found to be 2.6 days (52 percent) and 2.9 days (21 percent) shorter, respectively, in the deforested sites than in the forested. Similar findings have been documented in

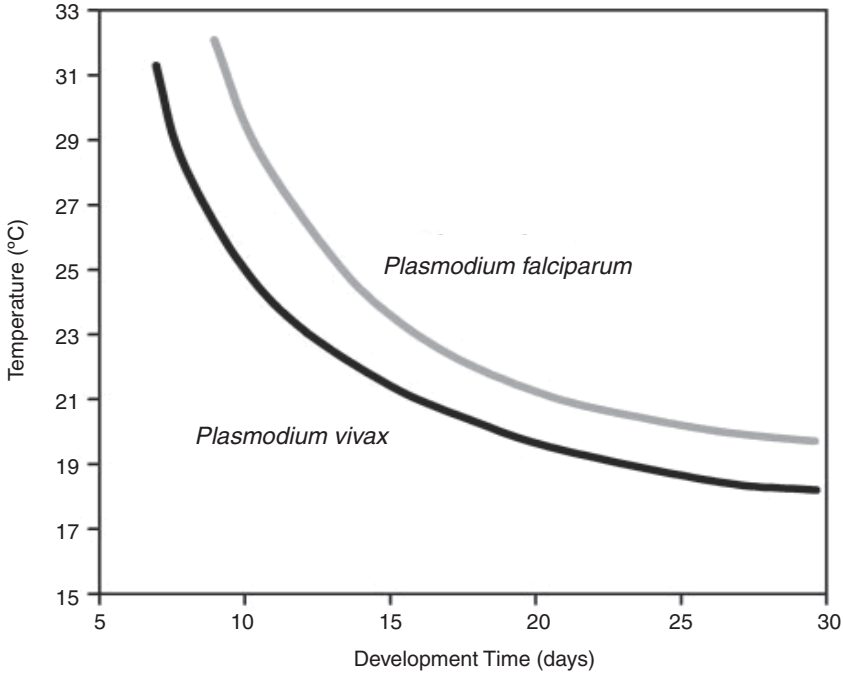

FIGURE 1-22 As this graph produced by MacDonald (1957) illustrates, air temperature has a marked effect on the extrinsic incubation periods (EIPs—the times taken by the parasites to produce sporozoites in their mosquito vectors) of *Plasmodium falciparum* and *P. vivax*. As air temperatures rise, EIP shortens and so infected mosquitoes become infectious sooner. At or below minimum temperature thresholds—of about 18°C for *P. falciparum* and 15°C for *P. vivax*—no sporogony occurs and the infected mosquitoes never become capable of transmitting the parasites.
SOURCE: Reprinted with permission from Oxford University Press.

Uganda, where temperatures in communities bordering cultivated fields have been found higher than those in communities adjacent to natural wetlands, and the number of *An. gambiae* s.l./house has been found to increase with increasing minimum temperature, after adjustment for potentially confounding variables (Lindblade et al., 2000). In Kenya, mosquito breeding sites in farmland have been found to be relatively warm and this warmth speeds up the development of the immature insects (Munga et al., 2006). Increased canopy cover in western Kenya is negatively associated with the presence of larval *An. gambiae* s.l. and *An. funestus* in natural aquatic habitats (Minakawa et al., 2002). In artificial pools, survivorship of the larvae of *An. gambiae* s.s. in sunlit open areas was 50-fold higher than that in forested areas, and also related to assemblages of predatory

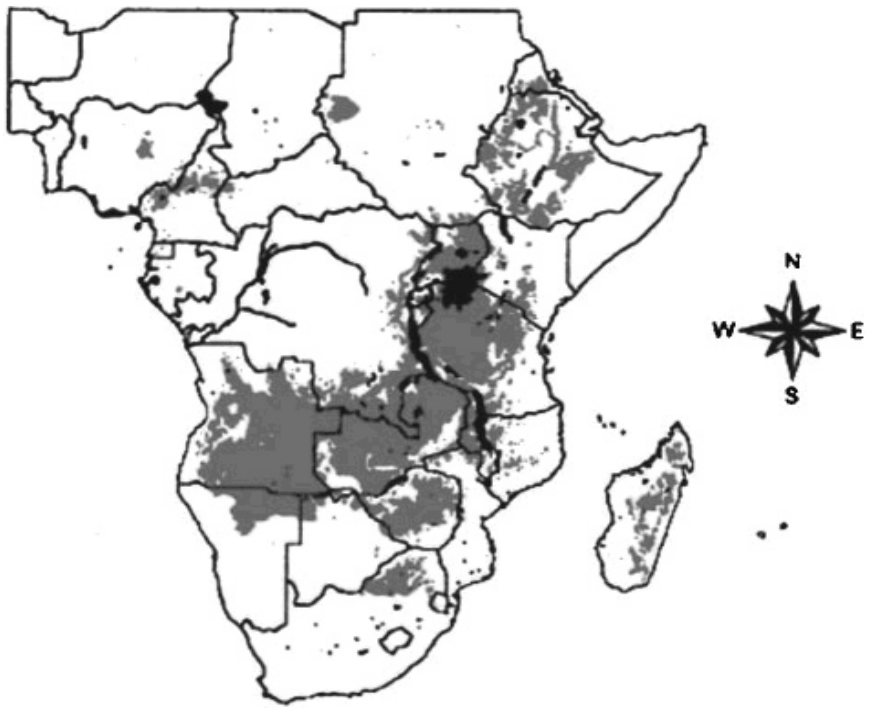

FIGURE 1-23 Areas of the African highlands that, though currently nonendemic, are probably vulnerable to malaria as the result of climate warming (■). These areas, which are at altitudes of .1000 m, have ratios of precipitation to potential evapo-transpiration that exceed 0.5 during the five wettest consecutive months of the year, and have minimum temperatures in excess of 15°C, are considered to be on the threshold of malaria transmission. Reproduced, from a figure in an article by Patz and Lindsay (1999), with the permission of Elsevier.

species (Tuno et al., 2005). In short, deforestation and cultivation of natural swamps in the African highlands creates conditions favourable for the survival of *An. gambiae* larvae, making an analysis of the effects of land-use change on local climate, habitat, and biodiversity key to any malaria-risk assessments.

Deforestation has also affected malaria in other regions, such as the Amazon basin (Guerra et al., 2006). Vittor et al. (2006) found a strong association between the biting rates of *An. darlingi* and the extent of deforestation in the Amazon; after controlling for the variation in human population densities, the biting rates of *An. darlingi* were still >200-fold higher in sites experiencing >80 percent deforestation than in sites with <30 percent deforestation.

Human activities have the capacity to shift the biodiversity of local ecosys-

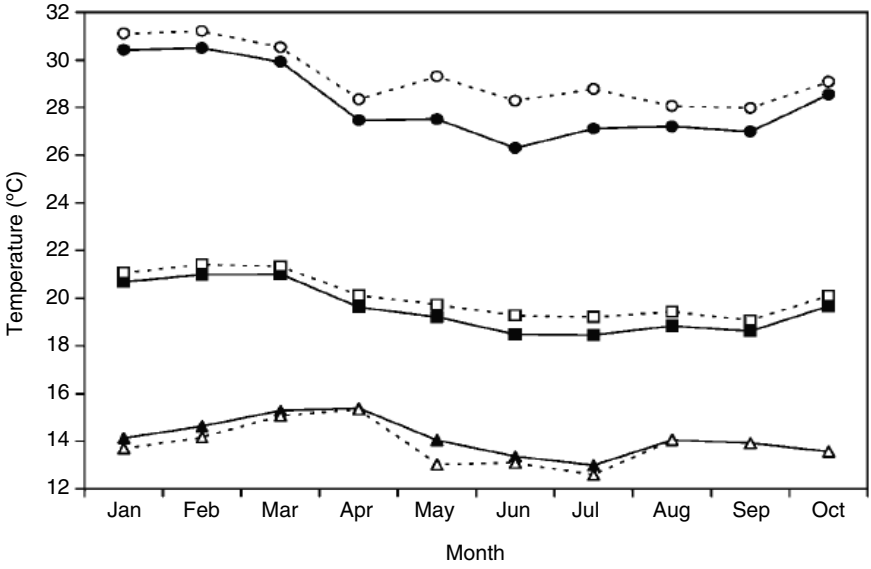

FIGURE 1-24 Comparison of the maximum (○), mean (□) and minimum (Δ) temperatures recorded within huts in deforested agricultural lands with the corresponding maximum (•), mean (▪) and minimum (▲) temperatures recorded within huts in forests. This graph was produced by Afrane et al. (2005), using data collected in western Kenya, and is reprinted here with the permission of the Entomological Society of America.

tems rapidly, intentionally and unintentionally increasing or decreasing malarial risk factors by altering the environment and mosquito habitat. The direction of the trend depends heavily on the *Anopheles* species present and on local conditions (Guerra et al., 2006). In north–eastern India, expansive deforestation has caused the numbers of *An. dirus* and *An. culicifacies* to decline (Dev et al., 2003). The effects of changing land-use patterns on the regulation of malaria (or other infectious disease) across a large area are species and site-specific, and therefore cannot be generalised.

Arboviruses Although *Aedes aegypti* is known to be strongly affected by ecological and human 'drivers' in urban settings, this species is also influenced by climate, including variability in temperature, moisture and solar radiation. Similar to the extrinsic incubation periods of malarial parasites (Figure 1-22), the rate of replication of dengue virus in *Ae. aegypti* increases directly with air temperature,

at least in the laboratory. Biological models have been developed to explore the influence of projected temperature change on the incidence of dengue fever. These models indicate that, given viral introduction into a susceptible human population, relatively small increases in temperature could significantly increase the potential for epidemics of dengue (Patz et al., 1998). In addition, for relatively small countries with presumably *some* climate uniformity, a climate-based dengue model has been developed that strongly correlates with the inter-annual variability seen in the incidence of dengue reported at the national level (Figure 1-25; Hopp and Foley, 2003).

Certain other arboviruses, such as Saint Louis encephalitis virus (SLEV), are also associated with climatic factors. In Florida, the appearance of SLEV in sentinel chicken flocks is preceded by a wet period followed by drought (Shaman et al., 2002). It has been suggested that spring drought forces the mosquito vector, *Culex nigripalpus*, to converge with immature and adult wild birds in restrictive, densely vegetated, hammock habitats. This forced interaction of mosquito vectors and avian hosts then creates an ideal setting for rapid transmission and amplification of SLEV. Once the drought ends and water sources are restored, the infected vectors and hosts disperse and transmit SLEV to a much broader geographical area (Shaman et al., 2002).

Climate variability may also have an effect on West Nile virus (WNV), a pathogen only recently introduced into the New World. Reisen et al. (2006) found that the strain of WNV that entered New York, during the record hot July of 1999, differed from the South African strain in that it required warmer temperatures for efficient transmission. It seems likely that, during the epidemic summers of 2002-2004 in the U.S.A., epicentres of WNV were linked to above-average temperatures.

Rodent-Borne Diseases

Hantavirus is transmitted to humans largely by exposure to infectious rodent excreta, and may then cause serious disease, with a high level of mortality. In the emergence of hantavirus pulmonary syndrome in the southwestern U.S.A., in 1993, it was the weather conditions, especially El Niño-driven heavy rainfall, that appear to have led to a growth in rodent populations and subsequent viral transmission (Glass et al., 2000).

Extreme flooding or hurricanes can lead to outbreaks of leptospirosis. In 1995, an epidemic of this disease occurred in Nicaragua after heavy flooding, and a major risk factor for the disease was found to be walking through the flood waters (Trevejo et al., 1998).

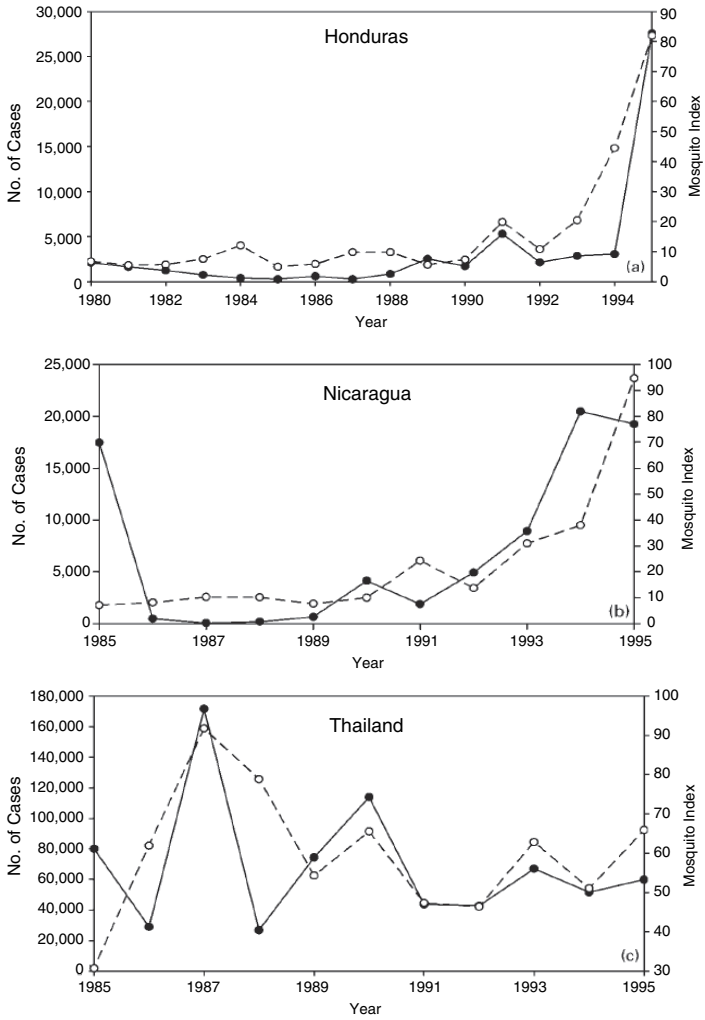

FIGURE 1-25 Correlation between simulated, climate-driven variations in *Aedes aegypti* mosquito density (○) and observed variations in the annual numbers of cases (•) of dengue, including dengue haemorrhagic fever, in three countries. Using a computer model of mosquito physiology and development, estimated changes in the relative abundance of *Ae. aegypti* that were driven only by month-to-month and year-to-year variations in temperature, humidity, solar radiation and rainfall were analysed. In Honduras, Nicaragua and Thailand (and many other 'small-area' countries of Central America and South–east Asia), disease incidence and the modelled mosquito densities were found to be significantly correlated ($P<0.05$ for each). These graphs are adapted from those of Hopp and Foley (2003) and are produced here with the permission of Nature Publishing.

Attribution of Disease Burden Resulting from Climate Change

The World Health Organization (WHO) has examined the global burden of disease already attributable to anthropogenic climate change up to the year 2000 and made model-based forecasts of the health risks from global climate change up to the year 2030 (McMichael et al., 2004). Conservative assumptions were made about climate-health relationships (e.g., that socio-economic conditions would prevent a climate-driven spread of vector-borne disease from endemic tropical regions to temperate regions) and many plausible health impacts were excluded for lack of quantitative models. The results indicate that the current burden from climate-sensitive diseases such as diarrhoea, malaria and malnutrition is so large that even the subtle climatic changes that have occurred since the mid-1970s could already be causing >150,000 deaths and approximately 5 million disability-adjusted life-years (DALY) each year. Although climate change is a global threat to public health, the WHO's assessment also revealed that the poorer regions of the world may be the most vulnerable (Figure 1-26). When the WHO's estimates of morbidity and mortality caused by human-induced climate change were extrapolated to 2030, it was found that the climate-change-induced excess risk of the various health outcomes considered could more than double by that year (McMichael et al., 2004).

Conclusions

The health outcomes from climate change are diverse and occur via multiple pathways of exposure. Whereas some disease resurgence has been attributed to recent warming trends, some of the long-term and complex problems posed by climate change may not be readily discernible from other causal factors. Accordingly, expanded efforts are required in both classical and future-scenario-based risk assessment, to anticipate these problems. In addition, the many health impacts of climate change must be examined in the context of many other environmental and behavioral determinants of disease. Increased disease surveillance, integrated modelling, and the use of geographically-based data systems will enable more anticipatory measures by the public-health and medical communities.

There are clear ethical challenges. The regions with the greatest burden of climate-sensitive diseases are often the regions with the lowest capacity to adapt to the new risks. Many of the regions most vulnerable to climate change are also those least responsible for causing the problem. Africa, for example, is thought to harbour about 70 percent of all malaria cases but has the lowest per-capita emissions of the 'greenhouse' gases that cause global warming. In today's globalized world, with its international trade and travel, an increase in disease anywhere on the globe can affect every country.

Health is just one of the many sectors expected to be affected by climate

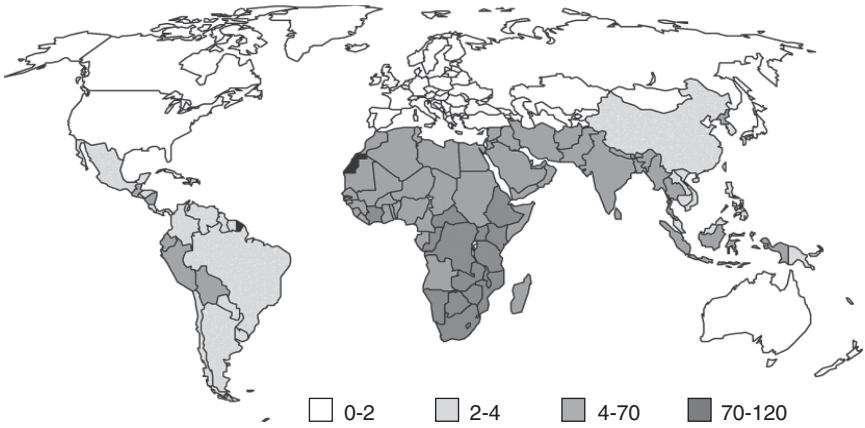

FIGURE 1-26 The World Health Organization's estimates of mortality attributable to climate change by the year 2000 (no estimate could be made for Western Sahara or French Guiana because of a lack of data). The Intergovernmental Panel on Climate Change's 'business-as-usual' scenario for greenhouse-gas (GHG) emissions (IS92a) and the HadCM2 general-circulation model of the Hadley Centre for Climate Prediction and Research (Exeter, U.K.) were used to estimate climate changes relative to the 1961-1990 levels of GHG and associated climate conditions used as a 'baseline.' The results of earlier quantitative studies on climate–health relationships were used to estimate relative changes in a range of climate-sensitive health outcomes for the years from 2000 to 2030. The outcomes considered (cardiovascular diseases, diarrhoea, malaria, inland and coastal flooding, and malnutrition) form only a partial list of the potential health outcomes, and there are significant uncertainties in all of the underlying models. The results should therefore be considered as conservative and approximate estimates of the health burden of climate change. Even so, the total mortality due to anthropogenic climate change by 2000 is estimated to be at least 150,000 people/year. Reproduced from a figure created, using data from McMichael et al. (2004), by Patz et al. (2005), and reprinted here with the permission of Nature Publishing.

change. It represents just a part of the interconnected context in which decision makers must implement strategies to prevent or reduce the adverse effects of such change. To achieve the greatest disease prevention, "upstream" environmental approaches, rather than assaults on single agents of disease, must form part of any intervention. If the truly global public-health challenge of climate change is to be adequately addressed, an unprecedented co-operation between natural and social/health scientists, as well as between rich and poor countries, must occur.

CLIMATE CHANGE AND VECTOR-BORNE DISEASE: UPDATE ON CLIMATE EFFECTS ON LYME DISEASE AND WEST NILE VIRUS IN NORTH AMERICA

Jonathan A. Patz, M.D., M.P.H.[19]
University of Wisconsin

Christopher K. Uejio, M.A.
University of Wisconsin

Introduction

Global climate change is expected to have broad health impacts. These could occur through various exposure pathways, such as the frequency or intensity of extreme heat waves, floods, and droughts. Warmer air temperatures could also influence local and regional air pollutants and aeroallergens. Less direct health impacts may result from climate-related alteration of ecosystems or water and food supplies, which in turn could affect infectious disease incidence and nutritional status. Finally, sea level rise could potentially lead to massive population displacement and economic disruption. Positive effects may include fewer winter-related deaths in some regions.

Changes in temperature, humidity, rainfall, and sea level rise could all affect the incidence of infectious diseases. Mosquitoes, ticks, and fleas are cold-blooded and thus sensitive to subtle temperature and humidity changes. But vector-borne diseases are also dependent on many other interacting factors. Although there has been a resurgence of infectious diseases in recent years, it is unclear that climate change has played a significant role. Other factors such as the movement of human and animal populations, the breakdown in public health infrastructure, changes in land use, and the emergence of drug resistance have been contributory.

The transmission of infectious diseases is strongly influenced by temperature, humidity, and rainfall (see Box 1-1). The distribution and seasonality of important infectious diseases are likely to be affected by climate change. Diseases transmitted by insect or rodent vectors have life cycles where much time is spent outside the human host, and therefore are more influenced by ambient conditions. There is a limited range of climatic conditions within which each such infective or vector species can survive and reproduce.

Mosquito-borne virus transmission is largely governed by vector population abundance, vector host-seeking behavior, and the dissemination of the virus through the vector's body to the salivary glands. The environment can be thought

[19]Associate Professor and Director, Global Environmental Health, Center for Sustainability and the Global Environment (SAGE), Nelson Institute for Environmental Studies and Department of Population Health Sciences, 1710 University Avenue, Madison, WI 53726. Phone: (608) 262-4775; Fax: (608) 265-4113; E-mail: patz@wisc.edu; Website: http://www.sage.wisc.edu.

of as contextually providing suitable conditions for the persistence of infectious disease agents or more directly driving the variability of vector and host populations and interactions. Environmentally mediated mechanisms explaining vector and host dynamics focus on nonlinear changes to time before an infectious mosquito can retransmit a virus or extrinsic incubation period (EIP), vector population explosions, or changing host-seeking behavior (Jupp et al., 1986; Kilpatrick et al., 2006; Reisen et al., 2006).

For a full discussion of the topic, refer to Patz and Olson (2006) earlier in this chapter. Next, we provide an update on the two most prevalent vector-borne diseases in North America: Lyme disease and West Nile virus.

Lyme Disease

Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, and tick-borne encephalitis are the most common vector-borne diseases in temperate zones in the northern hemisphere. Climate affects tick habitat, host and reservoir species, the interval between blood meals, and pathogen transmission.

Lyme disease is the most prevalent tick-borne disease in North America for which there is new evidence of an association with temperature (Ogden et al., 2006) and precipitation (McCabe and Bunnell, 2004). In the field, temperature and vapor pressure contribute to maintaining populations of the tick *Ixodes scapularis,* which, in the United States, is the microorganism's secondary host. A monthly average minimum temperature above –7ºC is required for tick survival (Brownstein et al., 2003).

The northern boundary of tick-borne Lyme disease is limited by cold temperature effects on the tick, *Ixodes scapularis*. Linking to future projections of climate via global climate models (GCMs), the northern range limit for this tick could shift north by 200 km by the 2020s, and 1,000 km by the 2080s. Plausible tick geographic ranges were developed from the Coupled Global Climate Model version 2 (CGDM2) and Hadley Centre Coupled Model, version 3 (HadCM3) models using the A2 Intergovernmental Panel on Climate Change Special Report on Emissions Scenario (Ogden et al., 2006).

West Nile Virus

Climate variability has been shown to affect West Nile virus (WNV), a disease only recently introduced into the New World in 1999. The summer adult WNV vector *Culex spp.* monthly abundance across diverse U.S. and Canadian biomes is largely controlled by antecedent moisture and temperature conditions (Raddatz, 1986; Day and Curtis, 1989; Andreadis et al., 2004). Optimal temperatures increase the rates of juvenile mosquito maturation, adult females biting, virus replication (decreases the extrinsic incubation period), and the total amount of virus transmitted (Madder et al., 1983; Buth et al., 1990; Rueda et al.,

BOX 1-1
Some Effects of Weather and Climate on Vector- and Rodent-Borne Diseases[a]

Vector-borne pathogens spend part of their life cycle in cold-blooded arthropods that are subject to many environmental factors. Changes in weather and climate that can affect transmission of vector-borne diseases include temperature, rainfall, wind, and sea level rise.

Rodent-borne pathogens can be affected indirectly by ecological determinants of food sources affecting rodent population size.

Examples of Temperature Effects on Selected Vector-Borne Pathogens

Vector

Survival can decrease or increase depending on the species.

Some vectors have higher survival at higher latitudes and altitude with higher temperatures.

Changes in the susceptibility of vectors to some pathogens (e.g., higher temperatures reduce the size of some vectors but reduce the activity of others).

Changes in the rate of vector population growth.

Changes in feeding rate and host contact (which may alter the survival rate).

Changes in the seasonality of populations.

Pathogen

Decreased extrinsic incubation period of pathogen in vector at higher temperatures.

Changes in the transmission season.

Changes in distribution.

Decreased viral replication.

Examples of Effects of Changes in Precipitation on Selected Vector-Borne Pathogens

Vector

Increased rain may increase larval habitat and vector population size by creating a new habitat.

Excess rain or snowpack can eliminate habitat by flooding, thus decreasing the vector population size.

Low rainfall can create habitat by causing rivers to dry into pools (dry season malaria).

Decreased rain can increase container-breeding mosquitoes by forcing increased water storage.

Epic rainfall events can synchronize vector host-seeking and virus transmission.

Increased humidity increases vector survival; decreased humidity decreases vector survival.

Pathogen

Few direct effects but some data on humidity effects on malarial parasite development in the anopheline mosquito host.

Vertebrate host

Increased rain can increase vegetation, food availability, and population size.

Increased rain can also cause flooding and decrease population size but increase contact with humans.

Decreased rain can eliminate food and force rodents into housing areas, increasing human contact, but it can also decrease population size.

Increased sea level

Alter estuary flow and change existing salt marshes and associated mosquito species, decreasing or eliminating selected mosquito breeding sites (e.g., reduced habitat for *Culiseta melanura*).

---

[a]The relationship between ambient weather conditions and vector ecology is complicated by the natural tendency for insect vectors to seek out the most suitable "microclimates" for their survival (e.g., resting under vegetation or pit latrines during dry or hot conditions or in culverts during cold conditions).

SOURCE: Gubler et al. (2001).

1990; Turrell et al., 2001; Dohm et al., 2002). Temperature's influence on vector abundance is place specific, dependent upon local conditions and time during the mosquito season. Mild winter, spring, and warmer early summer season conditions foster enhanced vector survival and replication (Takeda et al., 2003; Degaetano, 2005).

WNV vector abundance in mid-latitude locations generally increases directly with moisture variables such as precipitation or river run-off levels over the preceding month (Wegbreit and Reisen, 2000; Degaetano, 2005). Mosquitoes are r-strategists[20] with a competitive ecological advantage to preferentially reproduce in novel habitats created or activated by excessive precipitation. The wettest spring and summer in 100 years was significantly associated with increased WNV vectors abundance in the central United States (Vandyk and Rowley, 1995). Conversely, drought over the preceding year's summer season may also induce a mosquito population explosion by suppressing competitor and/or predator development (Chase and Knight, 2003).

Absolute and relative departures from summer long-term average temperature and precipitation conditions are hypothesized to be similarly important WNV transmission and epidemic drivers. High summer temperature and positive temperature anomalies have been observed in South Africa, Russia, and the United States (McIntosh et al., 1976; Jupp et al., 1986; Platonov et al., 2001; Reisen et al., 2006). Drought-like conditions or below-average summer or spring precipitation are common threads of Romanian, Russian, and French WNV outbreaks (Despommier, 2001; Han et al., 1999; Platonov et al., 2001). Abnormal or suitable moisture conditions conversely influence disease transmission in climatically sensitive South Africa. Extreme seasonal precipitation, subsequent breeding site creation, and normally hot temperatures coupled with existing irrigation and land use practices fueled two widespread South African epidemics (McIntosh et al., 1976). In the neighboring semiarid region, summer season average temperatures 1.1°C above normal and average precipitation may similarly have triggered the 1984 WNV epizootic (Jupp et al., 1986). A combination of antecedent winter/spring drought and above-average summer moisture controls vector and avian host aggregation and resulting virus amplification (Shaman et al., 2005). Human activities such as degraded housing infrastructure, which spawned abnormal vector population levels, also influence WNV transmission dynamics (Han et al., 1999).

Efficient transmission of the New York WNV strain is greatly reduced at low average temperatures compared to African isolates (Cornel et al., 1993; Reisen et al., 2006). The efficiency of WNV transmission from an infected *Cx. pipiens* to another vector directly increases as average temperatures rise from 18-30°C,

[20]The term r-strategist heuristically characterizes species that develop rapidly, produce abundant offspring, and have small body sizes. K-strategists conversely develop slowly and invest more resources in a larger body size and a small number of progeny (MacArthur and Wilson, 1967).

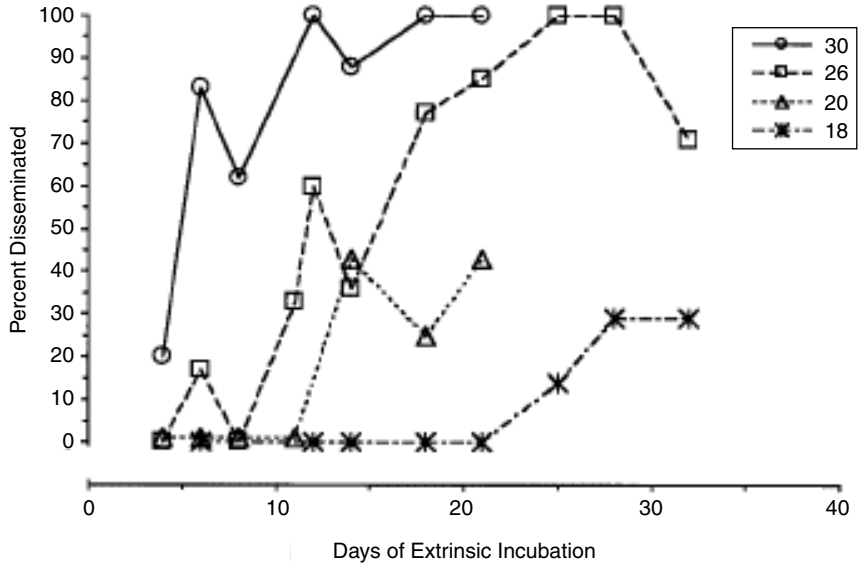

FIGURE 1-27 Decrease in the time before an infectious mosquito can retransmit a virus or extrinsic incubation period from laboratory experiments.
SOURCE: Dohm et al. (2002). Reprinted with permission from the Entomological Society of America. Copyright 2002.

(Figure 1-27). A mosquito's period of infectivity is sensitive to temperature such that relatively small seasonal temperature changes (1.3°C) may double WNV infection risk (Reisen et al., 2006). WNV transmission and epidemic genesis may therefore be more temperature limited in higher latitude locations. During WNV's march westward across the continental United States, above-average or average monthly temperatures qualitatively coincided with northern latitude regional epicenters (Figure 1-28) (Reisen et al., 2006). A straightforward model uses vector EIP to classify counties into "high" or "low" WNV transmission risk areas (Zou et al., 2007). Current temperature information drives the spatial explicit model, which has moderate but variable levels of over- and underprediction (Zou et al., 2007).

Land use and land cover metrics contain interrelated information on biophysical conditions and vector and host community assemblages that influence WNV transmission. Urban/suburban study sites consistently exhibit a modest positive association with infected avian hosts (Gibbs et al., 2006). Predominately white, moderately high income, suburban areas with housing built from 1940 to 1960 and moderate vegetation experienced as high as 3 to 8 times the WNV risk as the safest land use classification in two WNV epicenter cities (Ruiz et al.,

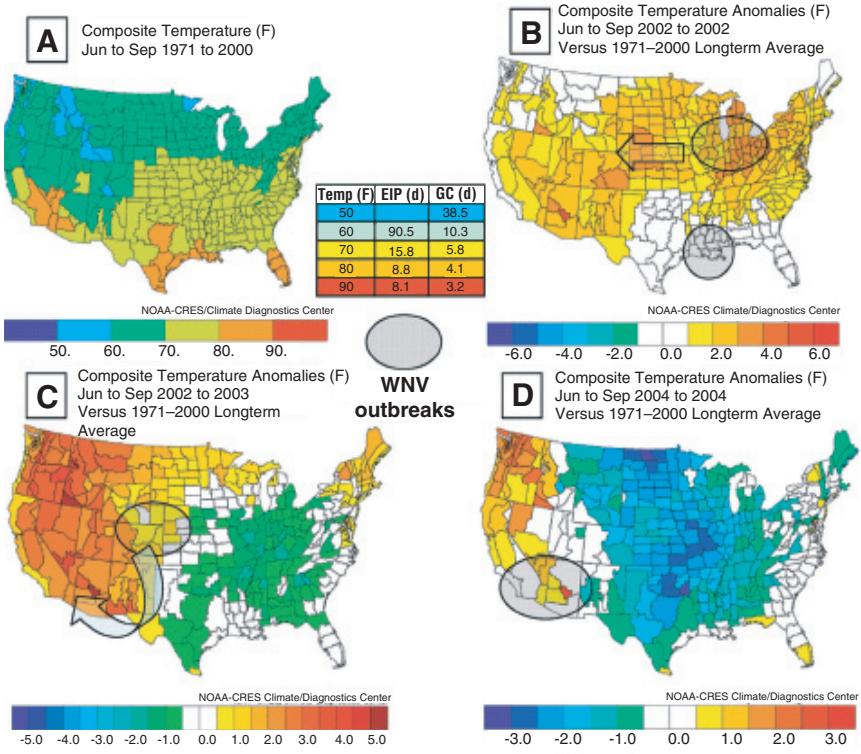

FIGURE 1-28 (A) Long-term climatological average summer (June-September) temperatures for the United States and (B-D) anomalies for each summer from 2002 to 2004. National epicenters with relatively high numbers of recorded human cases are encapsulated by a circle. The inserted table references the extrinsic incubation period and the length of the *Cx. tarsalis* gonotrophic as a function of temperature.
SOURCE: Reisen et al. (2006). Reprinted with permission from the Entomological Society of America. Copyright 2006.

2007). WNV vector infection prevalence tended to be lower in wetlands with greater community avian diversity than forest, shrub, or developed study sites (Ezenwa et al., 2007).

Conclusions

Climate change may affect the distribution and transmission intensity of a number of infectious diseases. Many of the linkages are complex and a range of other social, behavioral, and environmental factors also affect the health outcomes in question. Therefore, enhanced integrated assessment is required

to identify threshold conditions and to improve disease predictions. Due to the cross-cutting nature of risks posed by climate change, determining more upstream environmental risk factors should be of high priority, in addition to the ever-present need for improved surveillance and early warning.

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2

Vector-Borne Disease Detection and Control

OVERVIEW

Several workshop presentations focused on specific vector-borne diseases, permitting participants to explore them not only as diverse and unique public health challenges in their own right, but also more generally as examples that might inform the detection and control of other vector-borne disease agents. Workshop speakers described opportunities, successes, and obstacles in managing dengue, West Nile virus (WNV), Rift Valley fever (RVF), malaria, bluetongue, hantavirus pulmonary syndrome, and Sudden Oak Death (SOD).

Epidemiologists investigating infectious disease outbreaks seek to determine the route of transmission; in the case of vector-borne diseases, their efforts necessarily focus on the presence, abundance, and ecology of the vector, which in turn are frequently influenced by environmental conditions and human behavior. To illustrate these connections, Ned Hayes, of the Centers for Disease Control and Prevention (CDC), described his experiences investigating three different vector-borne diseases in diverse settings: pneumonic plague in Ecuador, 1998; dengue at the Mexico-Texas border, 1999; and tularemia in Martha's Vineyard, Massachusetts, 2000.

The investigation of each outbreak proceeded according to the following principles, as defined by Hayes:

- Determine that an outbreak exists.
- Categorize the outbreak by time, person, and place.
- Establish surveillance using an appropriate case definition.
- Collect and test diagnostic samples.

- Formulate hypotheses to explain risk of disease.
- Test hypotheses with one or more epidemiologic studies.
- Implement preventive interventions.
- Communicate results of the investigation through written reports or published papers.

Through the application of these principles, investigators attempt to determine the presence, abundance, and ecology of the vector; to identify reservoirs of infection; to evaluate modes of transmission and the ways in which they are influenced by the environment; and to implement disease control and prevention measures.

The plague outbreak in Ecuador occurred in a remote high mountain community with medieval housing conditions, in some ways reminiscent of Europe at the time of the Black Death. Based on their analyses, the researchers concluded that the first people infected had acquired plague from fleas that had previously bitten infected guinea pigs (which are raised locally for meat), and that the pathogen was subsequently transmitted directly among humans, abetted by primitive living conditions and poor access to health care. Hayes said that local climatic conditions, influenced by El Niño, had apparently influenced rodent population dynamics so as to favor the epizootic of plague that preceded the human outbreak.

A post-outbreak comparison of dengue incidence in the contiguous cities of Nuevo Laredo, Mexico, and Laredo, Texas, further illustrated the profound influence of environment on vector-borne disease (Reiter et al., 2003). There, Hayes and coworkers found that although the dengue vector, the mosquito *Aedes aegypti,* was abundant in the U.S. city, disease incidence was higher in its poorer Mexican neighbor, where far fewer houses were equipped with intact window screens and air conditioners. An investigation of a pneumonic tularemia outbreak on Martha's Vineyard, Massachusetts, which affected 10 adults, found that mowing lawns or cutting brush was the predominant risk factor for illness. The researchers findings point to small mammals, which presumably contaminated the foliage with the pathogen; the bacteria was then aerosolized and inhaled by workers during mowing. The single fatal case in this outbreak was a man who had limited access to health care. However, the ecological determinants that might explain why this outbreak—the second ever reported in the United States—occurred at that particular time remain unclear.

Turning from outbreak investigation to disease prevention, the authors of the chapter's first paper, workshop speaker Thomas Scott and Amy Morrison, of the University of California, Davis, present considerable evidence in favor of the use of locally adaptable tools and strategies for dengue prevention, a detailed set of goals for defining and measuring risk factors for human dengue infection, and four "conceptual shifts" in vector control strategy that, they argue, "will substantially improve dengue prevention." Central to the authors' recommendations are the observations that (1) dengue transmission risk is strongly associated with

adult (but not immature) vector population densities, and (2) that the vast majority of human dengue infections occur in the home. Advantages to insect control strategies focused within homes can transcend *Ae. aegypti* and dengue—and even vector-borne disease—by decreasing population densities and lifespans of various disease-transmitting insects, as well as those of pests such as bed bugs, cockroaches, and filth flies. Thus, Scott and Morrison conclude, "what was originally conceived as an *Ae. aegypti* control program can be leveraged into a cost and operationally effective public health program that reduces a variety of diseases and pest problems."

The second essay in this chapter, from Lars Eisen and workshop presenter Barry Beaty of Colorado State University, discusses initiatives by a private-public partnership, the Innovative Vector Control Consortium (IVCC; see also Summary and Assessment section, "Disease Prevention Strategies"), to reduce the impact of dengue. The consortium is funding the construction of a computer-based decision support system to inform the design and implementation of effective local and regional vector control programs, as well as the development and dissemination of proactive indoor vector control measures. A second paper by Beaty and Eisen in Chapter 3 reviews public health and scientific responses to a broad range of vector-borne disease issues raised in the Institute of Medicine report *Microbial Threats to Health* (2003).

A subsequent paper, by presenter Lyle Petersen of the CDC, describes the history and impact of WNV in the United States and identifies challenges to the surveillance and prevention of this emerging vector-borne disease in his contribution to this chapter. As part of its response to the 1999 WNV outbreak in New York City, the CDC established ArboNET, the first national human-animal disease surveillance system. Administered by the CDC, ArboNET is a real-time electronic reporting system that captures data on WNV in humans, dead birds, mosquitoes, horses, and live captive sentinels of disease (chickens). "A combination of human and veterinary surveillance will be essential to monitor the ongoing ecological impact of WNV and to guide disease prevention efforts," Petersen concludes. The experience with WNV demonstrates that the epidemiological pattern in areas of importation of an exotic arbovirus may bear little resemblance to that which occurred in its previously endemic area.

As discussed in the Summary and Assessment (see "Weather, Climate, and Prediction") and in Chapter 1, a climate-based model predicted a recent outbreak of RVF in Kenya, significantly improving response time and outcome. In his contribution to this chapter, workshop presenter C. J. Peters, of the University of Texas Medical Branch, Galveston, discusses the epidemiology and ecology of RVF—essential factors in its status as an emerging arboviral disease agent—and describes work in progress toward the development of veterinary and human vaccines to achieve better control of this deadly and costly disease. Peters warns of the potential of the RVF virus to expand its geographic range to the United

States and urges greater appreciation for the threat it poses to people and livestock throughout the world.

A combination of vector control and treatment with an effective drug are currently used to control malaria, the most burdensome of vector-borne diseases with regard to morbidity and mortality. In the chapter's fifth essay, presenter Michael Coleman of the Medical Research Council of South Africa and co-author Janet Hemingway of the Liverpool School of Tropical Medicine, United Kingdom, describe the use of routine entomological surveillance to increase the effectiveness of malarial vector control. Such surveillance permits earlier detection of, and response to, increases in pathogen transmission, which may indicate the development of insecticide resistance. The authors review vector surveillance techniques and describe their successful application to guide local vector control efforts. They also discuss potential uses of these techniques in modeling disease transmission and by decision support systems that inform national or regional vector control efforts.

Bluetongue, a viral disease transmitted primarily among ruminant animals (sheep and cattle) by biting midges of the genus *Culicoides*, results in economic losses worldwide of approximately $3 billion per year due to morbidity and mortality of animals, trade embargoes, and vaccination costs (FAO, 2007; Osburn, 2007). In his contribution to this chapter, presenter Bennie Osburn of the University of California, Davis, describes the history, distribution, and impact of the disease, which is present on six continents. Bluetongue has become established in Europe only within the past 5 years, coincident with abnormally high summer temperatures, and thus may provide insights into the behavior of other vector-borne diseases potentially expanding their geographic range with increasing temperatures associated with global climate change. Osburn notes that bluetongue has so far been adequately controlled in eastern and southern Europe; however, this has been achieved primarily through the use of modified live virus vaccines, which pose the threat of reassortment, via vector transmission, with wild-type viruses.

The chapter's final paper, by presenter Charles Calisher of Colorado State University and co-authors, describes a comprehensive, longitudinal study of the transmission of Sin Nombre hantavirus (SNV), the pathogen that causes the rodent-borne viral disease hantavirus pulmonary syndrome (HPS) among deer mice (*Peromyscus maniculatus*) in Colorado. The first human epidemic of HPS, reported in the spring of 1993, and a subsequent outbreak in 1998, occurred in the Four Corners region of the continental United States, where the borders of Utah, Colorado, New Mexico, and Arizona meet. Research by Calisher and coworkers on the transmission and maintenance of SNV reveals important environmental influences on these processes and thereby provides a model that may be extrapolated to other vector-borne zoonotic agents. Such longitudinal studies, they conclude, "may be the only current means available to identify predictors of risk for rodent acquisition of this virus and for subsequent transmission to humans." In

addition, they note, "although particular zoonotic diseases have particular etiologic agents, the controlling conditions for each may have enough similarities to provide us with predictors of risk for acquisition and, therefore, with bases for prevention and control measures."

As a rodent-borne viral disease, HPS has invited consideration of nonarthropod vectors of infectious disease. The role of "vector" might be further expanded to include humans in the case of SOD, an infectious plant disease that has been spread across wild lands by hikers, mountain bikers, and equestrians. Speaker David Rizzo, of the University of California, Davis, has worked to understand and mitigate the effects of SOD in California since shortly after its emergence there in the mid-1990s (see Summary and Assessment section, "Lessons Learned: Case Studies of Vector-Borne Diseases"). The disease was first recognized after it caused widespread dieback of several tree species in West Coast forests; it also causes nonfatal leaf disease in many other plants, including rhododendrons and California bay laurel, and has been detected in the United Kingdom and Europe (Rizzo and Garboletto, 2003).

The infectious agent of SOD is the fungus-like water mold *Phytopthora ramorum*, which thrives in the cool, wet climate of California coastal forests. Human visitors to these forests—who pick up *P. ramorum* spores on their clothes and shoes, equipment, and companion animals—appear to be the main "vectors" for the spread of this pathogen over long distances. However, because the SOD pathogen was identified only 7 years ago, researchers are still learning about its disease cycle and transmission dynamics.

As they probe the ecological context and epidemiology of SOD, Rizzo and colleagues are also working to manage the disease in natural ecosystems and in the nursery trade. To target monitoring efforts, they developed risk models based on findings from laboratory studies of the pathogen's sporulation behavior, combined with data on the distribution of host species and climate. Areas identified by the models are investigated by various methods, including aerial imaging, plot-based monitoring, and sampling streams to determine whether the pathogen is present within a watershed. If the pathogen is detected at a sufficiently early stage, the affected vegetation may be clear-cut and burned in hopes of eradicating the disease.

While this approach has not yet proven completely successful, Rizzo observed, it has significantly limited the spread of SOD. For areas where the pathogen is established, he and coworkers attempt to develop management schemes that avoid deleterious ecological consequences, such as the growth of invasive plant species following clear-cutting. In order to anticipate the potential effects of such management strategies, Rizzo collaborates with many ecologists. "Understanding the ecology of the forest is absolutely critical [to managing areas with established disease]," he said. "We've been doing a lot of work on how we can manipulate these [infected] forests, whether it's reintroducing fire [or] removing some hosts [through clear-cutting], to figure out a way that we can live with this disease."

LONGITUDINAL FIELD STUDIES WILL GUIDE A PARADIGM SHIFT IN DENGUE PREVENTION

Thomas W. Scott, Ph.D.[1]
University of California

Amy C. Morrison, Ph.D.
University of California

Introduction

When done properly, vector control is a well-documented and effective strategy for prevention of mosquito-borne disease. Familiar examples of successful mosquito vector interventions include the worldwide reduction of malaria in temperate regions and parts of Asia during the 1950s and 1960s (Curtis, 2000; Rugemalila et al., 2006), yellow fever during construction of the Panama Canal, yellow fever throughout most of the Americas during the 1950s and 1960s (Soper, 1967), dengue in Cuba and Singapore (Ooi et al., 2006), and more recently dengue in parts of Vietnam (Kay and Nam, 2005). That these programs significantly improved public health is indisputable. Why then is disease burden from vector-borne diseases like malaria (Sachs and Malaney, 2002) and dengue increasing (WHO, 2006a)? Why has vector control not been effectively applied more often so that it reduces or appreciably minimizes disease? Unsuccessful programs are often attributed to a lack of resources, lack of political will, or ineffective implementation (Attaran, 2004; Gubler, 1989b; Halstead, 1993; Killeen et al., 2002). Just as responsible for control failures are deficiencies in understanding relationships between vector ecology and pathogen transmission dynamics, the most appropriate methods for assessing and responding to appreciable risk, and the failure to use existing knowledge or surveillance information to make informed control decisions. It is reasonable to conclude that despite more than a century of vector-borne disease investigation, fundamental concepts in disease prevention remain incompletely defined and underutilized.

The goal of this paper is to illustrate the power of improved ecologic and epidemiologic understanding for increased effectiveness of vector control for dengue. The concepts and processes we discuss are not limited to dengue and, therefore, consideration should be given for their application to other vector-borne diseases. We assert that a better understanding of virus transmission dynamics, concepts, and tools and strategies for disease prevention will fundamentally change and significantly improve public health programs for dengue prevention. Current programs, which emphasize universally prescribed surveillance and control, have hindered development of an appropriate conceptual and factual foundation for

[1]Department of Entomology, Davis, California. E-mail: twscott@ucdavis.edu.

adaptive disease prevention programs and help to explain why contemporary vector control programs too often fall short of public health expectations.

Our principal recommendation is that enhancing dengue prevention will require locally adaptable tools and strategies. To accomplish this there is an urgent need for more comprehensive, longitudinal field studies of vector-borne diseases that (1) quantitatively define relationships between the most meaningful measures of risk and human infection and (2) use that information to direct public health measures that prevent or minimize disease. Information necessary to fill this knowledge gap should be obtained in the framework of interrelated longitudinal cohort studies that progressively build on one another, providing an increasingly detailed understanding of fundamental processes in pathogen transmission, epidemiology, and disease control. Based on our experience, critical missing knowledge of risk assessment and disease prevention can only be gained by carrying out integrative research that embraces the vector, pathogen, and human host. Too often vector-borne disease specialists study the arthropod vector, disease, or pathogen separately. Only by studying the system in total over a considerable period of time will we gain the greater insight into the complexity of interactions between components of transmission and disease that are essential for design, implementation, and evaluation of increasingly more successful disease prevention programs. In the case of dengue, until a vaccine or chemotherapy become available, control programs will continue to be limited to vector control, which in most cases means reducing mosquito vector populations. But do we understand *Ae. aegypti* and dengue virus (DV) transmission well enough to make specific recommendations for modifications in vector populations, short of vector eradication, that will result in a predictable public health outcome? Review of relevant literature clearly indicates that the answer to this critical question is no.

Dengue Epidemiology and Ecology

Worldwide, DV infections cause more human morbidity and mortality than any other arthropod-borne virus disease (Farrar et al., 2007; Gubler, 2002c, 2004; Gubler and Kuno, 1997; Kuno, 1995; MacKenzie et al., 2004; Monath, 1994). It is estimated that 2.5 to 3 billion people are at risk of infection in tropical parts of the world each year. In urban centers of Southeast Asia, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are among the leading causes of pediatric hospitalization. During the last 30 years dengue has emerged as a major international public health threat in the Americas (Rigau-Perez et al., 1998; WHO, 2006b).

Dengue fever (DF), DHF, and DSS are caused by four closely related, but antigenically distinct, single-stranded RNA viruses (DV-1, DV-2, DV-3, and DV-4) in the genus *Flavivirus*, family *Flaviridae*. All four serotypes cause a range of human disease, including asymptomatic infections, undifferentiated fever, and classic DF (Gubler, 2002c, 2004; Gubler and Kuno, 1997; Rothman and Ennis,

1999). Sequential infections with different serotypes are possible because infection with one serotype provides lifelong protection from a homologous infection, but is only briefly cross-protective against heterologous serotypes. The etiology of serious illness is not completely understood but is suspected to be due to immune enhancement and/or variation in virus virulence (Gubler, 2002c, 2004; Kochel et al., 2002; MacKenzie et al., 2004; Monath, 1994; Rothman and Ennis, 1999; Watts et al., 1999). It is estimated that annually there are between 50 and 100 million DF cases and 250,000 to 500,000 DHF/DSS cases worldwide. If untreated, the case fatality rate for DHF/DSS can approach 30-40 percent; with supportive therapy, less than 1 percent of severely ill patients die (Halstead, 1993).

DVs generally persist in endemic foci by a horizontal *Ae. aegypti*-human transmission cycle (Gubler, 1989a; Rodhain and Rosen, 1997). After an incubation period of 3-15 days (typically 4-7 days) in the human, disease symptoms are first observed (Focks et al., 1995; Waterman and Gubler, 1989). Viremia often precedes fever, typically lasts ~5 days, and usually subsides in concert with the inability to detect virus in the blood (Vaughn et al., 2000). Mosquito vectors become infective after biting a viremic individual and surviving an extrinsic incubation period of 7-14 days (Watts et al., 1987). Although other mosquitoes in the subgenus *Stegomyia* have been incriminated as vectors, *Ae. aegypti* is the most important dengue vector worldwide (Gubler and Kuno, 1997). Once infective, *Ae. aegypti* can transmit virus each time it probes its mouthparts into a human or imbibe a blood meal (Putnam and Scott, 1995a,b).

Ae. aegypti is uniquely adapted to a close association with humans and efficient transmission of DV. Immature forms develop primarily in artificial, man-made containers (Gubler, 1989a). Highly anthropophilic, females rest inside houses where they feed frequently and preferentially on human blood (Scott et al., 1993b, 2000b), which confers a fitness advantage (Scott et al., 1997; Morrison et al., 1999; Harrington et al., 2001a). Because food, mates, and substrates for laying eggs are readily available within the human habitations where female *Ae. aegypti* reside, dispersal beyond 100 m is not necessary and is detected in only a very small proportion of the adult population (Morland and Hayes, 1958; McDonald, 1977; Trpis and Hausermann, 1986; WHO, 1997, 1999; Edman et al., 1998; Harrington et al., 2001a,b, 2005). This indicates that most dispersal of DV occurs via movement of viremic human hosts. These features make *Ae. aegypti* an efficient vector and DV transmission can occur even when *Ae. aegypti* population densities are very low (Kuno, 1995).

Dengue Control

Presently, dengue control is dependent on the reduction or elimination of *Ae. aegypti*. Although dengue vaccines are a focus of attention (Pediatric Dengue Vaccine Initiative funded by the Bill and Melinda Gates Foundation[2]), currently

[2]See http://www.pdvi.org.

there is no licensed vaccine. Developing a dengue vaccine is a challenge because it will need to be tetravalent to avoid the risk of immune enhancement. Even after a vaccine or drug is available, we expect that vector control will remain important. The benefits of a vaccine will be limited by its safety profile, efficacy, cost, and capacity for delivery (DeRoeck et al., 2003; Shepard et al., 2004). Although a variety of dengue vaccines are being developed and there are promising leads for antidengue drugs at the time of this writing (Farrar et al., 2007), none of the vaccine candidates have been evaluated in Phase III trials, and licensing is not imminent for clinical use of prospective drugs. Critical information on efficacy and cost was, therefore, not available. Even with superior efficiency, which considering the complexity of dengue disease we can not assume without rigorous evaluation, a dengue vaccine will clearly not protect against infection with other mosquito-borne viruses. Furthermore, in order for there to be widespread application of a dengue vaccine in endemic countries the cost would need to be low (no more than $0.50 per dose) and preferably applied in a single dose (DeRoeck et al., 2003). In a best-case scenario there will be perfect protection against all DVs and perhaps some cross-protection for other *Ae. aegypti*-borne viruses in the genus *Flavivirus* (i.e., yellow fever). A dengue vaccine will not protect against infection with nonflaviviruses and, realistically, complete vaccine coverage seems unlikely. Conversely, effective vector control reduces risk of infection for all *Ae. aegypti*-borne arboviruses (e.g., dengue, yellow fever, and chikungunya) across the human population. This alone is a compelling reason for continuing *Ae. aegypti* control after an effective DV vaccine becomes available.

Current vector control methodologies for *Ae. aegypti* surveillance and control emphasize techniques that were developed for mosquito eradication to prevent yellow fever (see "Measuring Mosquito Density," below). Although those programs were initially successful in helping to define the role of vector eradication in disease prevention, the approach taken provided little insight into quantitative relationships between mosquito abundance and DV transmission (PAHO, 1994; Gubler and Kuno, 1997; Reiter and Gubler, 1997; Scott and Morrison, 2003). For a variety of reasons, mostly changing urban environments and limited economic resources, in 1994 the Pan American Health Organization (PAHO) departed from the eradication paradigm and declared eradication of *Ae. aegypti* an unattainable goal (PAHO, 1994). The new goal of dengue control programs is cost-effective utilization of limited resources to reduce vector populations to levels at which they are no longer of significant public health importance (Gubler, 1989b; PAHO, 1994).

Aedes aegypti control programs worldwide vary widely, in many cases driven by country-specific economic constraints on local health agencies. Most countries use a combination of vector surveillance, chemical treatment of *Ae. aegypti* larval habitats, and either regular or emergency applications of ultra low volume (ULV) space sprays. Aerosol insecticides are effective if they reach female *Ae. aegypti* resting indoors, where they otherwise avoid insecticide contact (Reiter and Gubler, 1997). This means that space sprays need to be applied inside houses

using backpack applicators rather than from high-profile trucks moving down city streets or from airplanes flying over houses. Farther up the product development pipeline, disease control based on genetic manipulation of mosquito vectors is being investigated in the laboratory (Beaty, 2000; James, 2005) and will require extensive field evaluation before it can be deployed (Scott et al., 2002; Louis and Knols, 2006). Successful dengue vector control programs in Singapore and Cuba (Ooi et al., 2006), promising results from trials with insecticide-treated materials in Latin America (Kroeger et al., 2006), and cost-effective larval control in Cambodia (Suaya et al., 2007) fortify the notion that properly done vector control effectively prevents dengue disease. Enhancing tools and strategies for vector surveillance and control should be a priority in the fight against dengue.

The PAHO strategy emphasizes vector surveillance, with the objectives of maintaining *Ae. aegypti* populations below or close to transmission thresholds, slowing DV transmission, and accordingly, reducing sequential infections with heterologous serotypes that can increase the incidence of serious disease (Vaughn et al., 2000). Although intuitively reasonable, this approach has not been systematically validated and the implication is that controlling serious disease rather than all disease is a viable public health goal. No well-controlled field studies have been published that clearly define the key relationships between vector density and human infection. There is an urgent need for entomological and epidemiological data that refine understanding of relationships among entomological risk factors, incidence of human infection, and clinical disease manifestations. This has rarely been done for any vector-borne disease, exceptions being arbovirus studies of western and St. Louis encephalitis viruses in southern California by Reeves and his colleagues (Reeves, 1971; Olson et al., 1979). Yet reduction of vector populations remains a prominent, underlying premise of many current public health recommendations for control of a long list of vector-borne diseases, including dengue. Prospective studies are urgently needed to test and refine fundamental assumptions of this strategy for dengue control.

Establishing Goals for Dengue Prevention Programs

A fundamental observation in dengue prevention is that there is no single method or approach that works in all situations (Scott and Morrison, 2003). Ecology and epidemiology of virus transmission vary from one place and/or time to another. To help establish dynamic goals for disease prevention programs that can be adapted across the diversity of situations in which dengue exists, we developed four interrelated questions that assist in goal setting. The concepts discussed are not limited to dengue, and therefore, can be applied to other vector-borne diseases.[3] Location-specific answers to these questions are important steps in the development of adaptive dengue control programs.

[3]See Scott and Morrison (2003) for additional discussion on each topic.

What is an acceptable level of dengue risk? This is a complex question. The answer will be situation- and location-specific depending on historical patterns of local DV transmission, available resources, and competing public health priorities. In order to reach properly informed decisions, entomologic and epidemiologic data will need to be considered. That will require appropriate coordination, sharing of relevant information, and teamwork among different public health entities (e.g., vector control and epidemiology departments) (Ooi et al., 2006). Goals will likely change as epidemiologic conditions and public health expectations change. This implies that the definition of what constitutes acceptable risk will vary from eradication of all clinically apparent dengue cases to "living with dengue but not DHF." Consideration of this issue is an important part of the paradigm shift away from universally prescribed control actions and toward local experts developing a dynamic system for repeatedly reevaluating what are the most effective control tools, strategies, and application protocols for their particular situation.

What are the mosquito densities (thresholds) necessary to meet agreed upon risk goals? The new policy for dengue control implies that although there may be some DV transmission, properly applied vector control will reduce or eliminate severe disease (Gubler, 1989b; PAHO, 1994). The objective, therefore, is to lower the force of infection and thus minimize severe disease by managing the density of mosquito vector populations. This is a tricky proposition. How does one know when vector populations have been reduced to levels at which they are no longer significant? What constitutes no longer significant? What exactly are the epidemiological objectives that guide this approach?

Control strategies that do not aim for vector eradication, like this one, require surveillance (entomological and epidemiological) that informs disease prevention responses. In this case, the objective is to identify an entomological threshold below which there will be no epidemic transmission. Values above the thresholds will trigger control actions. Although the concept is straightforward, implementation is challenging. Without the appropriate knowledge and analytical tools, it can be difficult to distinguish between the mere presence of a vector species and situations when vector control is required to prevent an epidemic (Peterson and Higley, 2002). Operationally friendly systems for estimating action thresholds from locally available surveillance, weather, and human population data would be a significant addition to the armature against dengue.

Thresholds for DV transmission can fluctuate depending on mosquito density, overall immunity of the local human population (i.e., herd immunity), introduction of novel virus serotypes or genotypes, the nature of contact between mosquito vectors and human hosts, human density, and weather (Scott and Morrison, 2003). Temperature is particularly important because of its inverse relationship with extrinsic incubation. Even after key parameters have been identified, estimation can require acquisition of data that are hard to obtain (e.g., site-specific herd immunity) or can be encumbered by complicated assumptions (e.g., spatially and

temporally explicit knowledge of mosquito density, survival, and human biting behavior).

Important features of threshold values are that they are dynamic (i.e., they vary through time and space) and estimation is difficult because they are often based on data that are difficult to obtain or that require assumptions that are difficult to accept. In a practical sense development of thresholds will require the use of models (i.e., Focks et al., 1993a,b, 1995) that can be used to make relative rather than absolute comparisons (Dye, 1992). An appropriate analogy is hurricane prediction, for which there are models that can be used with some degree of error to make life-saving decisions. Due to inherent variability in key dengue transmission parameters and the difficulty in some cases of obtaining accurate measurements, it would not be wise to establish a fixed threshold value for DV transmission even at the same location. We can expect, however, to be able to identify circumstances when the risk of transmission is particularly high and prioritize use of limited vector control resources to sites where they will do the most good.

Iterative modeling exercises can be used to systematically identify the most informative surveillance systems and predict intervention approaches with the highest probability of meeting local disease prevention goals. We are currently involved in a project (i.e., the Innovative Vector Control Consortium) (Hemingway et al., 2006) that includes upgrading and making more user friendly existing simulation models for *Ae. aegypti* population dynamics (Focks et al., 1993a,b) and DV transmission (Focks et al., 1995). Our goal is to make these models freely available as a component of a web-based dengue decision support system so that at a variety of different levels (e.g., national, regional, or local) public health, vector control, or government officials can contrast and select from different surveillance and control options under a variety of site and operationally specific circumstances.

Preliminary estimations indicate that entomological thresholds for DV transmission are quite low (Focks et al., 2000). The most important reason for this is *Ae. aegypti*'s uncommon feeding behavior. Most adult female mosquitoes engage in a feeding duality. They feed on plant sugars as a substrate for the synthesis of energy reserves (i.e., glycogen and lipid) that are used for flight and maintenance activities and blood for amino acids that are used for development of eggs (Clements, 1999). Female *Ae. aegypti* deviate from this pattern in ways that make them particularly dangerous vectors. In dengue-endemic situations where *Ae. aegypti* live in close association with humans, females seldom feed on plant carbohydrates (Edman et al., 1992; Van Handel et al., 1994; Costero et al., 1998). They meet their energetic and reproductive needs by feeding frequently and preferentially on human blood (Scott et al., 1993a,b, 2000a,b; Chow et al., 1993). Patterns of multiple biting on humans are consistent with facilitation of DV transmission. Multiple meals are taken from different people, bites are heterogeneously distributed so that some people are bitten more often than

others, and virus can be moved from one place to another by visitors who are bitten in homes where infected mosquitoes reside (Chow-Schaffer et al., 2000; DeBenedictis et al., 2003). Because *Ae. aegypti* tend not to disperse far (Morland and Hayes, 1958; McDonald, 1977; Trpis and Hausermann, 1986; Edman et al., 1998; Harrington et al., 2005), energy needs for flight are reduced. Nutrients in a diet limited to human blood support mosquito maintenance activities and reproduction as long as females feed multiple times in each egg-laying cycle (Harrington et al., 2001a). The unique feature of human blood that makes this possible is believed to be the low concentration of the amino acid isoleucine compared to other vertebrate sources of blood. From an epidemiologic perspective, frequent human biting increases the opportunities for mosquito vectors to acquire DV by biting an infected person and to transmit virus after becoming infectious. From an entomological point of view, feeding frequently and preferentially on only human blood confers a fitness advantage and, therefore, females that engage in that behavior have a selective advantage (Day et al., 1994; Scott et al., 1997; Naksathit and Scott, 1998; Costero et al., 1998; Morrison et al., 1999; Harrington et al., 2001a). Consequently, frequent and preferential human biting makes *Ae. aegypti* a remarkably efficient and, thus, dangerous mosquito. It does not take many *Ae. aegypti* to sustain unacceptable levels of DV transmission. The operational implications of efficient transmission are that entomological thresholds will be low and thus for vector control to be effective it will need to be thorough and sustained.

What are the most informative measures of dengue risk? To date, attempts to predict dengue epidemics have been largely unsuccessful. Public health departments worldwide remain perplexed and frustrated with their inability to assess dengue risk in a meaningful way. In places where fewer than all four serotypes are transmitted (i.e., Latin America and parts of Asia), surveillance systems have been proposed for detecting the introduction of novel DV serotypes (Gubler and Casta-Velez, 1991). In endemic regions of Southeast Asia, where there is an overall pattern of 3- to 4-year cyclical increases in disease (Hay et al., 2000; Cummings et al., 2004), viral surveillance has been more informative than current entomological techniques for managing DV transmission. Nevertheless retrospectively—and to some extent arbitrarily—prescribed entomological indices are heavily relied upon to assess dengue risk and the effectiveness of vector control programs (Focks and Chadee, 1997; Focks et al., 2000; Scott and Morrison, 2003). An operationally valuable early warning system for dengue, which is in great demand by public health officials (DeRoeck et al., 2003), will need to include data on human herd immunity, *Ae. aegypti* and human population densities, contact rates between vectors and humans, and ambient temperature.

Human herd immunity A key component in the transmission of an infectious disease is the proportion of people in the affected population that are susceptible

to infection (Anderson and May, 1991). This is especially true for a virus like dengue that causes sterilizing immunity (i.e., following exposure and an immune response a person is protected from reinfection with the same DV serotype). Results from dengue models clearly indicate that the vector densities necessary to prevent, interrupt, or decrease DV transmission are inversely proportional to seroprevalence rates of the human population (Newton and Reiter, 1992; Focks et al., 1995, 2000). For example, Focks et al. (2000) predicted that when other factors remain constant entomological threshold estimates necessary for epidemic DV transmission will increase 1.5-fold when the initial seroprevalence increases from 0 to 33 percent, 2.1-fold when it increases from 33 to 67 percent, and 3.2-fold when it increases from 0 to 67 percent. As the proportion of immune people in the population increases it is expected that it will become increasingly difficult for DV to sustain transmission. The most specific assay for detecting serotype-specific antibody responses to a DV infection is the plaque reduction neutralization test (PRNT) (WHO, 2006b). The PRNT unfortunately requires specialized laboratory facilities and equipment that are beyond the reach of most local public health units. Other serologic methods exist (e.g., enzyme-linked immunosorbent assays [ELISAs]), but they lack serotype specificity and in some cases cross-react with antibodies directed against flaviviruses that are closely related to DV. In most cases, therefore, timely and cost-effective transfer of population-based seroprevalence data is not available. There is a critical need for development of new, more cost and operationally amenable means to estimate herd immunity and, thus, susceptibility of local human populations to epidemic DV transmission.

Measuring mosquito density Below we review the most commonly used measures of *Ae. aegypti* density that are used to assess dengue risk:

- **Traditional measures of *Aedes aegypti* density** The shift in focus from eradication to control programs merits a reevaluation of *Ae. aegypti* surveillance techniques. Traditional entomological surveillance techniques are based on the premise/house index (HI; percentage of houses infested with larvae and/or pupae), container index (CI; percentage of water-holding containers infested with larvae and/or pupae), and Breteau index (BI; number of positive containers per 100 houses), which were designed to detect the presence or absence of *Ae. aegypti* larvae (Conner and Monroe, 1923; Breteau, 1954; Tun-Lin et al., 1995a; Focks and Chadee, 1997). Several investigators discussed the limitations of traditional *Stegomyia* indices for estimating *Ae. aegypti* density and noted their poor relationship with DV transmission (Tun-Lin et al., 1995a, 1996; Focks and Chadee, 1997; Reiter and Gubler, 1997; Scott and Morrison, 2003; Kay and Nam, 2005). The major problems are that they fail to account for larval mortality, heterogeneity in container productivity, and temporal differences in *Ae. aegypti* life stages. Put simply, we cannot assume a strong positive correlation between the presence of larvae and adult female mosquitoes in a household. Moreover, factors impacting

larval mortality and development such as container size, crowding, and availability of nutrients in aquatic larval habitats affect the relationship between larval and adult densities (Reiter and Gubler, 1997; Arrivillaga and Barrera, 2004).

- **Productivity analysis** (*Pupal and Demographic Survey*) Larval productivity indices (Chan et al., 1971; Bang et al., 1981; Tun-Lin et al., 1995a, 1996) and pupal surveys, which were developed to account for heterogeneity in container productivity (Focks and Chadee, 1997), are advances in entomological surveillance methods. Common to both is the quantification of either late instar larvae or pupae by container type or characteristic. Each does, however, have its limitations. The distribution of *Ae. aegypti*-infested containers and households can be highly clustered through time and space, making vector population estimates sensitive to sampling error and variation (Tun-Lin et al., 1995a, 1996; Focks and Chadee, 1997; Getis et al., 2003; Morrison et al., 2004a,b). Some containers are large, inaccessible, and difficult to sample adequately. Quantitative sampling strategies for immature *Ae. aegypti* include funnel traps (Kay et al., 1992; Nam et al., 1998; Russell and Kay, 1999) and standardized sweep methods using nets or dippers (Zhen and Kay, 1993; Tun-Lin et al., 1995b; Knox et al., 2007). Larval productivity indices are based on quantification of third and fourth instar larvae, which are expected to be subject to less sampling variation than pupae.

In contrast, the pupal/demographic survey methodology quantifies pupae rather than larvae (Focks et al., 1993a,b; Focks and Chadee, 1997) because in theory it is more practical to count the absolute number of *Ae. aegypti* pupae than other life stages (Southwood et al., 1972; Focks et al., 1981) and pupal mortality is slight and well-characterized. The number of pupae per person is correlated with the number of adults per person (Focks et al., 1981, 1995). The relative importance of a container type (i.e., production of adult mosquitoes) is defined as the product of the container abundance multiplied by the average standing crop of pupae (i.e., pupae per wet container). Theoretically, important container types, defined either phenotypically or functionally, can be identified and targeted in vector control campaigns providing a cost-efficient alternative to indiscriminate elimination of all potential habitats for immature *Ae. aegypti* development. Using pupal surveys as the basis of targeted control strategies is currently being evaluated in a multicountry study sponsored by the World Health Organization (WHO, 2006a).

- **Mosquito collection** Adult *Ae. aegypti* are difficult to capture; they do not readily enter traps (Jones et al., 2003). Population densities are generally low, which makes it difficult to estimate population sizes and to this point has precluded routine surveillance of adults (Reiter and Gubler, 1997). Adult capture techniques include human bait (e.g., Nelson et al., 1978; Trpis and Housermann, 1986), indoor sweeps with hand nets (e.g., Tidwell et al., 1990), and other manual methods. But these are labor intensive and subject to complex operator and loca-

tion influences (Reiter and Gubler, 1997). An attractant trap is being developed[4] but is not yet commercially available. The most effective currently available device for capturing adult *Ae. aegypti* is the battery-powered backpack aspirator (Scott et al., 1993a,b; Clark et al., 1994). Based on assessments in Thailand, backpack aspirators collect ~25 percent of adult *Ae. aegypti* in a house (Scott and Harrington, unpublished data). Aspirators can be used, therefore, to assess relative differences in adult population density. Entomological surveillance for dengue would be significantly advanced by the development of a simple, cost-effective trap for broad-scale sampling of adult *Ae. aegypti*.

Based on our research in Iquitos, Peru, immature *Ae. aegypti* indices can be informative for characterizing spatial patterns in vector infestations (Getis et al., 2003). It has been more difficult to associate mosquito density with DV transmission. In Iquitos, only immature indices were correlated with DV seroprevalence. Conversely, only adult indices captured temporal and spatial differences in DV incidence (Morrison and Scott, unpublished data). Oviposition traps (ovitraps) can be valuable for detecting the presence or absence of *Ae. aegypti*, especially when population densities are very low. We do not, however, recommend them for assessing vector abundance because they are susceptible to significant biases from competition with natural oviposition sites.

Ambient temperature Within a biologically amenable range (22-32ºC) (Focks et al., 2000), variation in ambient temperature has well-established, important effects on *Ae. aegypti* biology and seasonal trends in dengue transmission (Watts et al., 1987; Burke et al., 1980). At less than 20ºC *Ae. aegypti* eggs do not hatch. Combined mortality across all developmental stages is too high to allow populations to be sustained (i.e., $R_o<1$) at temperatures greater than 34ºC (Focks et al., 2000). Within the receptive range, temperature is negatively associated with *Ae. aegypti* development time (Gilpin and McClelland, 1979), survival (Focks et al., 1993a), and extrinsic incubation of DV (Watts et al., 1987). Conversely, blood feeding frequency is positively associated with temperature (Scott et al., 2000a,b). Because increasing temperature reduces the time necessary for pupation, Focks et al. (2000) predicted that increasing temperature only 4ºC, from 26 to 30ºC, could increase the number of adult *Ae. aegypti* by 45 percent. With regard to mosquito-virus interactions, Watts et al. (1987) detected DV-2 transmission to primates only at warm temperatures (30-35ºC) after 7-12 days of extrinsic incubation. Focks et al. (2000) predicted that 14 and 38 percent of females would survive extrinsic incubation with the potential to transmit virus to a human host when held at 22ºC versus 32ºC, respectively. Because temperature has the potential to significantly affect many important aspects of *Ae. aegypti*'s role in DV transmission, it should be considered an operationally viable component of large-scale surveillance programs.

[4]See http://www.biogents.com/en/index.html and Williams et al. (2006, 2007).

At what geographic scale should dengue surveillance and control activities be carried out? Risk factors, including measures of vector densities, can predict risk differently at different geographic scales. Geographic scale is especially important because of the modifiable areal unit problem (MAUP). MAUP refers to variation in results when data are combined into sets of increasingly larger areal units or alternative combinations of base units at equal or similar scales (Openshaw and Taylor, 1979). Both phenomena are common problems for dengue surveillance and control programs because data are most commonly reported for areal units defined by political rather than epidemiological boundaries. Historically, most *Ae. aegypti* ecologists have characterized temporal, rather than spatial, patterns in mosquito abundance (Sheppard et al., 1969; Gould et al., 1970; Yasuno and Pant, 1970). Recent studies utilized a myriad of spatial analytical tools, including point pattern analysis (Gatrell et al., 1996; Getis, 1999). The utility of these analytical tools are two-fold. First, they characterize spatial autocorrelation patterns in variables of interest. Using a practical example, we can ask if vector densities in households are more highly correlated with those in neighboring houses than houses farther away. Autocorrelation can be measured at different distances and the scale at which autocorrelation is no longer significant would represent the minimum geographic unit for which surveillance and control schemes should be applied. Recent studies demonstrate that entomological risk should be measured at a household scale (Getis et al., 2003; Morrison et al., 2004a), but the distribution of infested houses does not follow a normal distribution (Alexander et al., 2006). Consequently, sample sizes need to be high for prospective epidemiological studies and evaluation of vector interventions. Second, spatial analyses can reveal underlying patterns in different variables. For example, one can ask whether clustering patterns of dengue cases are primarily due to natural variation in *Ae. aegypti* population densities at households or whether clusters are merely the result of some a priori heterogeneity in the region where the study was conducted (Gatrell et al., 1996). In this way, specific foci of transmission can potentially be identified or evaluated in relation to proximity to specific features of interest, such as village meeting places, schools, or markets. In the case of dengue, not enough is known about the role of human movement in defining the geographic scale of transmission. Although there is clear evidence of clustering of dengue cases within households (Morrison et al., 1998), how human movement patterns affect the scale of dengue transmission remains a major knowledge gap. Defining the appropriate geographic scale for measuring entomological risk and DV transmission, which will not necessarily be the same, will be an important new contribution to dengue surveillance and control (Getis et al., 2003).

Recommendations for Improved Vector Control

After the capacity to account for inherent variation in dengue risk has been improved, it will be necessary to use that information to mitigate public health

threats. Just as it is for goal setting, enhancing dengue prevention requires rethinking current control principles and, in some cases, redirecting emphasis to topics that are presently unexplored or underdeveloped. In this section we examine four conceptual shifts in vector control that will substantially improve dengue prevention.

The Paradigm Shift from Top-Down Direction to Local Level Decision

The fundamental challenge for contemporary dengue control, regardless of the approach taken, is to develop a framework for determining in different ecologic and epidemiologic circumstances: (1) what control procedures should be used; (2) how they should be applied; and (3) how they should be evaluated and/or monitored (Box 2-1). The underlying principle will be that there is no single approach that will work across all locations or circumstances. Although some may counter that the concept of "one size does not fit all" in vector control has been known for a long time, there is no denying that it is presently underdeveloped and underemployed. Improved dengue prevention will require a paradigm shift away from the currently common practice of universally prescribed and

BOX 2-1
Key Questions for Development of Innovative, Sustainable, and Cost-Effective Dengue Prevention

- What should the site- and situation-specific goal(s) be for dengue prevention programs?
- How should control be monitored (i.e., what surveillance and risk assessment programs should be used)?
- What disease prevention tools are effective and currently available and which ones needed to be developed?
- What are the best integrated and adaptive control programs (e.g., dynamic application of vector control in concert with other disease prevention and management strategies)?
- What major steps need to be taken to develop, evaluate, disseminate, and ensure application of effective and sustainable dengue prevention?

Application will require:

(1) Validation with longitudinal cohort studies that examine mosquito vectors and human DV infection.
(2) Capacity for programmatic adaptation to site-specific circumstances.

applied strategies to one in which local control personnel decide for themselves what is the most operationally and cost-effective strategy for their particular situation. The new approach will need to be designed to account for variation in dengue transmission at different geographic locations and at different times at the same place. Local control personnel will need to constantly evaluate their surveillance and response methods. Their goals will have to be spatially and temporally specific, accounting for local variation in ecology, epidemiology, and availability of intervention resources.

An example of this would be use of pupal productivity analysis to target vector control at containers producing most of the adult *Ae. aegypti*. In some places most *Ae. aegypti* production is associated with water storage, and those containers are easily identified and treated with larvicides. In contrast, at other locations most production comes from unmanaged containers that are transient and often missed in routine entomological inspections. Control campaigns for these two extremes would be noticeably different. In Iquitos during a severe 2002 DV-3 epidemic, local health officials deemphasized an entrenched pattern of uniform larvicide applications in preference of enhanced public awareness and container clean-up. The change was motivated by solid entomological surveillance data, which indicated that adult *Ae. aegypti* were being produced primarily from unmanaged containers rather than water storage containers.

The shift from prescribed to adaptable strategies will require application of translational research, basic and applied, to the development of novel products and strategies that reduce disease. For example, dynamic, operational tools like virus transmission models and decision support systems will be necessary to guide site- and situation-specific dengue control. For a meaningful conversion of research to improved public health, it is imperative that those responsible for preventing DV transmission use surveillance information to inform their control decisions.

Surveillance and Control of Adult Versus Immature Mosquitoes

For more than half a century dengue prevention programs focused on immature *Ae. aegypti* for surveillance and control (PAHO, 1994). There are theoretical and empirical reasons for no longer strictly following that approach. With regard to surveillance, immature indices of *Ae. aegypti* density have not proven to be good predictors of DV transmission risk. Moreover, goals for immature *Ae. aegypti* surveillance are often vague and do not account for temporal and spatial variation in transmission factors. With regard to control, killing larvae is expected to have a relatively small impact on a reduction in the number of new human dengue infections, compared to killing adults.

Refocusing dengue surveillance and control on adult *Ae. aegypti* would be a significant step forward. One of the major road blocks to improved dengue surveillance is our inability to directly monitor the vector life form that transmits

virus (i.e., adult females). The need for an operationally and cost-effective way to monitor adult *Ae. aegypti* population fluctuations cannot be over-emphasized. And, even after we have a useful sampling technique we will need to think carefully about how best to use it. For example, unlike malariologists, dengue specialists do not have an informative measure of entomological risk like the entomological inoculation rate (EIR) (Scott and Morrison, 2003). Two obstacles to a dengue EIR are (1) the difficultly in collecting adult *Ae. Aegypti* and (2) the fact that virus infection rates in *Ae. aegypti* are typically too low (Kuno, 1997) to base a surveillance program on an EIR or its equivalent. An alternative approach would be to develop a dengue transmission potential (DTP) index. Leaving out mosquito virus infection status, a DTP could predict entomological risk based on the product of adult mosquito density, human-mosquito vector contact, serotype-specific susceptibility of the human population (ideally this would also include susceptibility to novel genotypes), and ambient temperature.

Dengue prevention would similarly benefit from greater attention to adult *Ae. aegypti*. Adult mosquito density has a positive nonlinear relationship with the basic reproductive number of vector-borne disease (Garrett-Jones and Shidrawi, 1969; Dye, 1992). Control strategies directed at immature mosquitoes can only reduce the density of adult mosquitoes. Killing adults similarly reduces adult density, but more importantly it shortens vector lifespan so fewer mosquitoes survive extrinsic incubation. Because extrinsic incubation for DV is expected to be relatively long compared to an average lifespan (Styer et al., 2007), killing adults before they become infectious has a greater impact on new human DV infections than does larval control. Encouraging the development of novel strategies for killing adult *Ae. aegypti* would exploit this fundamental concept and enhance dengue prevention.

We are not recommending abandoning larval control, especially in locations and cultures with strong community participation or where conditions are particularly favorable. For instance, in Vietnam biocontrol agents were available for treating a prominent and easily recognizable container class (Kay and Nam, 2005). Removal of immature *Ae. aegypti* development sites, through physical or chemical means that are targeted at containers that produce the most adults, should be considered valuable components of integrated dengue vector control programs (WHO, 2006a). Our main point here is that shifting attention from immature to adult mosquitoes for surveillance and control will stimulate development of more informative and effective methods with greater impact on reducing morbidity and mortality than an immature-centric approach.

Emphasis on Intradomicile Vector Control

Increased attention on surveillance and control of adult *Ae. aegypti* reveals the opportunity to attack them in human habitations, where they spend most of their time. Because adult *Ae. aegypti* rest, feed, mate, and reproduce in houses

(Scott et al., 2000b), it is believed that this is where they make the most frequent contact with humans (DeBenedictis et al., 2003), and thus, where most people are infected. The assumption that the home is the primary point of contact for human DV infection merits rigorous validation in prospective field studies. Nevertheless, based on existing information, attacking this species in homes is well justified. The efficacy of strategies such as indoor residual sprays (IRS) and intradomicile application of insecticide-treated materials (ITM) are strongly supported by encouraging results from a variety of *Ae. aegypti* field studies (Nam et al., 1993; Nguyen et al., 1996; Igarashi, 1997; Kroeger et al., 2006). Moreover, it has been known for some time that when insecticides do not reach *Ae. aegypti* inside homes they are ineffective (Reiter and Gubler, 1997). Novel products and systems for delivery of insecticidal products into homes will enhance broad-scale intradomicile dengue prevention programs. It is essential that means for detecting and managing insecticide resistance are incorporated into an overall plan for adult mosquito control programs to prevent dengue. Because intradomicile control is conceptually consistent with the current public health policy for dengue (i.e., managing disease by managing mosquito vector populations) (PAHO, 1994) it should be promoted to enhance disease prevention.

Advantages from this approach transcend *Ae. aegypti* and dengue. Intradomicile insect control will decrease densities and lifespans of dengue and nondengue insect vectors and pests and, thereby, help reduce the long list of public health problems that they represent. For example, in addition to dengue, the home is a major point of infection for pathogens like malaria, lymphatic filariasis, leishmaniasis, and Chagas disease. A variety of insect vectors (e.g., *Ae. aegypti, Anopheles gambiae, An. funestus, Culex quinquefasciatus*, sandflies, and triatomids) bite and infect humans in their homes. Pest insects (e.g., bed bugs, cockroaches, filth flies, and pest mosquitoes) are similarly too often abundant in homes and can lead to the perception that control measures directed at specific vectors (i.e., *Ae. aegypti*) are not effective. Knowledge gained from an improved understanding of peridomestic insect ecology can be effectively applied in intradomicile control strategies that address a variety of disease and pest problems. In so doing, what was originally conceived as an *Ae. aegypti* control program can be leveraged into a cost- and operationally effective public health program that reduces a variety of diseases and pest problems.

Integrated Disease Prevention: Vector Control and Vaccines

It is generally accepted that an integrated, multidimensional control strategy is superior to a single line of attack (Shea et al., 2000). Thus, vector control guidelines frequently and justifiably include recommendations for disease prevention that combine different vector interventions (WHO, 2006a). We propose to take the notion of integrated disease prevention a step farther, across disciplines that traditionally have not been used in combination by applying vector control and

a vaccine together. The justification for our recommendation is that in concert these two methods will act sooner and be more sustainable than either method by itself. The synergetic benefit, from vector control and chemotherapy, has been documented for lymphatic filariasis (Sunish et al., 2007). Proof of principle with another vector-borne disease justifies serious consideration of a similar strategy for dengue prevention. In this approach, we view both strategies as public health tools, rather than something intended to protect individuals. The overall goal is to sustain a lowered force of DV transmission, ideally so that the basic reproductive number (R_o) for dengue is less than one. If that is accomplished, disease would correspondingly decrease and DV transmission could conceivably be eliminated from treated areas.

The combined benefit of vector control and a vaccine comes from their complimentary impact on reducing R_o. The critical proportion of a population that must be vaccinated to eliminate transmission of a pathogen is derived by the equation $P_c = 1 - (1/R_o)$ (Anderson and May, 1991). Although, R_o for any pathogen varies through time and space, if we assume that for dengue $R_o = 10$ the critical proportion to vaccinate will be 90 percent. If R_o can be reduced by reducing the density of vector mosquitoes a smaller proportion of susceptible people will need to be vaccinated (i.e., if $R_o = 2$ then $P_c = 50$ percent). Vector control, therefore, makes it easier to meet vector-borne disease vaccine delivery goals.

The positive impact of a vaccine on vector control concerns the issue of sustainability. There are numerous examples of effective vector control over the short term (Ooi et al., 2006). The big challenge is to sustain disease suppression. This is because effective vector control lowers the incidence rate. The aim of vector control, short of vector eradication, is to lower the force of pathogen transmission. Recruitment into the population of susceptible people by birth is sufficient to gradually decrease herd immunity over time to the point where mosquito densities necessary to avoid unacceptable levels of transmission are so low that operationally they are close to vector eradication. Accordingly, over the long term, vector control becomes increasingly difficult to sustain. If, however, herd immunity can be artificially elevated by vaccination this difficult battle does not need to be fought. Vaccination can be used to sustain artificially elevated levels of herd immunity and at the same time the force of DV transmission can be diminished by vector control. The result is an operational capacity to sustain R_o below 1. Vaccination as a public health tool, therefore, makes sustained vector control a realistic possibility.

Clinical cures for dengue will be important for disease management, but are not likely to have a major impact on virus transmission because DV viremia is brief (i.e., 3-7 days), many DV infections are asymptomatic (Waterman and Gubler, 1989; Focks et al., 1995; Rigau-Perez et al., 1998), and most people do not seek medical attention until after they have been viremic for some time or after their viremia has subsided altogether (Vaughn et al., 2000). Drugs will be

valuable in a clinical setting but are not expected to reduce DV transmission unless applied prophylactically on a broad scale.

Conclusions

The transition from prescribed to adapted dengue prevention will need to be guided by meaningful goals and accomplished with effective tools. Goals will be reached if enhanced vector control is framed by an improved understanding of vector ecology in pathogen transmission. Longitudinal field studies that capture entomologic, virologic, and epidemiologic information are the most effective ways to assess fundamental assumptions and refine new techniques. The following are key tasks that need to be addressed to meet these objectives:

- Design operationally and epidemiologically effective ways to assess risk of DV transmission and set goals for disease prevention.
- Create an inexpensive and effective tool for monitoring adult *Ae. aegypti* population density.
- Develop a rapid, sensitive, specific, and inexpensive way to estimate serotype-specific herd immunity that can be used to predict risk of epidemic DV transmission.
- Encourage the use of dengue vaccines as public health tools to artificially elevate immunity in an integrated disease prevention program with vector control.
- Evaluate more effective and operationally feasible means of reducing adult *Ae. aegypti* density that can be readily adapted to situation-specific circumstances.
- Promote field-based prospective longitudinal cohort research in disease-endemic locations that assesses adaptive intervention strategies based on relationships among measures of entomologic and epidemiologic risk, dengue incidence, and severity of disease.

Accomplishing these tasks will translate into the most important attributable benefit from vector control for dengue—reduction of disease burden and death.

INNOVATIVE DECISION SUPPORT AND VECTOR CONTROL APPROACHES TO CONTROL DENGUE

Lars Eisen, Ph.D.[5]
Colorado State University

Barry J. Beaty, Ph.D.[5]
Colorado State University

Summary

Vector-borne diseases (VBDs) remain major threats to human health and well-being. The 2003 *Microbial Threats to Health* report from the Institute of Medicine challenged the global research and public health community to develop new tools, approaches, and capacities to predict, prevent, and control the emergence and resurgence of VBDs. Among these were recommendations to develop new computer-based systems and new approaches for vector control. The Innovative Vector Control Consortium (IVCC) is addressing these needs for dengue and malaria; this includes funding a Colorado State University project aiming to develop a computer-based Dengue Decision Support System (DDSS), syndromic surveillance for early detection of and intervention in dengue outbreaks, and a "Casa Segura" safe house proactive vector control approach. The need for a shift toward proactive vector control approaches and integrated vector management strategies also is highlighted.

Introduction

As an epidemiological group, VBDs, such as dengue, filariasis, leishmaniasis, malaria, onchocerciasis, trypanosomiasis, and other vector-borne bacterial, parasitic, or viral diseases, are the causes of inestimable misery, morbidity, and mortality in humans and impediments to socioeconomic development in many parts of the world (IOM, 2003; see also Beaty and Eisen in this report). A number of actions to address major needs in prediction, prevention, and control of VBDs were suggested in the *Microbial Threats to Health* report from the Institute of Medicine (IOM, 2003). In this paper, we will describe ongoing initiatives and activities pertinent to two of these recommendations:

- Expand efforts to exploit geographic information systems (GIS) and robust models for predicting and preventing the emergence of vector-borne and zoonotic diseases, and exploit innovative systems of surveillance that capitalize on advances in information technology.

[5]Arthropod-borne and Infectious Diseases Laboratory, Department of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins, Colorado.

- Develop new and expand upon current research efforts to enhance the armamentarium for vector control, including improved pesticides and formulations, novel strategies to prolong pesticide usage, new repellents, and new biopesticides and biocontrol agents to augment chemical pesticides.

The IVCC is helping to address these needs for dengue and malaria by funding projects to develop new tools and approaches to enhance vector and disease surveillance and control. This paper will focus primarily on dengue, which is caused by four dengue virus serotypes (DENV 1-4), and is transmitted primarily by the yellow fever mosquito *Aedes aegypti*. Epidemic dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) have increased dramatically throughout the tropics in recent decades (Gubler, 2002a, 2004; Guzman and Kouri, 2003; IOM, 2003). There are critical needs and opportunities for new tools and approaches for control of dengue and other VBDs.

New Initiatives, Approaches, and Tools for Vector-Borne Disease Prediction, Prevention, and Control

The response of the nation and world to the challenges associated with VBDs has been generally positive. The Bill and Melinda Gates Foundation has numerous programs involving vector control, including one of the Grand Challenges, and the World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases (TDR) has initiated a new program—Innovative Vector Control Interventions. The portfolio of vector grants has exploded at the National Institutes of Health (NIH). Finally, the Innovative Vector Control Consortium is directly aligned with the Institute of Medicine recommendations concerning GIS and modeling approaches and the development of new tools, approaches, and public health insecticides for vector control.

The Innovative Vector Control Consortium

The IVCC was formed to improve control of mosquito-borne diseases (Hemingway et al., 2006). Consortium institutions include the Liverpool School of Tropical Medicine, the London School of Hygiene and Tropical Medicine, the Medical Research Council of South Africa, Colorado State University, and the University of California, Davis. The overarching goal of the IVCC is to improve vector control in and around the home, where many VBDs are preferentially transmitted. Malaria in sub-Saharan Africa, Chagas disease, dengue, filariasis, and leishmaniasis are transmitted to humans principally indoors by endophagic and/or endophilic vectors. The IVCC established two major objectives to address these VBDs:

1. Develop new public health insecticides and formulations for vector control
2. Develop new tools and approaches for vector control

In objective 1, the IVCC is partnering with industry to facilitate and expedite discovery, development, and deployment of new public health insecticides and/or formulations for vector control. The rationale and approach for IVCC objective 1 activities are provided by Hemingway et al. (2006).

In objective 2, the IVCC is funding projects to develop new tools and approaches for vector control. The current objective 2 project portfolio targets malaria and dengue and includes product development projects focused on operational tools for rapid detection of insecticide resistance (Vector Population Monitoring Tool project) and determination of efficacy of insecticide-treated materials (Pyrethroid Quantification Kit project). Three additional objective 2 projects focus on malaria and dengue modeling and development of decision support systems for vector and disease control program operational management (Malaria Decision Support System, Dengue Decision Support System, and Dengue Modeling projects).

Decision Support System Approaches to Facilitate Control of Vector-Borne Diseases

Computer-based decision support systems have been evaluated and used extensively in clinical and diagnostic medicine (e.g., Miller, 1994; Del Fiol et al., 2000; Montgomery et al., 2000; Colombet et al., 2003; Sefion et al., 2003), veterinary medicine (e.g., Stärk et al., 1998; Gu et al., 1999; Sanson et al., 1999), and for agriculture and forestry pest management (e.g., Knight, 1997; MacLean et al., 2000; Hearn and Bange, 2002). This approach has great potential for improving surveillance, prevention, and control of VBDs affecting humans. Vector control programs implementing a decision support system will benefit from improved logistical capacity for data management and analysis and an emphasis on evidence-based and rational decision making, leading to the implementation of effective control program strategies, methodologies, and management.

Following the emergence of West Nile virus (WNV) in the United States, the ArboNET system was developed to achieve a rapid flow of information of WNV activity in vectors, domestic and wild animals, and humans from local and state health departments to a national database managed by the Centers for Disease Control and Prevention (CDC). Map outputs showing up-to-date activity of WNV and other arboviruses included in ArboNET are available through a website managed by the U.S. Geological Survey.[6] A similar system for WNV surveillance has been implemented in Canada (Gosselin et al., 2005). Other examples from North

[6]See http://diseasemaps.usgs.gov.

America include a web-based multimedia spatial information system to document *Ae. aegypti* breeding sites and dengue fever risk along the U.S.-Mexico border (Moreno-Sanchez et al., 2006) and the use of GIS for malaria surveillance and control in Mexico (Hernandez-Avila et al., 2006).

The Ross River virus Early Detection and Surveillance (RREDS) system managed by the Queensland Institute of Medical Research, Australia, is another example of a web-based system to achieve rapid flow of information regarding arbovirus activity from local health authorities to a central database (Ryan et al., 2006). In addition, the RREDS system generates a near-real-time comparison of the current intensity of virus activity (expressed as activity over a 3-week moving window) to a historical average for the same time period; this allows for early warning of increased virus activity (alert threshold) relative to the "normal" situation. In the global arena, WHO's DengueNet[7] provides a variety of dengue-related data, which can be accessed in table and map formats. Similar information for malaria in Africa is available from the MARA/ARMA—Mapping Malaria Risk in Africa project[8] and the Malaria Atlas Project.[9]

Perhaps the best examples of operationally functional computer-based GIS or decision support systems for VBDs in the developing world comes from systems for malaria surveillance and control and insecticide resistance management developed by the Medical Research Council of South Africa (Booman et al., 2000, 2003; Martin et al., 2002; Coleman et al., 2006; Sharp et al., 2007a). Other positive examples include systems for urban malaria control in India (Srivastava et al., 2003), management of human African trypanosomiasis in Ethiopia and Zambia (Robinson et al., 2002; Sciarretta et al., 2005; Symeonakis et al., 2007), and vector and dengue surveillance and control in Brazil and Singapore (Ai-leen and Song, 2000; Teng, 2001; Rosa-Freitas et al., 2003).

Development of a comprehensive decision support system for management of a VBD needs to take into account data related to vector, pathogen, and disease surveillance as well as vector control, pathogen control, clinical information, diagnostic testing, behavior and education of the human population, and demographic and socioeconomic conditions. We are currently developing a DDSS that will support local and regional vector control programs, will be made freely accessible for self-application by end-users through application packages offered from a website, and will be rationally designed to promote information flow between local, regional, national, and even international stakeholders. The computer-based DDSS will aid and systematize the process of gathering and analyzing information, gaining new insights, generating alternatives, and ultimately, making evidence-based decisions regarding vector and disease surveillance and control (Figure 2-1).

[7]See http://www.who.int/csr/disease/dengue/denguenet/en/index.html.
[8]See http://www.mara.org.za.
[9]See http://www.map.ox.ac.uk/MAP_data.html.

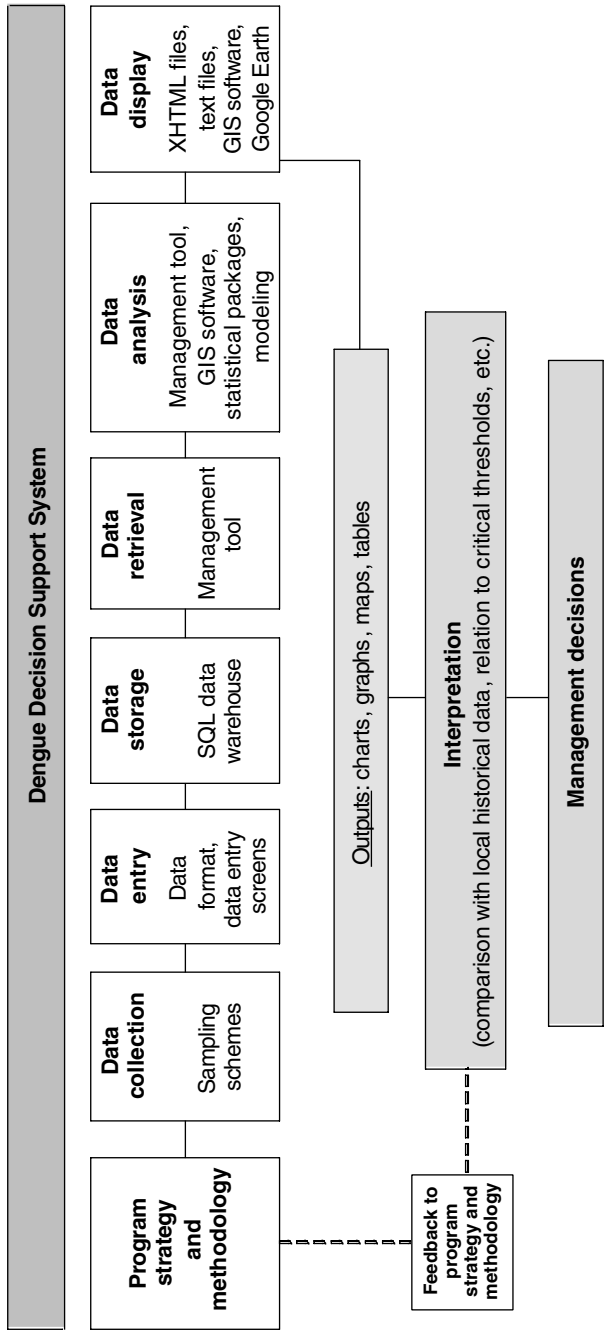

FIGURE 2-1 Flow scheme for a Dengue Decision Support System.

The potential for developing decision support systems for management of VBDs has been enhanced by the emergence of GIS technology and the rapidly increasing availability of cartographic, demographic, socioeconomic, and environmental GIS-based data. Using dengue as an example, GIS provides capacity for the presentation of spatial and spatiotemporal patterns of risk of exposure to vectors and dengue virus based on location-specific information (e.g., Morrison et al., 1998, 2004a; Indaratna et al., 1998; Carbajo et al., 2001; Teng, 2001; Ali et al., 2003; Getis et al., 2003; Muttitanon et al., 2004; Siqueira et al., 2004; Sithiprasasna et al., 2004; Tran et al., 2004; Chadee et al., 2005; van Benthem et al., 2005); and development of predictive spatial risk models based on correlates between GIS-derived data and vector or disease measures (Peterson et al., 2005; Rotela et al., 2007). Free mapping software tools providing access to high-quality satellite imagery (e.g., Google Earth, MS Virtual Earth) are a powerful complement to GIS software for presentation of information overlaid on an image showing the physical environment (Figure 2-2).

FIGURE 2-2 Example from Chetumal, Mexico, of quality of imagery accessed through Google Earth.

Incorporation of a GIS spatial backbone into the DDSS framework and collection of spatial reference information for vector- or disease-related data (see Figure 2-3) will allow the user to readily link information from different data categories (e.g., disease case locations, implementation of vector control measures, and insecticide resistance in local vector populations) for analysis and display. An outline of data categories and data types potentially included in a full-capacity DDSS for implementation in a resource-rich environment, including the downstream potential for a vaccine against dengue virus, is shown in Figure 2-3. The flexibility of the DDSS framework will, however, allow for implementation of locally adapted and scaled-down DDSS versions to fit other resource environments. For example, in a resource-poor environment perhaps only the vector control, vector surveillance, and passive disease surveillance components will be used together with a very basic spatial backbone.

Expected key outcomes from implementation of the DDSS include improved capacity for data collection, entry, storage, retrieval, analysis, and display; and evidence-based decision making and use of locally appropriate vector/disease control program strategies and methodologies.

Syndromic Surveillance and Use of Priority Areas for Emergency Vector Control to Facilitate Early Dengue Outbreak Response

The severity of dengue outbreaks can be exacerbated by slow and unfocused vector control responses. Vector control programs commonly do not initiate reactive control measures until they receive laboratory diagnosis of dengue infections. Several weeks to a month may elapse before diagnostic results become available and during that time a dengue outbreak may spread rapidly through a city and overwhelm vector control resources. This underscores the need for implementation of an effective dengue surveillance system (Rigau-Perez and Gubler, 1997; Gubler and Casta-Valez, 1991; Gubler, 2002b), and, indeed, argues for use of a syndromic surveillance approach to achieve early warning of dengue outbreaks. In a computer-based DDSS, we envision clinical data to be entered into an electronic case report form at local health clinics and syndromic surveillance information, either based on physician diagnosis or an algorithm to separate dengue from other commonly occurring diseases based on symptomology, to reach the vector control program in real time, thus minimizing vector control response time. The feasibility of the syndromic surveillance approach will be operationally tested in Merida, Mexico, in collaboration between Colorado State University, Universidad Autonoma de Yucatan, the Servicios de Salud de Yucatan, Centro Nacional de Vigilancia Epidemiologica y Control de Enfermedades, and Instituto Nacional de Salud Publica. Another problem commonly facing vector control programs is that dengue cases spread rapidly throughout a city and overwhelm vector control response capacity. In this situation, it is critical to have a rational spatial response plan where high-risk priority areas are treated before areas with lower risk. Des-

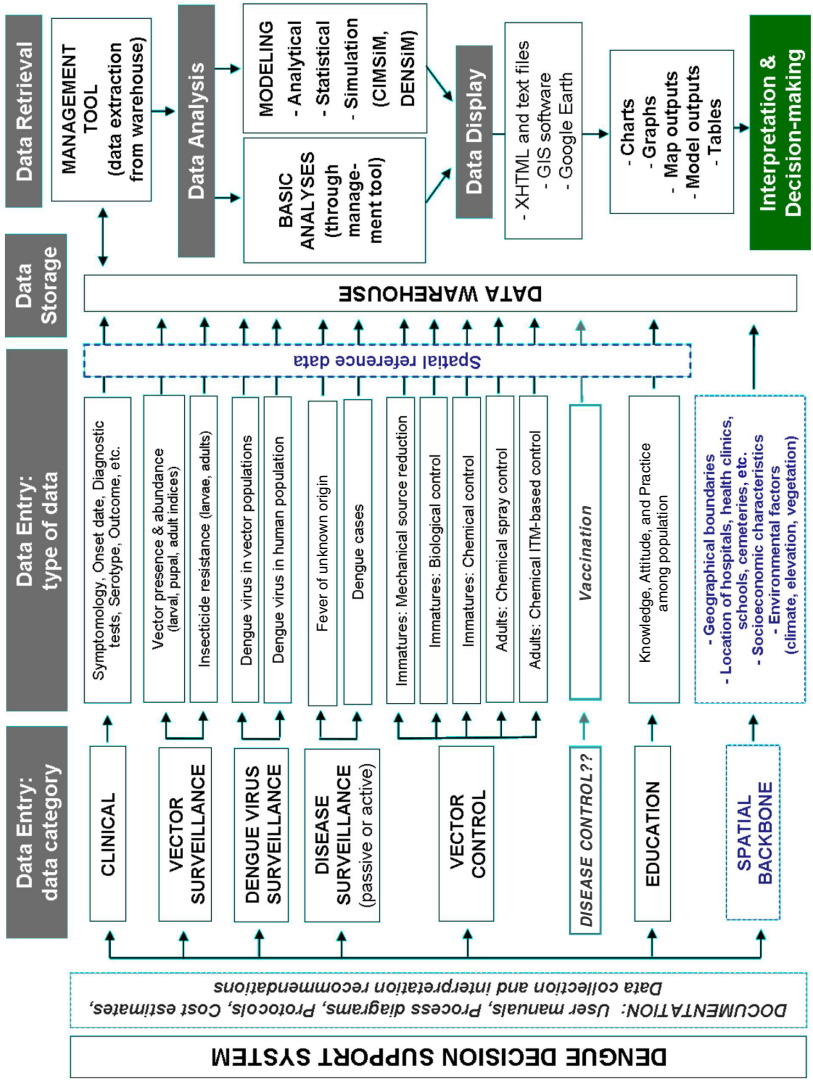

FIGURE 2-3 Outline of data potentially included in a full-capacity Dengue Decision Support System.

ignation of priority areas for emergency vector control can be based on historical entomological and epidemiological data and adjusted in near real time based on syndromic surveillance data from the DDSS. Combined, syndromic surveillance and use of priority areas for emergency vector control will provide unprecedented capacity to intervene in impending dengue epidemics.

Management of Insecticide Resistance and the Development of New Insecticides

Insecticides will remain the front line of control of mosquito-borne diseases for the foreseeable future. Unfortunately, no new public health insecticides for adult mosquitoes have been developed in more than 30 years, and the number of insecticides available for mosquito control is severely limited (Hemingway et al., 2002, 2006). The recent report of reduced efficacy of bednets and indoor residual spraying (IRS) associated with pyrethroid resistance in Benin (N'Guessan et al., 2007) is of great concern. In the case of *Ae. aegypti*, numerous studies have documented resistance to commonly used insecticides, potentially removing them from the armamentarium used by vector control programs. Increasing resistance to temephos, which is widely used for control of *Ae. aegypti* immatures, has resulted in a shift toward the operational use of *Bacillus thuringiensis israelensis* (Bti) in parts of Brazil (Lima et al., 2003; Braga et al., 2004). Resistance to pyrethroids is being documented in many dengue-endemic countries (e.g., Rodriguez et al., 2001, 2005; Houng et al., 2004; da-Cunha et al., 2005; Flores et al., 2005; Paeporn et al., 2005; Ponlawat et al., 2005), with potential ramifications for operational control of adult *Ae. aegypti*.

Routine operational testing for insecticide resistance in dengue virus and malaria vectors is still lacking in many disease-endemic areas, and positive examples of evidence-based insecticide resistance management schemes are scarce. Examples include the switch to Bti in response to tempehos resistance in Brazil mentioned earlier and the development in South Africa of an evidence-based decision support system for rational insecticide choice in the control of African malaria vectors (Coleman et al., 2006; Coleman and Hemingway, 2007). Indeed, decision support systems provide exceptional capacity for monitoring and mitigating resistance, developing insecticide resistance management schemes, and evaluating the efficacy of new insecticides (Hemingway et al., 2006; Coleman et al., 2006; Coleman and Hemingway, 2007). These systems also will facilitate critically needed evaluations of the operational impact of insecticide resistance on the efficacy of specific insecticide-based vector control measures (for example, use of insecticide-treated bednets or curtains to reduce pathogen transmission in the home environment). The IVCC-funded Dengue and Malaria Decision Support System projects will monitor insecticide resistance in targeted vector populations, thereby permitting better stewardship of insecticides and improved vector control (Hemingway et al., 2006; Coleman and Hemingway, 2007).

The "Casa Segura" Safe House Approach to Control of Vector-Borne Diseases

Targeting the vector in the domicile offers great potential for control of VBDs that are transmitted indoors. Indeed, much of the success of DDT in the past was attributed to its ability to kill or repel endophagic vectors (Roberts et al., 1997; Gratz, 1999; Attaran et al., 2000). In this regard, one of few success stories in VBD control in recent times has been the dramatic reduction of Chagas disease (American trypanosomiasis) in South America following implementation of the Southern Cone Initiative (Schofield and Dias, 1999; Dias et al., 2002). This initiative included a combination of IRS to control reduviid vectors and screening blood donors to avoid transfusional transmission. The IRS approach dramatically reduced the prevalence of *Triatoma infestans* vectors in the domiciles and, ultimately, resulted in near elimination of Chagas disease in parts of southern South America. Many other VBDs are also transmitted in large part indoors (e.g., malaria in much of sub-Saharan Africa, dengue, leishmaniasis, and filariasis), and are thus susceptible to similar domicile-targeted interventions. The advent of long-lasting insecticide-treated materials (LL-ITMs), which can remain efficacious for more than 5 years, for use in bednets for malaria control has also been a public health success (e.g., N'Guessan et al., 2001; Hawley et al., 2003; Tami et al., 2004; Dabire et al., 2006); these materials also offer great potential for control of other diseases transmitted in the house. We are exploring a "Casa Segura" safe house approach for control of dengue using LL-ITMs as curtains. This approach is predicated upon previous studies demonstrating the potential for using ITMs as curtains to reduce vector abundance and dengue virus transmission in Southeast Asia (Nam et al., 1993; Nguyen et al., 1996; Igarashi, 1997; Madarieta et al., 1999) and the Americas (Kroeger et al., 2006). Entomological indices were not only dramatically reduced in and near intervention homes, but there was also a community effect on vector abundance (Kroeger et al., 2006). Currently studies are being initiated in an urban setting in Merida, Mexico, in collaboration with local, state, and national public health officials to assess the protective efficacy of LL-ITMs in a 3-year longitudinal study. Conceptually, a "Casa Segura" provides protection similar to a well-built and air-conditioned home. The presence of window screens and air conditioning recently was shown to be a key factor explaining discrepancies between outdoor abundances of *Ae. aegypti* immatures and dengue incidence between "sister cities" on opposite sides of the U.S.-Mexico border (Reiter et al., 2003). LL-ITMs in the form of curtains or wall hangings can potentially protect homes, schools, or other structures where people are exposed to bites by *Ae. aegypti* for multiple years at low cost. Protection may also extend to other disease vectors or pest insects, including nuisance-biting *Culex* mosquitoes, thereby making LL-ITMs a broad-spectrum public health product, rather than one stove-piped to protect against a single disease. For example, use of insecticide-treated curtains in the Americas may offer protection against vectors of dengue, Chagas disease, cutaneous leishmaniasis,

and malaria (Xavier and Lima, 1986; Figueiredo et al., 1998; Kroeger et al., 2002, 2006; Herber and Kroeger, 2003). Finally, LL-ITMs and other future low-cost interventions to create a "Casa Segura" also provide a business opportunity since the approach can be implemented both as part of a proactive vector control program and as a private homeowner initiative.

The Need for Proactive Vector Control Approaches and Integrated Vector Management Strategies

The limited success of reactive vector control approaches (especially vehicle-based ultra low volume [ULV] spraying in response to detection of dengue cases) to combat dengue over the last decades highlights the need for a shift toward more proactive vector control approaches implemented as part of an integrated vector management strategy (Reiter and Gubler, 1997; Gubler, 2002c; Townson et al., 2005; Kroeger and Nathan, 2006). The "Casa Segura" approach discussed earlier is one example of a proactive vector control measure targeting the adult mosquito. In an integrated vector management strategy, the "Casa Segura" could be implemented together with promising proactive approaches for control of immature mosquitoes (i.e., targeting of chemical or biological control measures to especially productive container types [Alexander et al., 2006; Focks and Alexander, 2006; Nathan et al., 2006] and community-based programs for source reduction, such as the Patio Limpio program now being widely implemented in Mexico).[10] The latter type of program may, however, need to be supported by legislation and fines for noncompliance to ultimately become an effective and sustainable vector control measure.

Although there has been a recent resurgence in dengue, Singapore provides a positive example of how an aggressive, proactive, and multifaceted approach can reduce dengue transmission compared to that in surrounding areas (Goh, 1995; Reiter and Gubler, 1997; Ooi et al., 2006). The Singapore model was based on a program initiated in the late 1960s and combined aggressive implementation of vector surveillance and control measures, health education, slum clearance, improvements in water supply and storage practices to reduce vector breeding sites, and legislation (the 1968 Destruction of Disease Bearing Insects Act, which later was replaced by the 1998 Control of Vectors and Pesticide Act) to ensure public compliance in removal of vector breeding sites from the domestic environment (Chan and Counsilman, 1985; Lok and Bos, 1987; Ooi et al., 2006). This was later complemented by the use of GIS for vector and disease surveillance and to identify dengue virus transmission hotspots for improved targeting of vector control activities (Ai-leen and Song, 2000; Teng, 2001). Several possible explanations for the recent resurgence of dengue in Singapore despite its comprehensive vector/dengue control program have been offered (e.g., overall lowered

[10]See http://www.cenave.gob.mx/dengue/default.asp?id=81/.

herd immunity of the human population and an increase in adult cases, emphasis away from vector surveillance toward detection of dengue case clusters followed by reactive implementation of vector control measures). Further insights into this matter will provide valuable information facilitating the process of restoring the Singapore program to its former level of performance.

To achieve a global shift in resource allocation from reactive to proactive vector control approaches, there is a need for partnerships between academic institutions conducting research on outcomes of different proactive vector control approaches and the public health community ultimately charged with deciding how available resources should be allocated between proactive vector control measures, vector surveillance, dengue surveillance, and reactive emergency vector control measures.

Conclusion

Although the challenges are great, there is currently considerable excitement in the field of VBDs for the development of new tools and approaches to predict, prevent, and control disease. Exciting new advances in information technology, disease modeling, GIS-based risk assessment, and long-lasting insecticide delivery mechanisms (e.g., LL-ITMs) offer great potential for improved management of VBDs. Our new mandate is to translate the explosion of new information into field-relevant tools and management strategies, and to train a new generation of vector biologists and medical entomologists capable of incorporating the new methodologies into daily vector and disease control operations. To facilitate this process, there is a need for new research and training programs, and for partnerships between academic institutions, business interests, and the public health community.

Acknowledgments

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WEST NILE VIRUS

Lyle R. Petersen, M.D., M.P.H.[11]
Centers for Disease Control[12]

The West Nile virus (WNV) is a single-stranded RNA virus belonging to the family *Flaviviridae,* genus *Flavivirus.* Several of the nearly 70 known viruses in this genus are human pathogens; some cause encephalitis or febrile illness, including hemorrhagic fevers such as dengue and yellow fever (hence "flavi," meaning yellow). They are grouped into three phylogenetic clusters: one has no known arthropod vector; one is tick-borne; one, which includes WNV, is mosquito-borne (Kuno et al., 1998). WNV is part of a serocomplex that includes Japanese encephalitis and its close relative, St. Louis encephalitis, a disease with a long history in North America. WNV and its close relatives are primarily bird viruses that produce low viremias in humans and horses, which therefore serve as non-amplifying hosts.

WNV was first isolated in 1937 from the blood of a febrile woman in the West Nile district of what is now Uganda. Subsequently, it was commonly found in humans, birds, and other vertebrates in Asia, Eastern Europe, and Africa, and was associated with sporadic cases of febrile illness, meningitis, and encephalitis in numerous countries (Murgue et al., 2002). From the 1940s through 1980, outbreaks of varying size occurred throughout these regions and mainly in Israel (Marberg et al., 1956); only one, which occurred in an Israeli nursing home in 1957 (Spigland et al., 1958), was associated with a high incidence of severe morbidity. A major WNV outbreak in South Africa in 1974 caused tens of thousands of cases of febrile illness without a single reported case of meningitis or encephalitis.

Beginning in 1994, WNV outbreaks with a high incidence of severe morbidity occurred in Algeria (1994), Romania (1996), Tunisia (1997), Russia (1999, 2000, and 2001), Israel (2000), and Sudan (2002) (Mackenzie et al., 2004). The 2000 Israeli outbreak is notable because it was accompanied by bird mortality. It was this neuroinvasive strain, or its very close relative, that was imported into the United States to cause the first domestic outbreak in 1999, in New York City (Lanciotti et al., 1999). Similar strains, all of which are associated with bird mortality and mouse neurovirulence, constitute a new group within the phylogenetic tree of WNV, as shown in Figure 2-4. Researchers (Brault et al., 2007) have subsequently demonstrated that increased bird mortality due to these strains resulted from a single nucleotide change in a nonstructural protein.

[11]Director, Division of Vector-Borne Diseases, Fort Collins, Colorado.

[12]The findings and conclusions in this report are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.

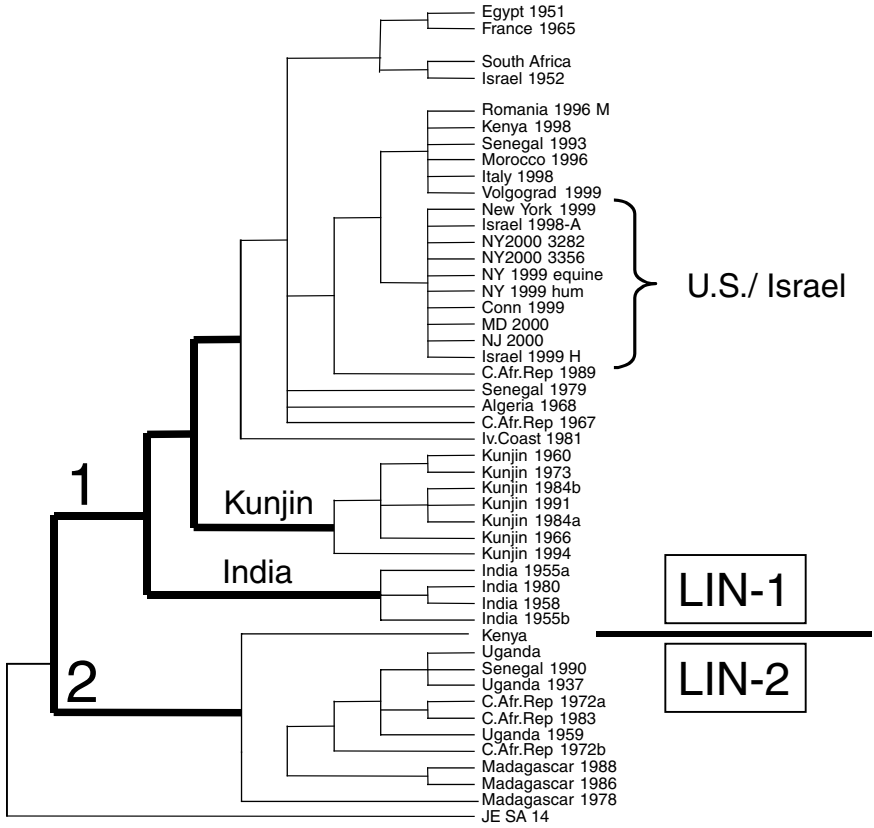

FIGURE 2-4 Phylogenetic tree of West Nile virus. Only lineage 1 viruses are frequently associated with human or animal disease. Note the genetic similarity of isolates identified from recent human outbreaks in Romania, Senegal, Morocco, Russia, Israel, and the United States. The U.S. isolates are nearly genetically identical to those found in Israel, suggesting importation from the Middle East.
SOURCE: From Lanciotti et al. (1999). Reprinted with permission from the American Association for the Advancement of Science.

Surveillance

Response to the 1999 New York City outbreak included the creation of the first and currently only national human-veterinary disease surveillance system, called ArboNET. Administered by the Centers for Disease Control and Prevention (CDC), ArboNET is a real-time electronic reporting system that captures data on WNV in humans, dead birds, mosquitoes, horses, and live captive sentinels (chickens) (Gubler et al., 2000). These data are collected and reported to CDC

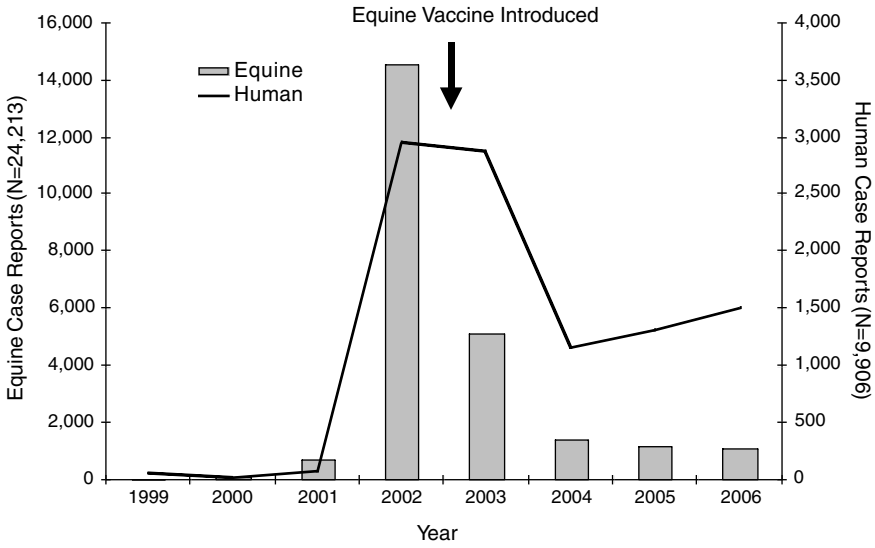

FIGURE 2-5 Equine and human West Nile virus neuroinvasive disease cases, by year, United States.

by health departments across the country. Between 1999 and 2006, ArboNET has detected 62 species of mosquitoes that are positive for WNV—a huge number for an arbovirus—although more than 98 percent of infected mosquitoes collected belong to the genus *Culex* (CDC, 2007a). WNV is associated with an enormously high prevalence of virus in mosquitoes, such that during WNV outbreaks, infection rates are measured in percents of mosquitoes infected, rather than per thousand, a more typical rate of infection for an arboviral vector.

From 1999 through 2006, 317 species of WNV-positive dead birds were reported to ArboNET (CDC, 2007a). In 2006, American crows and blue jays accounted for 62 percent of the total reported (however, some reporting bias is likely as both species are relatively common in urban settings, large, and morphologically distinct). Recent data indicate that declines in crow and other susceptible bird populations have accompanied the introduction of WNV into an area (LaDeau et al., 2007). Figure 2-5 illustrates trends in cases of neuroinvasive WNV disease among humans and horses. The introduction of an equine WNV vaccine before the 2003 transmission season has markedly decreased the incidence of disease in horses.

A Hidden Epidemic

Table 2-1 summarizes reports of human WNV cases in the United States to date, including more than 9,900 cases of neuroinvasive disease in the form of

TABLE 2-1 Reported West Nile Virus Disease Cases in Humans, by Clinical Syndrome, United States, 1999-2006

Year	WNND[a]	Fever	Other[b]	Total	Deaths
1999	59	3	0	62	7
2000	19	2	0	21	2
2001	64	2	0	66	9
2002	2,946	1,160	50	4,156	284
2003	2,866	6,830	166	9,862	264
2004	1,148	1,269	128	2,539	100
2005	1,309	1,607	99	3,000	119
2006	1,495	2,616	194	4,269	177
Total	9,906	13,489	637	23,975	962

[a]WNND = West Nile virus neuroinvasive disease.
[b]Other = Other clinical syndrome or syndrome unspecified.

encephalitis, meningitis, and acute flaccid paralysis. These numbers are probably accurate because the vast majority of patients with neuroinvasive disease are hospitalized and reported. On the other hand, the 13,000 reported cases of West Nile fever significantly underestimate the number of actual cases. Serosurveys show that about 75 percent of WNV infections are asymptomatic; the other 25 percent develop West Nile fever, and about 1 in 140 of these individuals develops neuroinvasive disease (Tsai et al., 1998; Mostashari et al., 2001). Extrapolations of these ratios to the number of neuroinvasive disease cases reported indicate that approximately 1.4 million infections have occurred in the United States (thus, the actual number of fever cases to date is approximately 323,000). This "hidden epidemic" of WNV poses a serious threat to the U.S. blood supply, as will be subsequently discussed.

Geographic Patterns of WNV Neuroinvasive Disease Incidence

The series of maps shown in Figure 2-6 depicts the incidence of WNV neuroinvasive disease in U.S. counties each year since the inception of surveillance in 1999. In that year, all of the cases occurred around New York City, but WNV activity was detected in animals and mosquitoes across a much wider area. In 2000, WNV moved northward in the spring along with migrating birds, then southward again in the fall (CDC, 2000). This is the only really clear evidence, provided by ArboNET data, for the importance of bird migration to the spread of WNV in the continental United States.

In 2001, as expected, an enzootic area formed in the southeastern United States, resulting in sporadic human cases of WNV neuroinvasive disease (CDC, 2001). Although human cases were limited to this region as well as the Northeast, the virus spread to the Mississippi River and beyond. The first large outbreak

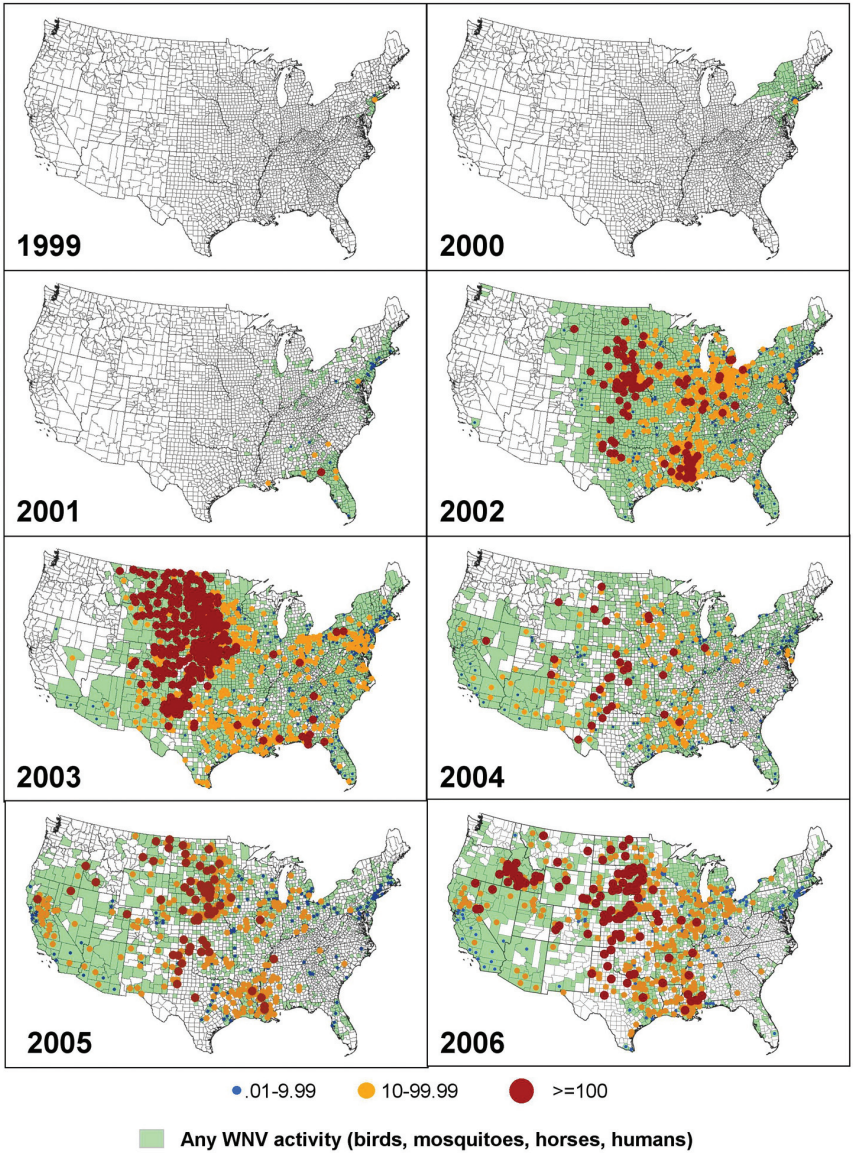

FIGURE 2-6 West Nile virus activity and human neuroinvasive disease incidence per million population, by county, United States, 1999-2006.
SOURCE: CDC (2007c).

of WNV disease occurred in Chicago and other cities near the Great Lakes, Mississippi, and Louisiana in 2002 (O'Leary et al., 2004); like the 1999 New York City outbreak, this outbreak occurred during a heat wave, as did outbreaks that spanned much of the Midwest in 2003, and again in 2005 and 2006 (CDC, 2007a). By 2004, WNV had become endemic in much of the United States and had reached the West Coast. Outbreaks occurred in desert locations, such as Phoenix, Arizona; this seems remarkable until one realizes that these places have been transformed by humans—who have built golf courses, swimming pools, and reservoirs—into urban oases capable of supporting extensive mosquito breeding. An analysis of data from 2002 through 2006 showed that North and South Dakota, Wyoming, Colorado, and Nebraska had a cumulative incidence of human neuroinvasive disease of more than 15 per 100,000 population, while Montana, Louisiana, and Mississippi had cumulative incidences from 10 to 14 per 100,000. These same states historically have had high incidence of St. Louis encephalitis (SLE) virus, a related flavivirus with similar ecology to WNV. A ranking of the counties in terms of mean annual incidence for WNV neuroinvasive disease reveals a pattern of persistent high incidence of disease in counties along the Platte and Missouri Rivers and the southern Mississippi River.

Predicting Future Outbreaks

As illustrated by the epidemic curve for WNV in 2006 (Figure 2-7), human case incidence increases very quickly in mid-summer; often, human epidemics

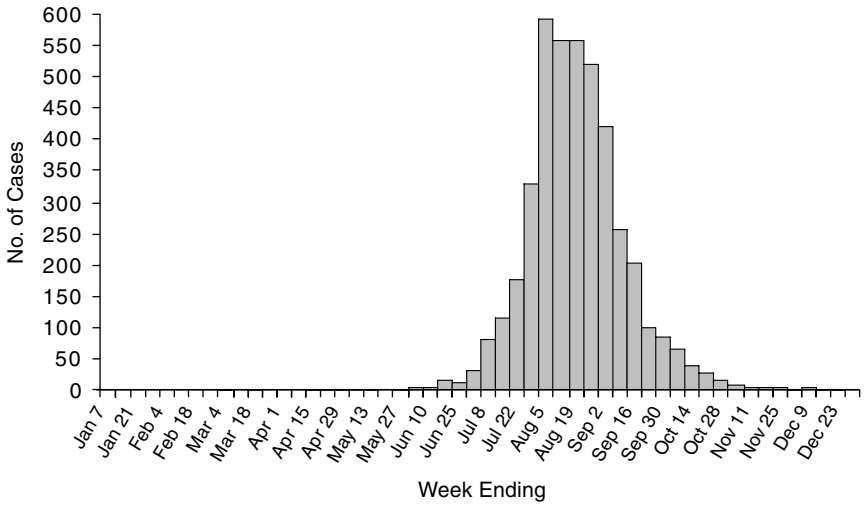

FIGURE 2-7 Reported number of human West Nile virus disease cases, by week of symptom onset, 2006, United States.

are not recognized until they are well under way. Thus, predicting where and when epidemics are likely to occur is a key goal of ArboNET.

For clues to WNV behavior in the future, one might look at long-term SLE incidence patterns. Unfortunately, as shown in Figure 2-8, such a pattern is not discernable from 70 years of SLE incidence data. Because WNV has an ecology similar to that of SLE, it is likely that WNV will behave in a similarly unpredictable pattern. However, WNV produces considerably higher levels of viremia in birds, affording it much greater epidemic potential (Komar et al., 2003). Although both WNV and SLE outbreaks, particularly in the northern United States, have often occurred during heat waves, it is noteworthy that the largest U.S. outbreak of SLE was not associated with a heat wave or with any other readily identifiable weather anomaly.

Ecological surveillance can be somewhat helpful in predicting WNV outbreaks. In North America, chickens, mosquitoes, horses, and birds have demonstrated increased activity prior to the onset of, or early in, human outbreaks of WNV illness (Eidson et al., 2001; Kulasekera et al., 2001). However, at best, ecological surveillance provides only a few weeks' warning before a human WNV outbreak. In Latin America, extensive serological data from ecological surveillance in birds and horses shows that WNV has spread from the Caribbean as far south as Argentina (Morales et al., 2006; Komar and Clark, 2006),

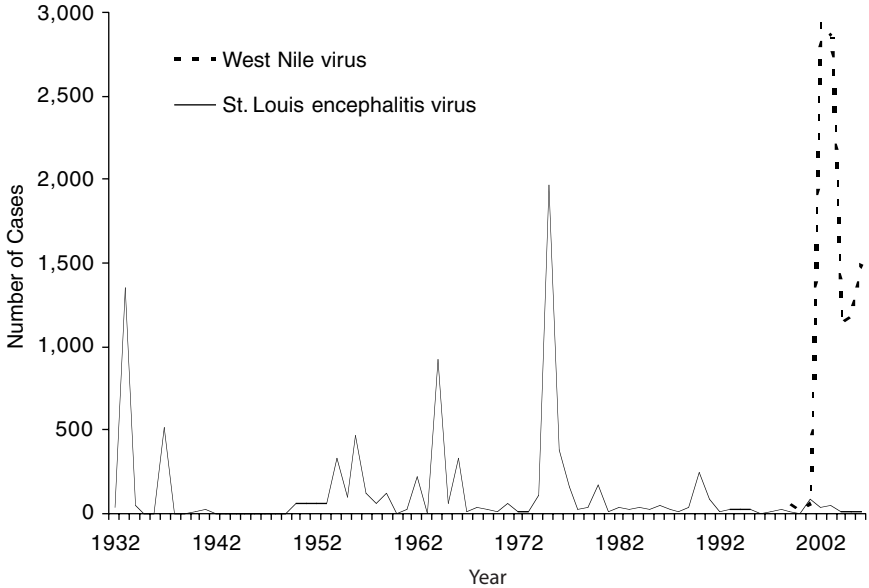

FIGURE 2-8 Human cases of West Nile virus and St. Louis encephalitis neuroinvasive disease, by year, 1932-2006, United States.

yet relatively little human or horse morbidity has occurred in these areas. Since considerable serological cross-reactivity exists among flaviviruses, interpretation of such serological data is difficult. Perhaps an unknown serologically cross-reactive WNV-related flavivirus is actually circulating in the region, or it could be that, for some yet-unknown reason, WNV produces relatively little morbidity in this part of the world.

Outcomes and Impact of WNV Illness

The clinical spectrum of WNV illness is complex. Whereas fever, meningitis, encephalitis, and acute flaccid paralysis were initially considered to be separate outcomes of WNV infection, there now appears to be considerable overlap among these syndromes (Sejvar and Marfin, 2006). Many people with fever also have some meningitis symptoms; likewise, both encephalitis and meningitis are present in many patients. Acute flaccid paralysis can occur with any of the other three syndromes, but some people have developed WNV paralysis in the absence of any other symptoms. It is perhaps not surprising, then, that the full impact of acute WNV illness in the United States remains to be determined. A 2002 study in Louisiana, limited to people with neuroinvasive disease, estimated the economic impact of that year's outbreak on the state at $20 million (Zohrabian et al., 2006). The economic impact of long-term effects of acute WNV illness has not been studied but may be considerable. For WNV encephalitis, long-term effects include persistent disabling neurological sequelae, tremors, and movement disorders in about half of all patients 2 years post-diagnosis; these patients also often report that they have difficulty with memory and concentration (Sejvar, 2007). Nearly all patients with WNV paralysis experience persistent weakness and functional impairment. Within a year of diagnosis, about one-third of patients approach baseline recovery; another third improve significantly but still have severe functional disability; the remaining third experience little or no recovery (Sejvar et al., 2006).

The considerable underreporting of WNV fever and misunderstanding of its true morbidity have created the perception that WNV fever has little public health significance. Recent studies show that West Nile fever, initially considered to be a mild febrile illness, can result in hospitalization and/or symptoms that often last weeks to months (Watson et al., 2004; Patnaik et al., 2006). Nearly four-fifths of persons with WNV fever missed work for a median of 16 days.

Finally, deaths due to WNV illness are also probably underreported in our surveillance system since persons with a delayed death from WNV may not be reported or deaths attributed to their primary cause (e.g., cardiovascular disease) may have been precipitated by WNV.

Risk Factors for Infection and Illness

According to data accumulated from 1999 to 2006, a person's risk of acquiring WNV neuroinvasive disease steadily increases from birth through advanced age—a risk that is, overall, significantly higher in males than in females (CDC, 2007a; O'Leary et al., 2004). In addition, organ transplant recipients have about 40 times the risk of the population at large for developing severe neurological disease after WNV infection (Kumar et al., 2004a,b). Patients with hematological malignancies also appear to be especially vulnerable to severe WNV neurological disease (Southam and Moore, 1954), but relative risk has not yet been calculated for this population. Weaker evidence suggests that diabetes, hypertension, alcohol abuse, chronic renal disease, and cardiovascular disease increase the risk for developing WNV neuroinvasive disease (Patnaik et al., 2006; Bode et al., 2006; Murray et al., 2006).

Novel Modes of Transmission

Several instances of non-mosquito-borne WNV transmission have been reported, including two cases resulting from organ transplants (Iwamoto et al., 2003; CDC, 2005), and one case from breast milk in which the infant remained asymptomatic (CDC, 2002a), although this mode of transmission seems to be rare (Hinckley et al., 2007). One case of transplacental transmission in which the infant experienced a severe outcome has been reported (CDC, 2002a); however, a study of 72 cases in which mothers were infected with WNV during pregnancy showed no conclusive evidence linking WNV infection to congenital malformation (O'Leary et al., 2006). Percutaneous, occupational exposure to WNV has been well described (CDC, 2002b); there was also one case of infection following conjunctival exposure to the brain tissue of an infected bird (Fonseca et al., 2005).

WNV and Transfusion Safety

The risk of WNV infection via blood transfusion has led to a new paradigm in blood donation screening. It was proven in 2002 that WNV could be transmitted via transfused blood (Pealer et al., 2002). At that time, models indicated that WNV was the most common, unscreened, transfusion-transmissible viral agent by far, due to its extraordinarily high incidence (particularly since viremia due to WNV lasts only approximately 6 days) (Biggerstaff and Petersen, 2003).

All proven transmissions of WNV via the blood supply have occurred in patients transfused with IgM- and IgG-negative blood (Pealer et al., 2002; CDC, 2007b), thus the virus could not have been detected with antibody tests such as those used to identify human immunodeficiency virus (HIV) or hepatitis C virus (HCV). As a result, in 2003, the U.S. blood supply was screened by

mini-pool nucleic acid amplification tests (MP-NATs), a technique that is also used to detect HIV and HCV as a supplement to antibody testing; WNV is currently the only infectious agent to be screened solely by this method. To date, approximately 1,800 viremic donors have been identified, but nine breakthrough transmissions have occurred through donors whose viremia was lower than the detection limit for mini-pool MP-NAT (CDC, 2007b). Screening the U.S. blood supply for WNV is enormously costly: cost estimates range from about $2.5 to $7 per donation screened (Custer et al., 2005; Korves et al., 2006), which would amount to $34 to $95 million annually. This is greater than the approximate $33 million budget spent by CDC in 2006 for WNV surveillance, prevention, and control programs.

Viral Evolution

WNV has spread rapidly across the Americas since its introduction in 1999, arriving at the Pacific Coast within 4 years and in Argentina within 7 years. Figure 2-9 depicts network analyses of viral isolates obtained from blood banks and other sources that show the relatedness of WNV strains, both by year and by region (Herring et al., 2007). Chronological analysis indicates that the 1999 New York strain has been replaced by descendants of the 2002 strain, which have a single nucleotide change in the envelope gene (Herring et al., 2007; Davis et al., 2005). Compared to the 1999 virus, this newly emergent genotype is transmitted earlier and more efficiently in *Culex* mosquitoes (Ebel et al., 2004; Moudy et al., 2007). Regional analysis suggests that new WNV clades are emerging in different areas of the country, most notably the Pacific Coast (Herring et al., 2007).

Summary and Conclusions

In the years since WNV was introduced to the United States, we have gained considerable knowledge of the virus in several key areas. We know that bird migration and random bird movement profoundly influence viral spread; the role of humans in this process remains to be determined. Many possible important avian hosts and competent mosquito vectors have been identified for WNV, many of which contribute to its unprecedented epizootic activity. WNV has also had a significant impact on wildlife and domestic animals. In some cases, ecological surveillance can provide indicators of impending human outbreak several weeks in advance. Clearly, a combination of human and veterinary surveillance will be essential to monitor the ongoing ecological impact of WNV and to guide disease prevention efforts.

An estimated 1.4 million WNV infections have occurred in the United States to date. The resulting incidence of WNV illness reveals a persistent epidemic/endemic pattern without a clear temporal trend. No other region of the world experiences repeated WNV outbreaks, year after year, as have occurred in the

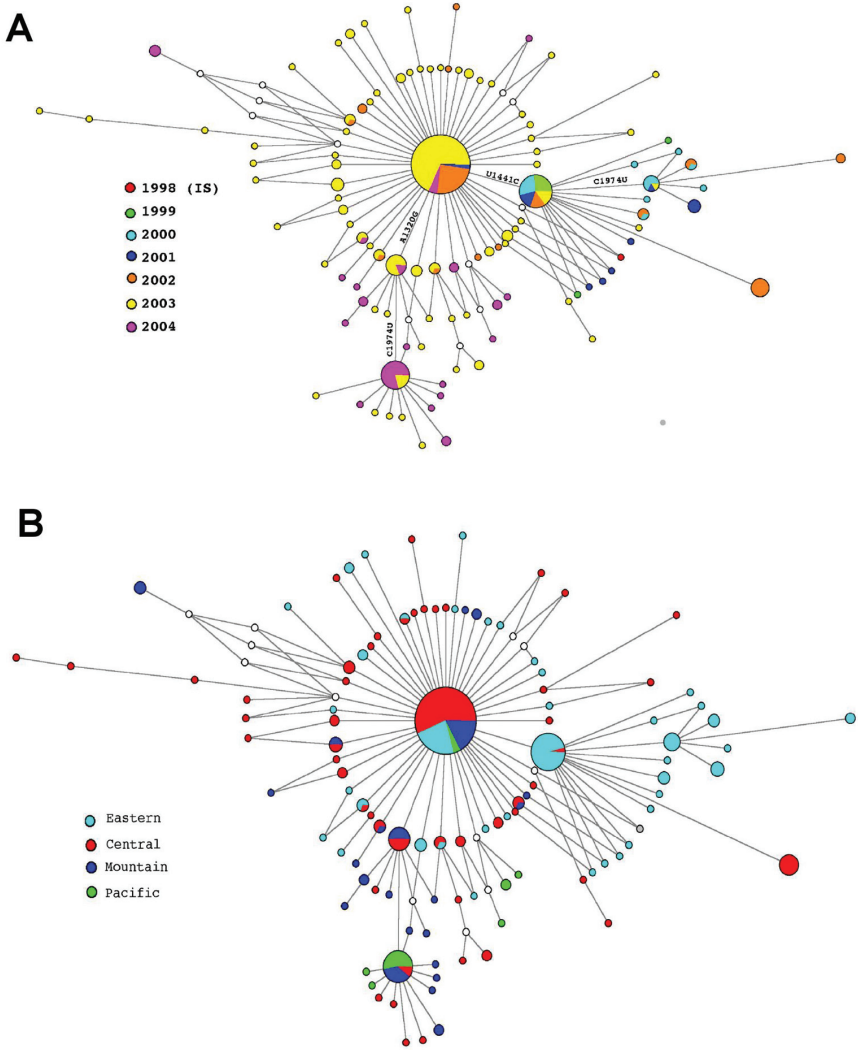

FIGURE 2-9 Phylogenetic analysis of West Nile virus E gene sequences, by (A) year and (B) location, United States.
SOURCE: Reprinted from Herring et al. (2007), with permission from Elsevier.

United States. The experience with WNV demonstrates that the epidemiological pattern in areas of importation of an exotic arbovirus may bear little resemblance to that which occurred in its previously endemic area.

WNV has had considerable regional and local variation in incidence and persistence in the United States. Incidence appears to be highest in the midwest-

ern United States and, in part, has been facilitated by land use, such as irrigation of farm land. Such wide temporal and geographic variations in WNV incidence challenge traditional clinical trial-based approaches to evaluating vaccines and therapeutics, which are usually based in a few centers, often in urban areas. A different strategy is clearly required—one reliant on surveillance to rapidly identify areas where outbreaks are occurring or likely to occur and that allows rapid recruitment of patients in rural and suburban hospitals in those areas.

Severe underreporting of WNV fever, and of the apparently common chronic sequelae of both WNV fever and neuroinvasive disease, are hiding a serious epidemic of which the consequences remain to be fully understood. Changes in patient population demographics and medical care are likely to increase the population at risk. A variety of nonvector transmission modes have been discovered for WNV, most notably via blood transfusion. WNV has become a significant and costly threat to blood safety in the United States due to the high incidence of asymptomatic infection; in a similar scenario, another vector-borne viral pathogen, dengue, now appears to be compromising blood supplies in Puerto Rico and other endemic areas. While alternate transmission modes for vector-borne pathogens may be of limited overall public health significance, they could result in considerable public concern and expense (as demonstrated by the cost of screening the U.S. blood supply for WNV) and thus require new methods of control.

Genetic variation in WNV, including relatively small changes in the virus, has been associated with avian mortality and human outbreaks of unusual severity. The original New York 1999 strain has disappeared and has been replaced by a strain that is transmitted earlier and more efficiently in vector mosquitoes; there has been subsequent temporal and regional viral evolution, with variants appearing and disappearing. In such a complex and fluid situation, a multidisciplinary approach will be required to understand the linkages between WNV ecology, epidemiology, and genetics.

RIFT VALLEY FEVER IS AN EMERGING ARTHROPOD-BORNE VIRUS

C. J. Peters, M.D.[13]
University of Texas Medical Branch

Epidemiology and Ecology

Rift Valley fever (RVF) appeared at the turn of the 20th century as an epidemic disease of domestic livestock in Kenya. The virus (RVFV) was isolated in 1930 (Daubney et al., 1931) and shown to cause the acute febrile disease that occurs in

[13]John Sealy Distinguished University Chair in Tropical and Emerging Virology; Director for Biodefense in the Center for Biodefense and Emerging Infectious Diseases.

most infected humans. In the 1950s the virus began to cause widespread epidemics in South Africa and nearby Zimbabwe (Swanepoel and Coetzer, 2004). The common ecologic denominator among the three areas was the presence of depressions that filled with water only when heavy rainfall occurred; these were known as damboes in Kenya (Linthicum et al., 1985), vleis[14] in Zimbabwe (Swanepoel and Coetzer, 2004), and pans in South Africa (Gargan et al., 1988b). The previous concepts of RVFV were based on movement of the virus from areas of heavy rainfall into regions with intermittently strong precipitation where it might utilize several different mosquito vectors for intensive epidemic transmission (Meegan and Bailey, 1988), but later data showed that there was a very different model that has more explanatory power. The virus was transovarially transmitted in floodwater breeding *Aedes* mosquitoes, and this formed the basis for persistence of RVFV in the environment (Linthicum et al., 1985). Heavy rainfall led to the accumulation of water in these depressions, which connect with groundwater aquifers, and this saturation in turn triggers the hatch of transovarially-infected *Aedes* ova and the introduction of RVFV into the environment. Later hatches of these and other species of mosquitoes provide vectors that are efficient in horizontal transmission of the virus. One of the important characteristics of RVFV is that it readily orally infects many species of mosquitoes found worldwide, and then can be transmitted when they feed on laboratory hosts, demonstrating their potential vector competence in propitious ecological circumstances (Gad et al., 1987; Gargan et al., 1988a; Jupp et al., 2002; Jupp and Cornel, 1988; McIntosh et al., 1973; Turell and Kay, 1998). These alternate vectors are very important in continuing propagation of epidemics.

The finding of *Aedes mcintoshii* as an important transovarial host of RVFV in East Africa (Linthicum et al., 1985) left questions about the ecology of RVFV elsewhere. It is clear that low levels of RVFV transmission occur in many areas during interepidemic periods (Davies, 1975; Davies et al., 1992; Fontenille et al., 1995; Swanepoel, 1976; Thonnon et al., 1999). The best example is in the Senegal River basin. A serosurvey conducted as part of an environmental impact study before the construction of a dam at the mouth of the river showed ~7 percent seroprevalence in human populations, establishing the presence of the virus even though it had never been described in that region (Digoutte et al., 1989). When the dam was closed in 1987, there was flooding that resulted in a major epidemic of RVF in that area. This massive epidemic would likely not have been detected if it were not for two French army physicians posted to Rosso, Mauritania; even then, they thought the epidemic of hemorrhagic fever they observed was yellow fever. Fortunately, they connected with the Pasteur Institute in Senegal and the correct virological diagnosis was made. Interestingly, the epidemic that called attention to the situation in West Africa was only part of the story; remote sensing shows that there was increased moisture in a much broader area. When transmission was sought, virus activity

[14]Fertile wetland areas.

was found to occur far away from the river flooding including the Ferlo region of Senegal (Wilson et al., 1994) and as far south as The Gambia (Ksiazek et al., 1989). Subsequent studies in the area isolated RVFV from new species of floodwater *Aedes* mosquitoes, which are candidates for the transovarial reservoirs of the virus (Fontenille et al., 1998). With improved surveillance low-level endemic and intermittent epidemic virus activity has been found (Nabeth et al., 2001; Thonnon et al., 1999; Zeller et al., 1995, 1997).

While the finding of transovarial transmission of RVFV provided a key finding in the natural history of the virus, many other questions remain. Although vertical transmission of the virus can explain persistence at some level, it proved impossible to colonize *Ae. mcintoshii* mosquitoes to study the efficiency of the process or any of its quantitative aspects; *Rickettsia* (now *Orientia*) *tsutsugamushi* and its trombiculid mite host provide the only known system which has 100 percent vertical transmission. Thus, we infer that there is almost certainly a vertebrate amplifier involved; but viruses are "old" and we also suppose RVFV must have been present for hundreds or thousands of years. To date, there has been no native African vertebrate amplifier identified, and it is believed that sheep, cattle, and goats were only introduced into Africa 3,000 to 5,000 years ago. In addition, most arboviruses generally are not pathogenic for their amplifier host, whereas domestic animals have a substantial case fatality rate and a very high abortion rate (Swanepoel and Coetzer, 2004). One possibility is that the virus we know as RVFV has evolved only recently. Nichol and colleagues have recently published an analysis of 33 strains using a Baysian approach and believe that the oldest common progenitor of our modern virus strains emerged in the late 1800s (Bird et al., 2007). This is a time when major changes in sheep and cattle raising occurred, including introduction of new breeds from Europe and raising of large herds. Although we lack the strains to test it, this hypothesis would put RVFV in the same category as Venezuelan equine encephalitis virus (VEEV) (Weaver, 2005). This agent evolved to produce high viremias and change mosquito vectors after the introduction and proliferation of equines with the Conquistadores in the 1500s. In fact, there are several similarities, including adapting from a defined set of endemic vectors (*Culex* in the subgenus *Neomelanoconion* versus floodwater *Aedes*) to utilize multiple epidemic vector species, using a "new" vertebrate amplifier (equines versus sheep and cattle), incidentally infecting humans, and having great human economic impact on the amplifer species. Like VEEV, RVFV also has the potential for emergence in distant areas. VEEV exhibited this through its march up Central America through Mexico to reach Texas in 1971. RVFV has been making tentative gestures in this direction since 1977 when it caused a massive epidemic in Egypt (Meegan, 1979). It has now spread from continental Africa for the first time; in the wake of the large East African epidemic in 1997-1998 (Woods et al., 2002), the same strain was found in an epidemic in nearby Yemen and Saudi Arabia (Shoemaker et al., 2002) and may have been reintroduced into Egypt as well (Abd el-Rahim et al., 1999).

Control Through Prediction

Undoubtedly one of the reasons RVFV has not been introduced into the United States is that in Africa it is a rural disease, and the movement of domestic livestock and rural dwellers is not common. Contrast this with West Nile virus that came to the United States during an epidemic in Israel caused by a strain of virus that seems to be unusually virulent and that is vectored by an urban mosquito. Thus, the ability to predict, monitor, and control RVFV in Africa could be of extreme importance, and some progress has been made in this area. The first observations related to the high, prolonged precipitation associated with epidemics in Kenya (Davies et al., 1985). Then it was shown that this could be assessed in a dambo in Kenya by using the National Oceanic and Atmospheric Adminstration (NOAA) satellite and Advanced Very High Resolution Radiometer (AVHRR) readings to measure leafy biomass (Linthicum et al., 1987). Several studies (Anyamba et al., 2006a,b; Linthicum et al., 1999) culminated in a system that can combine AVHRR readings (which are readily available and inexpensive to obtain). This system, which is maintained on the Department of Defense Geographic Emerging Infections Surveillance website (Al Hazmi et al., 2003), utilizes the historical information on RVFV epidemics and the NOAA databases. Real-time sattelite observations make it possible to predict immediately arising problems, but this system can be linked to long-term climate prediction, which is becoming increasingly accurate. It has become clear that the East African epidemics are linked to El Niño/Southern Oscillation conditions. Climate prediction in turn can be coupled with the detailed geographic information systems mapping of Africa as developed by many institutions, including the U.S. Agency for International Development Famine Early Warning System, to examine the impact of issues such as water accumulation, run-off, soil types, and groundwater considerations. In addition, there are evolving modeling systems using the susceptible-exposed-infected-resistant (SEIR) modeling system (Gaff et al., 2007). These eventually will be linked to climate and satellite data to help in control decisions such as deployment of vaccines, mosquito larviciding, and other strategies in Africa and in the case of introduction into the United States.

Clinical Disease and Therapy

Most Americans fail to grasp the huge gaps between our understanding of many important diseases in developing countries and our information on diseases that are much less common but are studied in medical centers in the United States. In addition to the lack of infrastructure and skilled observers, many cultures do not permit post-mortem examinations. This understanding is, of course, basic to developing therapeutic approaches to RVFV. Only a handful of human RVFV patients have been studied in detail. As one example of this, the recent Saudi Arabian epidemic resulted in severe cases being moved to tertiary care hospitals

that, for the first time, performed systematic renal function, hepatic function, and coagulation tests on patients (Al Hazmi et al., 2003; Madani et al., 2003). These tests and clinical observations suggested there was an association between severe systemic disease and central nervous system involvement. Isolated renal disease was also seen in virus-confirmed cases. Because of the hiatus in clinical description of cases, we took the 2006-2007 outbreak in Kenya as an opportunity to make first-hand clinical observations on patients with a U.S.-trained infectious disease physician. He was linked to the United States using telemedicine so that the institutional base at the University of Texas Medical Branch at Galveston could support him (Kahlon, Peters, King, White, and LeDuc, unpublished observations). New descriptions of clinical manifestations were obtained, broadening our understanding of the pathogenesis of the disease and also educating U.S. physicians in understanding the clinical presentation of RVFV infection through direct telemedicine observation.

It is also unappreciated that we actually know very little about the actual incidence of the different severe manifestations of infection, such as hemorrhagic fever, encephalitis, and retinal disease. Retinal vasculitis has been said to occur in 1-10 percent of patients with most suggestions being toward the low end. A recent retrospective combined serological and ophthalmological study in Kenya suggested that seropositive persons were much more likely to have retinal disease and optic atrophy than controls, perhaps several percent of total infections (LaBeaud, King, Muchiere, and Peters, unpublished observations).

Vaccines

The rapidity with which RVFV moves in epidemics makes a safe potent vaccine with rapid onset of immunity after a single dose basic to control of livestock disease. No such vaccine now exists (Botros et al., 2006; Coetzer and Barnard, 1977). We have begun to work with an attenuated strain developed in the mid-1980s (Caplen et al., 1985) as such a vaccine and also as a human vaccine. We have developed a reverse genetic system to be able to manipulate the vaccine and the wild-type virus (Ikegami et al., 2006) and are exploring the critical mutations and seek deletions to define attenuation. The major obstacles we have found are the presence of the predictable mutability of RNA virus genomes and the existence of quasispecies or multiple polymorphisms in viral populations (Lokugamage, Makino, Ikegami, Morrill, and Peters, unpublished data). The outlook is nevertheless good for the human vaccine because it seems to be overall genetically stable, and other successful RNA virus vaccines also have multiple polymorphisms in their populations (e.g., yellow fever, mumps, measles, polio vaccines). We believe it will be possible to develop such a tool for control of dissemination to mosquitoes via viremic domestic animals and to protect humans in laboratory, veterinary, and endemic settings.

Conclusions

RVFV has been emerging in our consciousness since the beginning of the 20th century and continues to cause devastating human and animal epidemics in Africa. It has the potential to extend its range and it is very likely that the United States and other areas are receptive to virus transmission. Research has been slow for lack of appreciation of the threat and lack of infrastructure in involved areas. It seems likely that some measure of control in endemic areas could be achieved by prediction of epidemics and application of live attenuated vaccines for animals and humans. This would also decrease the risk of distant natural spread. If either natural or intentional introduction of the virus to this country should occur, then these vaccines would be urgently needed, and successful vaccine development is likely to be possible using newly developed reverse genetics systems.

THE IMPLICATIONS OF ENTOMOLOGICAL MONITORING AND EVALUATION FOR ARTHROPOD VECTOR-BORNE DISEASE CONTROL PROGRAMS

Michael Coleman, Ph.D.[15]
Medical Research Council

Janet Hemingway, Ph.D.[16]
Liverpool School of Tropical Medicine

Malaria control currently relies on the use of an effective drug and an effective vector control program. Most National Malaria Control Programmes (NMCPs) focus their resources on monitoring morbidity and mortality of people, neglecting the implications that insecticide-based vector control is having on the mosquito population. Routine entomological monitoring allows for the earlier detection and response to potential insecticide failure and increases in malaria transmission. Through this rapid response it is possible to avert increases in morbidity and mortality that currently occur before program failure is recognized.

This paper reviews some of the simple entomological techniques available for use by NMCPs and indicates how they can be successfully implemented. This paper focuses on entomological surveillance aspects for malaria control. The concepts presented here have cross-cutting implications to other arthropod vector-borne diseases.

[15]Malaria Research Programme.
[16]Director.

Introduction

There are a large number of human pathogens in nature that are transmitted by arthropods. These vector-borne pathogens typically infect, replicate, and develop in both the vector and human host. There are over 100 countries at risk from malaria encompassing almost 50 percent of the world's population (Hay et al., 2004; WHO, 2002). There are up to 300 million episodes and 1 to 3 million deaths a year from malaria (Breman et al., 2004; Snow et al. 2005). This disease has major economic and health impacts for a disease-endemic country (Gallup and Sachs, 2001).

A public health surveillance system, based on the systematic collection of relevant information and the analysis and timely dissemination of data, to those responsible for controlling the disease, is essential. For a vector-borne disease, a good surveillance system should include the following:

- Disease detection via passive (patient data from health facilities) or active surveillance (visiting the community and testing individuals)
- Entomological surveillance through monitoring of species density, infectivity (sporozoite rate), and insecticide resistance
- Environmental surveillance including climate and geographical data

Successful malaria control currently relies on effective drug treatment and vector control. Vector control is insecticide-based mainly through indoor residual spraying (IRS) or deployment of insecticide treated bednets (ITNs).

Entomological Surveillance

There are over 100 species of anopheline mosquito that are able to transmit malaria. *Anopheles gambiae*, *An. Arabiensis*, and *An. funestus* are the three main vectors in Africa.

Species Density

Only older adult female mosquitoes are able to transmit malaria. Vector control aims to reduce the numbers of mosquitoes in a population that are able to transmit malaria. Vector population species density can be reduced to a threshold that interrupts transmission. Our ability to reduce vector populations varies with species and locality. *An. funestus* is highly endophilic, and hence, susceptible to IRS and has been eradicated from parts of southern Africa (Sharp et al., 2007a,b; Maharaj et al., 2005).

Vector density surveillance measures the direct impact of the control program on vector population size. There are a number of methods available for collecting vectors. Collection methods are varied and dependent on the questions that

are being answered. For example, collecting resting mosquitoes will give a more representative idea of the population for sexes and the feeding states than a trap that will predominantly catch feeding or recently fed females. However, sampling resting mosquitoes is time-consuming and more suited to research projects than an NMCP, which would favor a less-intensive collection method such as passive window exit traps. For an in-depth review of methods see Service (1971, 1993).

Relative vector density is an adequate surveillance method for most NMCPs. Collections should ideally be assessed against a baseline and established before the onset of control activities.

A good example of how relative species density is informative is from the ongoing malaria control program on Bioko Island, Equatorial Guinea. Species density is measured through a series of window traps at sentinel sites; in year one the IRS program with a pyrethroid had a significant impact on the *An. funestus* population but not the *An. gambiae* population. This was shown to be due to knockdown resistance (*kdr*) in the *An. gambiae* population; when the insecticide changed to a carbamate it had a significant impact on both vector species (Figure 2-10) (Sharp et al., 2007b).

The sustainability of IRS is controversial. However, this mode of control has been linked to some of the world's most successful malaria campaigns including the near eradication of malaria from Sri Lanka in the 1960s, South America in

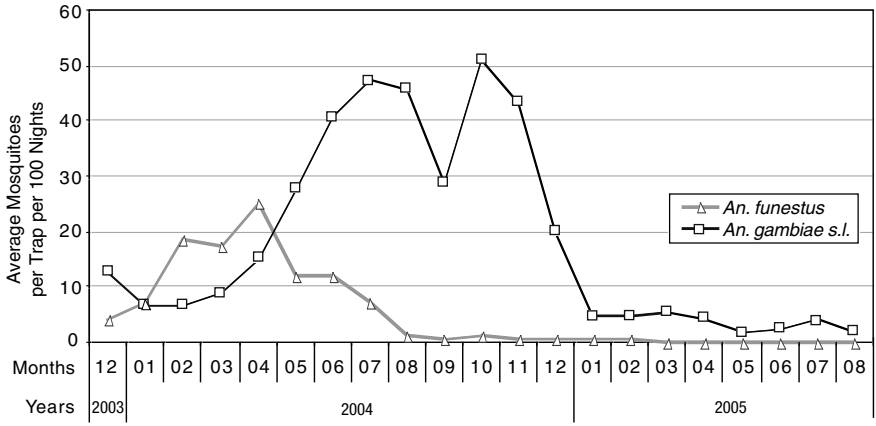

FIGURE 2-10 By monitoring the species density on Bioko Island, Equatorial Guinea, the malaria control program was able to detect a reduced impact of IRS with pyrethroid on *An. gambiae* compared to *An. funestus*. Further investigation detected *kdr* resistance in *An. gambiae* and a change in insecticide policy that resulted in a reduction of both vector species.
SOURCE: Sharp et al. (2007b).

1950-1960 (Alilio et al., 2004; Carter and Mendis, 2002), and Mexico in the 1990s (Chanon et al., 2003).

Sporozoite Rate

Transmission of malaria varies with location and vector species. Parameters may vary depending on factors such as the human biting rate, sporozoite rate (infectivity of mosquitoes) and entomological inoculation rates (EIRs). EIR is the number of infective bites that an individual receives over a set period of time (Killeen et al., 2000; Antonio-Nkondjio et al., 2002). Determining these aspects of entomology is labor-intensive and time-consuming, which is not compatible with NMCP continuous surveillance activities.

Operationally, a more passive format of mosquito collection via fixed traps is preferred. Monitoring the vector infectivity, or sporozoite rate, can be achieved using exit traps on houses. Mosquitoes can be analyzed for sporozoite by dissection or more sophisticated techniques of polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) (Bell and Ranford-Cartwright, 2004; Moreno et al., 2004).

Various studies demonstrate that transmission can be interrupted by reducing vectorial capacity. This was achieved in Bioko, where sporozoite rates in *An. gambiae* were reduced despite the control measure having a lower impact on this species than on *An. funestus* (Sharp et al., 2007b). This is most likely due to the impact of control measures on the age structure of the mosquito population. A second threshold measure that can be achieved is a reduced daily mosquito survivorship. If this is reduced significantly, so that death occurs before the mosquito becomes infective (typically 10 days after an infected blood meal), then vectorial capacity is reduced and transmission is blocked.

Insecticide Resistance

Insecticide resistance in mosquitoes threatens the long-term ability to control disease vectors. The numbers of insecticides formulated for indoor residual treatment and recommended by the World Health Organization (WHO) via its Pesticide Evaluation Scheme (WHOPES) (WHO, 2001) are severely limited. Insecticide resistance surveillance was recently reviewed (Coleman and Hemingway, 2007).

The WHO-led malaria eradication campaign (1955-1969) was built on the twin pillars of DDT-based control of the insect vectors and chloroquine treatment of malaria cases. This campaign had many notable successes, eradicating malaria from several countries and dramatically reducing transmission in others (Trigg and Kondrachine, 1998), but the campaign was ultimately seen as a failure, with issues of DDT resistance often cited as a major reason for the lack of eradication in many malaria-endemic countries (Coleman et al., 2006).

Resistance to DDT was first noted just 10 years after its introduction (WHO, 1957). As DDT resistance spread, the faster-acting pyrethroids were introduced; this class of insecticides replaced DDT in many malaria control programs. As pyrethroid resistance started to develop, many control programs attempted to revert back to DDT. However, because these insecticide classes share a common target site (Soderlund and Bloomquist, 1989), the sodium channel and cross-resistance had developed to both insecticide classes in many locations (Martinez-Torres et al., 1998; Ranson et al., 2000). The spread of pyrethroid resistance may be critical for sustainability of ITNs, as this is currently the only insecticide group recommended for net impregnation. Figure 2-11 shows insecticide resistance in Africa between 1950 and 2006.

The economics of developing, registering, and marketing insecticides means that new insecticides are primarily developed for large agricultural markets. Some of these insecticides eventually cross over into the public health arena, which means that vectors breeding in agricultural areas may have previously been

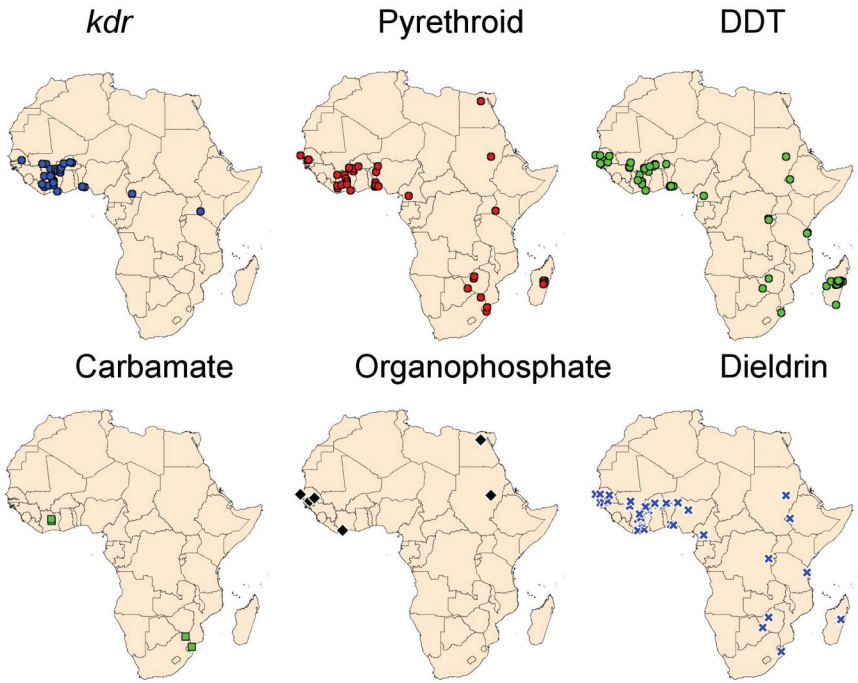

FIGURE 2-11 Resistance in Africa, 1950-2006.
SOURCE: Reprinted from Coleman et al. (2006), with permission from the Entomological Society of America. Copyright 2006.

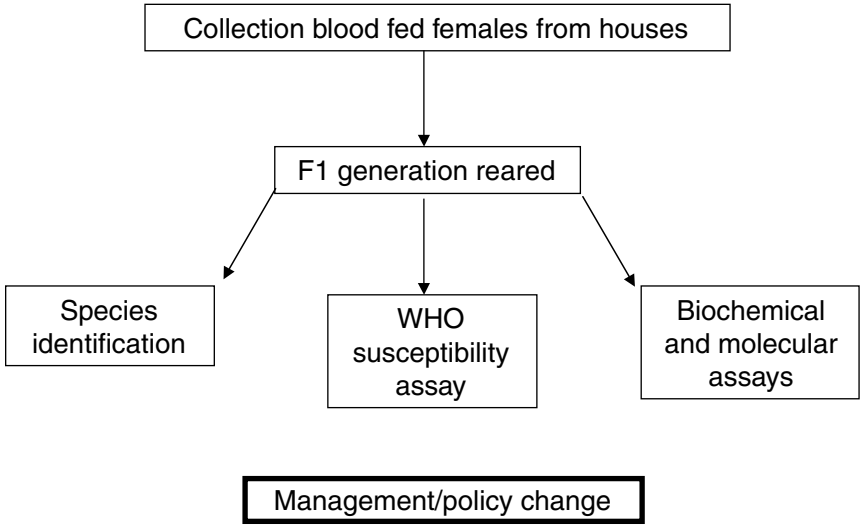

FIGURE 2-12 Insecticide resistance monitoring methods.
SOURCE: Adapted from information in Coleman and Hemingway (2007).

exposed to these chemicals. In West Africa, DDT and pyrethroid resistance due to *kdr* is widespread. This resistance was selected for by the evolutionary pressure of DDT used in growing cotton and other cash crops (Mouchet, 1988).

Surveillance of resistance within a population can be done by several methods. The simplest is to measure insecticide dose response, where insects are exposed to a range of concentrations of insecticide and the dose that kills either 50 or 95 percent (LD_{50} and LD_{95}, respectively) of the population. Populations may be compared by calculating the resistance ratio. Alternatively, and more commonly in an NMCP, a single diagnostic dose of insecticide is used that kills susceptible insects. Alternatively, resistance may be measured at a mechanistic level using biochemical or molecular methods. Although technically more demanding, these methods provide more predictive and accurate information (see Figure 2-12).

Studies to determine the baseline of resistance should ideally be completed before an insecticide is selected (Casimiro et al., 2006a,b). Changes in this baseline can be monitored over time and insecticide treatments switched when required. This has been a component of the Lubombo Spatial Development Initiative (LSDI), a tri-national malaria control program between South Africa, Swaziland, and Mozambique to control malaria (Sharp et al., 2007a). Prior to

1999, there was no systematic collection of entomological information on the susceptibility levels of malaria vectors. In 1999, Maputo Province, Southern Mozambique, became part of the LSDI and an insecticide susceptibility baseline was established. A high level of pyrethroid resistance was detected in the vectors (Casimiro et al., 2006a,b). This resulted in a policy change and the carbamate bendiocarb® replaced lambda cyhalothrin in 2000. As dependence on the use of a single insecticide class in the long term was likely to be problematic, an extensive resistance surveillance program was initiated. Based on data from this surveillance and a requirement to reduce costs (Conteh et al., 2004), DDT was reintroduced in 2006 for IRS in malaria control in southern Mozambique. The insecticide susceptibility profile continues to be monitored operationally in the two major vectors in this region (see Figure 2-13) (Casimiro et al., 2007; Coleman et al., in press).

Resistance in Mozambique is monitored by both bioassay and biochemical and molecular assays. Metabolic resistance involves a small number of enzyme families (Hemingway et al., 2002). Elevated levels of these enzymes are detectable using simple biochemical assays (Hemingway and Smith, 1986; Penilla et al., 1998).

Resistance to insecticides may also be due to an alteration in the target site. *Kdr* gives cross-resistance between DDT and pyrethroid. This has been studied extensively in West Africa (Coleman et al., 2006; Coetzee et al., 1999). Monitoring has been simplified by the development of a simple PCR to detect this single-point mutation (Martinez-Torres et al., 1998; Ranson et al., 2000).

Simpler and more cost-effective tools to monitor insecticide resistance monitoring are required to sustain this component of routine monitoring for an NMCP. Currently research is underway to develop simple PCR methods that are able to detect associated markers of insecticide resistance by replacing the biochemical assays and reducing the need for live or frozen insects. This will increase the ability of an NMCP to complete resistance surveillance without the reliance on external scientific research.

Monitoring of resistance allows for resistance management policies to be implemented that will result in the extended life span of insecticides for vector control. This work was pioneered in Mexico, where a 7-year program demonstrated that at an operational level, annual rotation of insecticide groups was efficient (Figure 2-14) (Hemingway et al., 1997).

Models

Models help us to understand how a disease outbreak, epidemic, and spread may occur by understanding each component of the system (Bailey, 1982). A modified Reed-Frost equation (Fine, 1980) describes the dynamics of vector-borne disease through the average number of infective bites an individual may experience. This is intrinsically linked to the vectorial capacity (i.e., the number

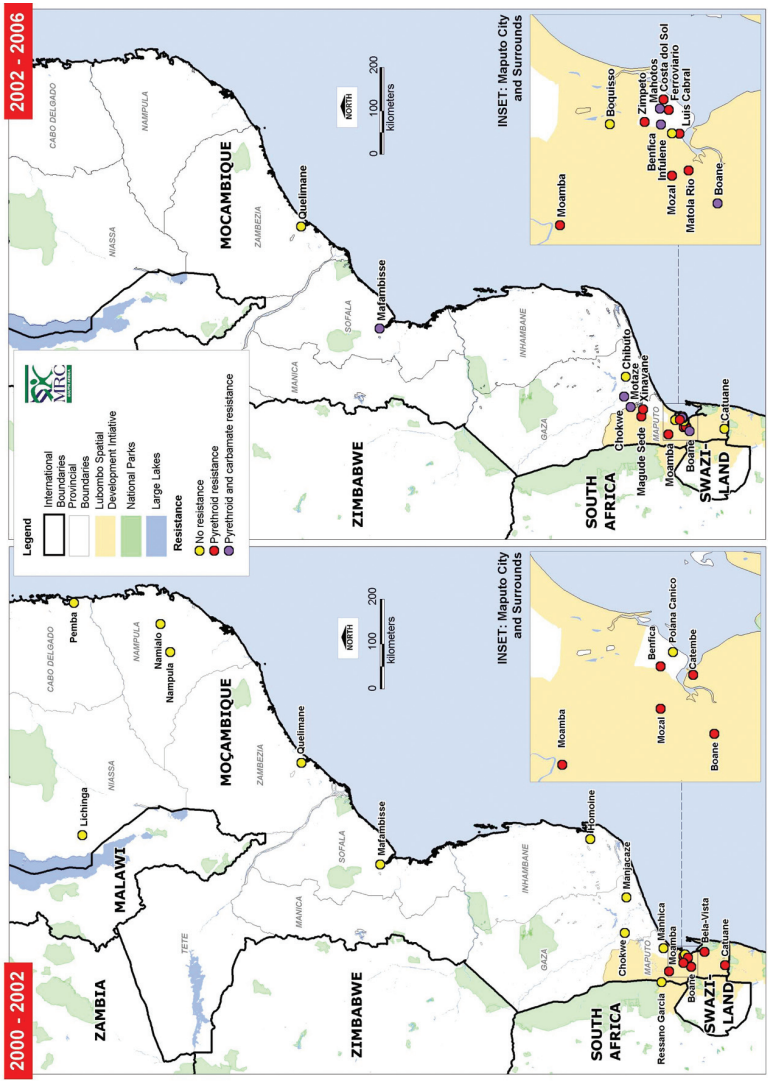

FIGURE 2-13 Monitoring of insecticide resistance in Mozambique has resulted in several policy changes on the insecticide of choice for the country's IRS program. Ultimately this will result in the sustainability of malaria control.
SOURCE: Adapted, with permission from Casimiro et al. (2006b). Courtesy of the Medical Research Council.

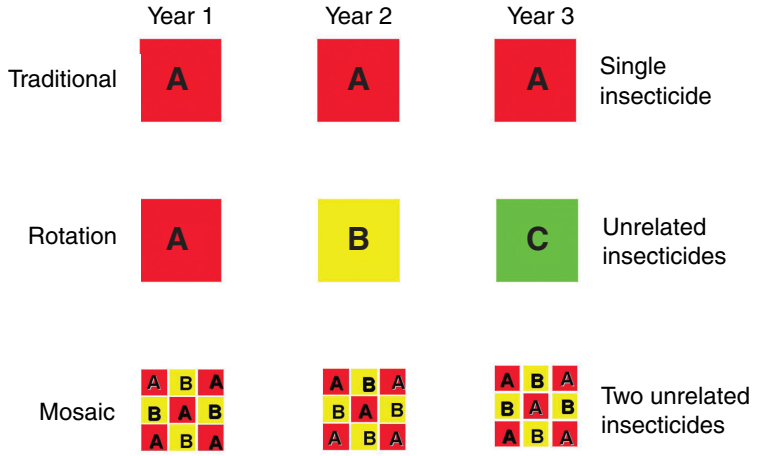

FIGURE 2-14 Insecticide rotation.

of infective bites that an individual may receive in 1 day). McDonald (1977) pioneered the use of vectorial capacity to study the transmission of malaria dynamics in Africa. Today we are left with a modified form of this (Garrett-Jones, 1964).

Using this model McDonald predicted that adulticides rather than larvicides would best reduce malaria transmission in Africa. ITNs were not an option at the time. However, models have flaws due to assumptions that must be made. McDonald's model for instance, does not account for fluctuations in vector density caused by seasonality effects, survivorship, or age composition.

Ultimately models help our understanding of the factors that may affect a control program and predict what the outcome will be. Analysis of large data sets such as those generated in the Garki Project (Molineaux and Gramiccia, 1980) or the LSDI (Sharp et al., 2007a) will shed more light on the role of models in control. In order to be utilized, models must be incorporated into surveillance systems and not require a mathematical background.

Decision Support Systems

Sustainable malaria control is often jeopardized by insufficient public health resources. By utilizing information in a geographic information system (GIS) it is feasible to rationally target limited resources. Although GIS has been advocated for NMCP (Sharma and Srivastava, 1997) there has been little use of its capabilities for entomological surveillance (Coleman et al., 2006).

GIS has been used most often in research to identify environmental factors responsible for vector and pathogen survival; it has been combined with a malaria

notification system to plan a malaria control program (Booman et al., 2000). This system creates risk maps of disease incidence at town level, allowing for more focused vector control.

Larviciding is not generally used for large-scale malaria vector control, due to difficulties in targeting breeding sites and the numbers of larvae that need to be killed to reduce the subsequent numbers of adult females able to transmit disease. However, targeted larviciding can add value to an ITN or IRS program. Studies have identified variations in environmental factors at the village level, which, if mapped, would be amenable to focal larviciding strategies (Smith et al., 1995; Singh et al., 1990). Similar systems are being created in other areas to assess entomological malaria risk factors, including EIR and locality of vector breeding sites in order to effectively target control measures (Srivastava et al., 2003; Vanek et al., 2006; Dev et al., 2004). In Sri Lanka, where malaria is seasonal, focused larviciding of river banks as water levels recede in the post rainy season, the NMCP can offset the peak malaria vector abundance by 3 weeks (Wijesundera et al., 1990; Wickramasinghe, 1981). The result is a delayed and shorter malaria season.

The usefulness of GIS for making control decisions and planning depends on the availability of accurate and timely data. A key component to the success is the integration of such systems into the NMCP itself.

Control programs that utilize IRS and ITNs to interrupt the transmission cycle are only effective if a high coverage of the community is achieved. Monitoring and evaluation is needed if IRS is used to ensure effective application and avoid wastage (Goodman and Mills, 1999). A successful computerized IRS surveillance system has been developed utilizing a database and spatial mapping GIS tool (Booman et al., 2003). ITN coverage has traditionally focused on the number of bednets distributed, with little focus on actual use until recently. While usage has in some cases been determined during Malaria Indicator Surveys (WHO, 2000; Korenromp et al., 2003), these surveys are not appropriate for surveillance.

The complex interrelationship between data and information needs to be integrated and simple analysis tools developed to aid control programs to assess and monitor malaria control and decide how best to respond to changes in information that is received. This can all be accomplished via a decision support system (Figure 2-15).

Disease Surveillance

Although not within the scope of this paper, it is essential to measure malaria prevalence to determine the impact of vector control on disease. Monitoring disease can be either passive, through cases presenting within the health system, or through active surveillance by going into the community and searching for cases. The speed at which it is possible to monitor for malaria parasites in blood smears has increased with the advent of sensitive rapid diagnostic tests (RDTs)

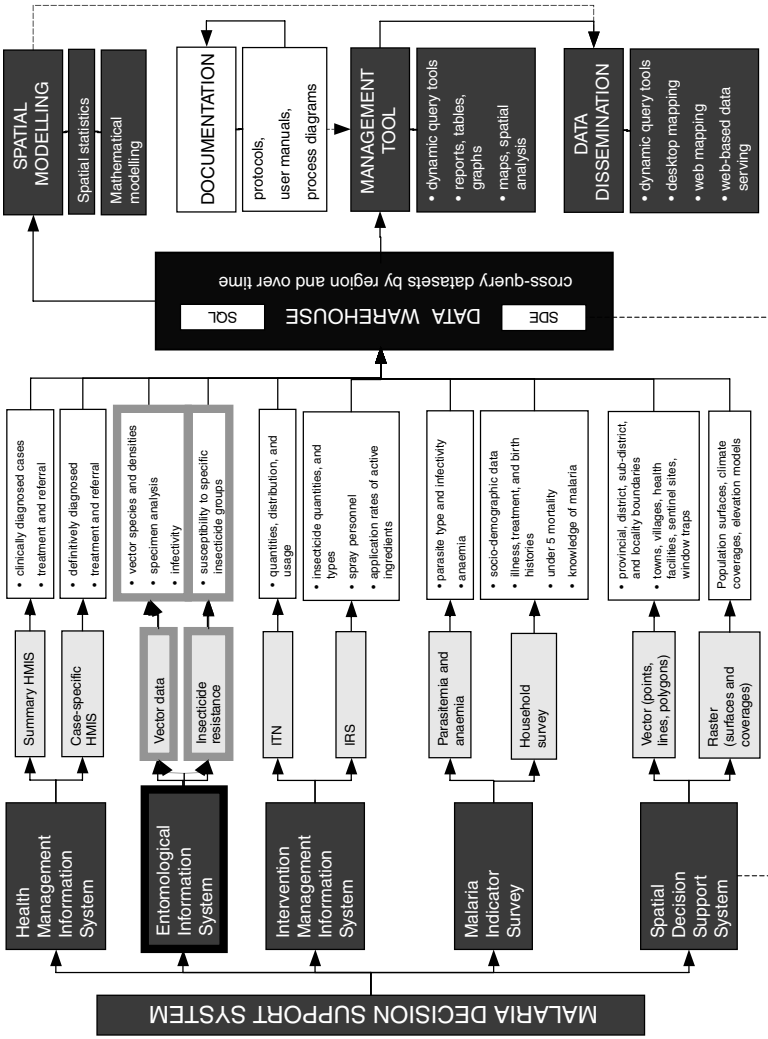

FIGURE 2-15 Malaria Decision Support System. Courtesy of the Medical Research Council.

replacing microscopy (Craig and Sharp, 1997; Craig et al., 2002). This has led to a drive to put RDTs into clinics in Africa, but it has been a slow process and clinical diagnosis remains the norm for malaria case information.

Summary

Countries need to build field entomological capacity. It is the field entomologist that should be involved in routine surveillance and interpretation of data for the NMCP.

The aim of a public health surveillance system is to provide relevant information to make informed and timely decisions guiding interventions. Increased sharing of data is essential in the fight to prevent disease. A number of networks and databases have been developed, including AnoBase,[17] MARA,[18] and VectorBase,[19] to do just that. The Innovative Vector Control Consortium (IVCC) (Hemingway et al., 2006) is facilitating the refinement and practical implementations of entomological decision support systems (DSS). Currently the IVCC project portfolio has DSS being developed for malaria and dengue.

To date these systems have relied on an interaction with a set of specialized and skilled scientists including entomologists, spatial epidemiologists, and statisticians. These skills are not found in the average malaria control program, resulting in nonintegration of systems. Newer systems are looking at ways of simplifying data collection and interpretation to reduce the need for these skills at a local level.

Research projects are generally intensive and concentrated on a few aspects of malaria in a small area. In order to fully understand the implications of research there is a need to scale research up to operational levels in an NMCP. Few examples of large-scale operational malaria research projects exist and those that do are slow in publishing results due to the pressure on scientists for novel publications.

We are addressing the balance through new operational research in Malawi, Mozambique, and Zambia. Open-source databases are currently being developed that will allow relevant research to be shared with the malaria community ahead of schedule. Practical, affordable, and effective surveillance systems for integrated vector management in an NMCP will be developed. Researchers cannot support every NMCP operational activity in Africa; they cannot equally support routine surveillance—this must be an integral part of the NMCP if the NMCP is to succeed.

[17]See http://www.anobase.org.
[18]See http://www.mara.org.za.
[19]See http://www.vectorbase.org.

VECTOR-BORNE ZOONOTIC DISEASES AND THEIR ECOLOGICAL AND ECONOMIC IMPLICATIONS: BLUETONGUE DISEASE IN EUROPE

Bennie I. Osburn, Ph.D., D.V.M.[20]
University of California, Davis

Introduction

Vector-borne diseases are of increasing importance because they are associated with new and emerging diseases. Many of the viral and microbial agents associated with vector-borne diseases are zoonotic, affecting both animals and humans. The close association of the viral agents with vectors limits the distribution of these agents and the diseases associated with them. The appearance of West Nile virus in the United States in 1999 serves as a prime example of how arboviruses can be picked up by susceptible vectors in the United States and spread rapidly across the country. In its wake are countless losses of wild bird populations, equine and companion animal disease, and deaths as well as human suffering and death.

This paper will focus on an animal disease, bluetongue (BT) disease, which primarily effects ruminants and is transmitted by the biting midge, *Culicoides spp*. BT is caused by one of the 24 bluetongue viruses (BTVs) (Erasmus, 1985; Walton, 2004). BTVs are segmented double-stranded RNA viruses consisting of 10 genome segments. Although BTVs are found on six continents, the selective distribution of the viruses on continents is controlled by the vectors and specific genome segments. The confinement of the various serotypes of virus to continents depends on a variety of factors including weather, environmental conditions, and vector competence and capacity. BTVs on occasion move outside of recognized zones when climatic condition changes carry the vectors into areas where there are susceptible mammalian host species.

The Disease

BT was first recognized as a disease entity in the late 1800s when European sheep were introduced into South Africa (Erasmus, 1985). Many of these sick animals developed facial edema and, at the time of death, there was often a protruding swollen blue tongue, hence the name bluetongue. In the early 1900s, South African veterinary scientists were able to demonstrate that the disease was of infectious origin. The typical clinical signs in sheep were those of depression, facial edema, high fever, erosions of the oral mucosa, arched back, reluctance to move, difficulty walking, reddened coronary bands, and 30 percent mortality. Less frequently, there were reports of clinical bluetongue in cattle. These

[20]Dean, School of Veterinary Medicine.

animals rarely died; however, they would show signs of vesicular lesions on the oral mucous membranes, which evolved into erosion. In addition, the cattle would have a vesicular dermatitis, which would often lead to erosions and dermal ulceration (Anderson et al., 1985). The skin was often thickened from edema, and the cows developed lameness because of coronitis. BT also affects some species of wild ruminants where the disease is associated with a hemorrhagic syndrome and sudden death (Stallknecht and Howarth, 2004). These animals also show depression and a high fever.

Bluetongue has also been associated with congenital lesions and death in newborn ruminants and dogs (MacLachlan and Osburn, 1983; Akita et al., 1994). Fetal lambs and calves infected in utero early in gestation will develop a necrotizing lesion in the developing brain, leading to hydranencephaly or porencephaly and retinal dysplasia (Osburn and Silverstein, 1972). Although the lambs and calves may be born alive, the lesions are incompatible with life. Pregnant bitches, accidentally infected with live virus vaccines containing BTV-contaminated fetal calf serum will abort infected fetal pups or the pups will die shortly after birth (Akita et al., 1994). Chick embryos used to culture BTVs develop a hemorrhagic syndrome associated with their death (Tyler et al., 1980). It appears that the BTV associated with the fetal deformities and neonatal deaths have been modified or selectively adapted in cell or chick embryo cultures.

The pathogenesis of BTV in susceptible sheep, wild ruminants (white-tailed deer and prong-horned antelope), and chick embryos is centered on the predilection of the virus for vascular endothelium (Mahrt and Osburn, 1986; MacLachlan et al., 1992; MacLachlan, 2004). This is associated with hemorrhagic lesions and edema. Some of the hemorrhagic lesions will lead to necrosis of striated muscles in the heart and skeletal muscles. A hallmark feature of sheep dying of BTV infections is pulmonary edema. This is brought about because of cardiac necrosis as well as the virus attack on vascular endothelium in the lungs (Mahrt and Osburn, 1986; MacLachlan, 2004). The pathogenesis of the fetal lesions in the developing nervous system appears to be neuronal and microglial necrosis due to virus infection of these developing cells and possibly, vascular invasion by the virus leading to infarction and liquefaction necrosis of nervous tissue (Osburn and Silverstein, 1972; MacLachlan, 2004). Cattle sensitized with inactivated BTV followed by challenge virus infection developed an IgE response with the subsequent release of prostaglandins and cyclooxyengases leading to edema (Anderson et al., 1985). It is not known whether this occurs in acute infections in naturally occurring field outbreaks.

The Viruses

BT is caused by arthropod-borne viruses which are the prototype of the *Orbivrus* genera in the family *Reoviridae* (Murphy et al., 1999). Globally, there are 24 distinct serotypes based on serotyping. BTVs are icosahedral in structure

and 69 nm in diameter. The genome consists of 10 double-stranded RNA segments that can be observed on polyacrylamide and agarose gels. Seven of the genes code for structural proteins and three segments for nonstructural proteins, listed in Table 2-2. The genome is surrounded by 32 caposomeres in the nucleocapsid. The diffuse outer layer coat of proteins is made up of viral structural protein (VP) 2 and VP5 with VP2 serving as the neutralizing protein in mammals. VP3 and VP7 are the major internal core proteins. VP7 is important for viral attachment in the insect vector and plays an important role in the ecological distribution of the viruses. This viral protein is often used as the group antigen for serological testing of BTVs.

Even though 24 serotypes of BTVs have been identified throughout the world, not all serotypes have been identified on a single continent. The genetic heterogeneity of BTVs occurs as a result of genetic drift and shift (Bonneau and MacLachlan, 2004; deMattos et al., 1994). These two phenomena result in a remarkable heterogeneity among strains of BTVs that circulate or cocirculate in endemic regions. BTVs reassort gene segments, both in the infected ruminant as well as in the insect vector following infection with different strains or serotypes of viruses leading to the genetic shifts (deMattos et al., 1996). The accumulation of nucleotide substitutions within individual BT genes leads to genetic drift.

The Vectors

Early in the 20th century, South African scientists recognized that BTV was transmitted by midges (Erasmus, 1985; Walton, 2004). Later studies revealed

TABLE 2-2 Viral Proteins and Functions

	Function	Characteristics
Structural Proteins		
VP1	RNA polymerase	Replication and capping
VP2	Outer capsid	Cell attachment and penetration
VP3	Core structural protein	Topotyping
VP4	RNA capping	Replication and transcription
VP5	Outer capsid	Destabilization of endocytic vesicle Infective for culicoides
VP6	Helicase	
VP7	Core protein	Replication and transcription
Nonstructural Proteins		
NS1		
NS2	Inclusion body	
NS3	Morphogenesis and release	Topotyping Influences vector transmission

that the most important vector was a small fly of the *Culicoides* species. Initially, BT disease was thought to be confined to Africa, and the principle means of transmission in Africa was by *C. imicola*. However, when BT was recognized outside of Africa in the 1940s and 1950s, it was assumed that the introduction of the virus into other countries of the world was by animals carrying the virus. This then led to extensive quarantine and trade restrictions involving the movement of animals. The fear was compounded by reports of persistently infected cattle and the global dissemination of BTV through semen of bulls (Luedke, 1985). These reports pushed the emphasis of insect vectors as disseminators of BTV into the background. Extensive research failed to verify the early reports of persistent infection in cattle, and the failure to confirm shedding of virus in bull semen then led to reevaluation of the insects as important vectors of BTV (Bowen et al., 1985; Sawyer et al., 1992).

In addition to these observations, it was recognized that BTVs were present in many countries on all continents with the exception of Antarctica (MacLachlan and Osburn, 2006). Of the 1,254 *Culicoides spp.* recognized around the world, only 30 have been incriminated in transmitting BTVs to some degree (Tabachnick, 2004). There are nine species of *Culicoides* that have been identified as the major transmitters of BTVs, as shown in Table 2-3.

The distribution of the different *Culicoides spp.* in the different parts of the world is also associated with different serotypes of BTVs (Figure 2-16). This has led to the concept of episystems, which is used to describe the species and environmental aspects of an epidemiological event in a particular ecosystem, which affects the distribution and dynamics of a pathogen and disease (Tabachnik, 2004). This is an important concept in complex systems such as that of BTVs. Bluetongue viruses in these episystems are integral to the maintenance and transmission of the viruses to susceptible ruminant animals, leading to economically important disease.

The distribution of BT-infected *Culicoides spp.* in episystems is not fully understood. However, it appears to include phylogenetic relationships, vector competence, vector capacity, environmental temperatures, and breeding sites. The

TABLE 2-3 Location of *Culicoides* Vectors for Bluetongue Virus

Vectors	Countries / Continents
C. imicola	Africa, Mediterranean Europe
C. sonorensis	North America and northern Mexico
C. insignis	Central and South America
C. brevitaris, wadii, fulvus	Southeast Asia
C. brevitaris, wadii	Australia, Java
C. obsoletus, pulicaris	Central and southern Europe
C. dewulfi, obsoletus complex[a]	Northern Europe

[a]Meiswinkel et al. (2007).

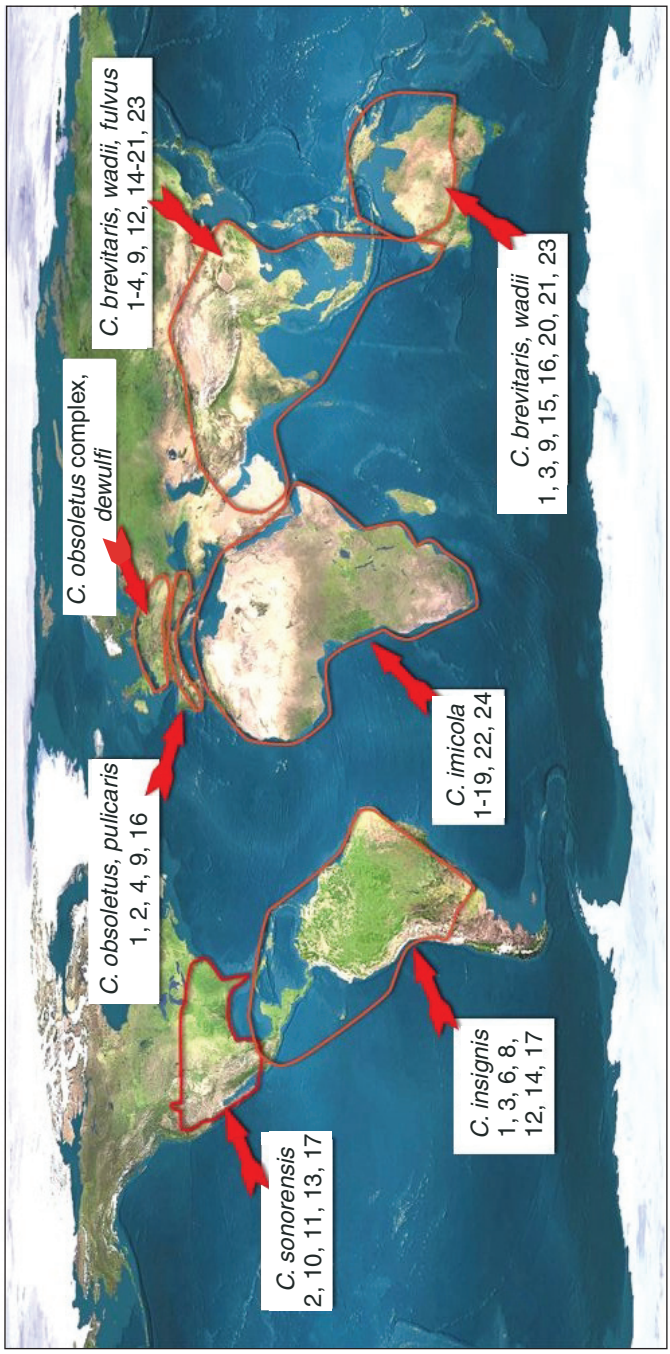

FIGURE 2-16 Distribution of *Culicoides* episystems and bluetongue virus topotypes. Created by John Gardiner, School of Veterinary Medicine, University of California, Davis.

vectors appear to adapt to certain ecosystems and the ruminant or other animal species that serve as blood meal sources for the insects. Some of the factors are undoubtedly genetically controlled, whereas environmental factors will impact the ability of the vectors to survive and actively produce infective virus. Until recently, the rule of thumb was that C*ulicoides spp.* carrying infected viruses were confined to 40°N and 35°S latitudes (Sellers, 1992; Walton, 2004).

Distribution

The worldwide distribution of the 24 different serotypes of BTVs is governed by the virus and insect vector. Two different gene segments, VP3 and VP10, play roles in expressing the viral structural protein VP3 and the nonstructural proteins (NS) NS3 and NS3A, respectively, which make up the topotype classification controlling the distribution of the viral serotypes in the different episystems on the six continents (Figure 2-16) (Bonneau and MacLachlan, 2004; Gould et al., 1992). VP3 is a structural protein in the inner core of the virus, which is associated with the topotypes. NS3 and NS3A play an important role in viral release from the cells and appear to have evolved with the competent *Culicoides spp.* vectors. The other factors which play an important role in viral distribution include climatic conditions such as environmental temperature, soil, water, and vertebrate host populations, which serve as sources of blood meals (Sellers, 1992; Mellors, 2004).

Although BT disease is primarily limited to the temperate regions of the world, the introduction of susceptible animals (sheep) from temperate or northern climates readily come down with BT disease. The inference is that animals in tropical and subtropical areas of the world develop herd immunity to the BTVs in their areas. Most likely, the passive immunity in the maternal colostrum bestows immediate immunity to the newborn. Circulation of endemic BTVs continually reimmunizes these newborn animals through adulthood. Hence, the immune animals are not incapacitated by active infections during their life.

BT disease is seasonal and dependent upon the infected *Culicoides spp.* vectors, which are in the ecosystem (Figure 2-17). Viral replication in the *Culicoides spp.* vectors requires warm temperatures. Although virogenesis can occur in *Culicoides spp.* at 15 to 25ºC, the ideal temperature range is from 25 to 32ºC (Mullens et al., 2004). The high virus titers require more blood meals, which in turn brings higher virus loads to the ruminants upon which they feed. The first animal cases usually show up in the late summer and early fall and persist until the first frost or freezing temperatures. Late summer and fall are the very time that the *Culicoides spp.* vectors are at their peak in numbers, and the virus titers in ruminants are also high. The combination of elevated virus titers in both the insect and the ruminant populations sets the stage for acute infections and disease in the recipient animal hosts. Once the killing frost reduces the population of infected vectors, the outbreaks and transmission of viruses stops.

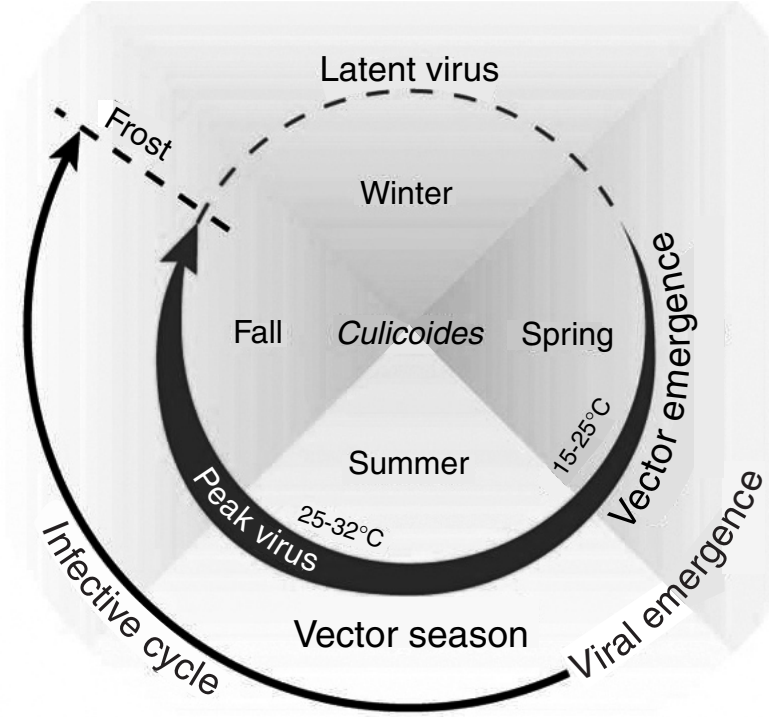

FIGURE 2-17 Bluetongue virus and *Culicoides* vector cycle. Created by Rick Hayes, School of Veterinary Medicine, University of California, Davis.

The appearance of BT disease in ruminants is usually the first indication that the virus is circulating in the ecosystem. Unless an active surveillance system of virus isolation or serological testing is in place, disease manifestation is the only indication that the virus is in the region. Viral identification is complicated by the need for rapid methodology, such as PCR identification. Virus isolation by chick embryo or cell culture is slow and laborious. Serological results are delayed until after an immune response has taken place; most susceptible animals will have already shown clinical signs of disease.

The means by which the virus is introduced into the ecosystem is wind, which transports BT-infected *Culicoides* (Sellers, 1992). This concept is thought to be the way that incursions of *C. imicola* carried BTVs into southern Europe from North Africa in the mid-1950s and in the 1980s. Fortunately, the vectors and the virus did not persist, as the climatic conditions did not permit their establishment in succeeding years. BTVs also may appear in new areas by transport of viremic BT-infected animals, which then serve as a source of virus-infected

blood meal for susceptible local *Culicoides*. These vectors may then feed on other animals in the ecosystem and quickly serve as a new outbreak of BT infection and disease. This is the principal way that the viruses become established in temperate climates that have resident susceptible *Culicoides* populations. There is also some evidence that BTVs may survive over winter through transovarial transmission of the viruses in *Culicoides* (White et al., 2004). These midges may then be a source of virus during the next summer season.

In the temperate and northern climates, BTVs vary each year depending on climatic conditions and the distribution of the infected *Culicoides spp.* vectors. Many of the newborn animals may be born during the winter months, and the passive immunity in the colostrum will have been depleted by the time the vectors carrying BTVs are circulating in the ecosystem. This new susceptible naïve population is available for BT infection and disease.

The distribution of BT disease, caused by the BTVs, is directly associated with the insect vectors critical to viral transmission. It is important that the appropriate medium for the incubation of eggs and larvae be used for virus isolation and identification. These breeding sites depend on the species of *Culicoides*. For instance, *C. sonorensis* breeds in streams with slow-moving water with a mix of cow dung and silt along the edge, whereas *C. brevitarsis* utilizes cow dung or patties as its primary breeding site (Mellors, 2004).

Case Study: Progression of Bluetongue Disease in Europe

BTV infection and disease appears to have been established in Europe over the last 5 years (Mellors, 2004; Goffredo and Meiswinkel, 2004). Although the cause for this is not entirely clear, there are some factors that are becoming more apparent, such as changing climatic conditions including the possibility of global warming, and the adaptation of virus to a new species of *Culicoides*. The sequence of events is depicted nicely by the movement of the *C. imicola* boundary in 1999 from North Africa, Spain, Portugal, and Turkey to the southern European countries of Greece and Italy in 2001. Along with the incursion of the vectors was the appearance of BT disease in sheep (Goffredo and Meiswinkel, 2004). By 2005, BT disease was reported in sheep at nearly 45°N latitude; and in 2006, BT disease in sheep and cattle had reached above 50°N latitude (Figure 2-18).

Culicoides imicola remained at around 40°N latitude and was the primary vector of BTVs up to that location (Baylis et al., 2004). Two other *Culicoides* appeared to be the primary vectors above 40°N latitude. *Culicoides obsoletus* and *C. pulicaris* appeared to have fed on BTV-infected animals, and in turn, became the vectors of importance in transmitting BTV serotypes 1, 4, 9, and 16. Over 500,000 sheep were infected in Italy (WAHID-OIE, 2007). BTV serotype 2 was introduced into the western part of southern Europe from North Africa. In 2006, the appearance of BTV serotype 8 in over 2,000 cattle and sheep in northern Europe was unexpected (Goffredo and Meiswinkel, 2004). The vectors

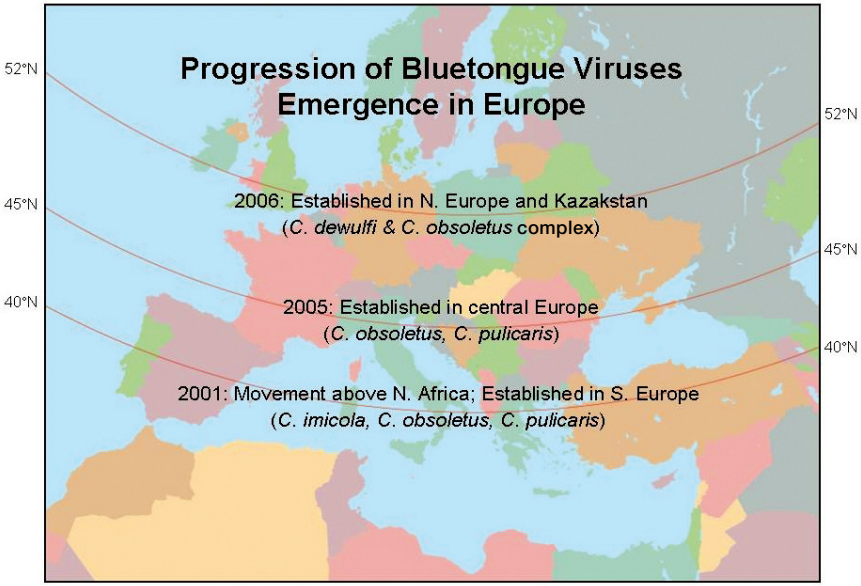

FIGURE 2-18 Progression of bluetongue viruses emergence in Europe. Created by Rick Hayes, School of Veterinary Medicine, University of California, Davis.

were different, possibly *C. dewulfi* and *C. obsoletus* complex, and appeared to be the primary vectors in Germany, France, the Netherlands, Belgium, and Luxembourg (Meiswinkel et al., 2004). These vectors are well-adapted and acclimated to northern Europe. The other environmental factors that appear to have played a role were global warming and more importantly, the unusual flow of warm weather from southern Europe. The temperature in northern Europe was 3°C warmer during the 2006 autumn than had been recorded before (WMO, 2007). Also, the vector season was extended into November because of unusually warm temperatures. This elevated temperature may have permitted virogenesis to easily occur in *C. dewulfi* and *C. obsoletus* complex.

Another factor of interest was the appearance of BTV serotype 8 in northern European countries. Serotype 8 had not been reported north of Nigeria. It is unusual for serotypes to move over such a great distance. The explanation for the appearance of serotype 8 in northern Europe has not been resolved.

It is of interest that BT disease has been reasonably well controlled in eastern and southern Europe; whether this is due to the effectiveness of vaccines or whether BTVs 1, 2, 4, 9, and l6 have not been able to become established with *C. imicola*, *C. obsoletus*, and/or *C. pulicaris* in that environment, only time will tell.

Vaccines

The control of BTV infection in animals is based primarily on vaccination with modified live virus directed to the serotypes in the area. Since this type of vaccine virus has been associated with modified live vaccines, it is recommended that the vaccines be administered during the winter months when the vectors are inactive. The use of these vaccines protects the susceptible animals from disease as long as the appropriate serotypes are included in the vaccine. In Italy, modified live virus vaccine containing serotypes 2 and 9 was used to control the disease (Santi et al., 2004). Both sheep and cattle were vaccinated. In the Mediterranean islands, vaccination with modified live virus vaccines including serotypes 2 and 4 was also effective in preventing disease. There is a need for effective recombinant vaccines that can be used in the face of an outbreak. Inactivated viral vaccines have not been effective in preventing disease.

Summary

The biology of BTV infections is complex: 24 serotypes of virus carried by at least 9 different *Culicoides spp.* on 6 different continents presents a variety of scenarios that must be dealt with. BTV is a double-stranded RNA virus which easily reassorts the segments during dual infections, and the virus is also subject to mutations and genetic drift. The distribution of BTV serotypes is controlled by the *Culicoides spp.* (episystems) and the genetic characteristics of the virus (topotypes). Many other factors have an interplay including climatic conditions, water, and mammalian host species required for blood meals. In order for the virus to be successful in the vectors requires favorable vector capacity and vector competence. The impact of the virus on mammalian systems includes devastating hemorrhagic disease in sheep and wild ruminants, an IgE-mediated response in cattle, and a necrotizing and liquefying neuronal lesion in fetal lambs and calves leading to retinal dysplasia and hydranencephaly. The challenges facing BTV infections include disease control, which for the most part is vaccines. At this time, the most widely accepted and efficacious vaccines are modified live virus vaccines. These vaccines present problems since they may be picked up by vectors and transmitted to other ruminants where they can reassort with wild-type viruses in nature.

There is a need to better understand the biology of the vectors; vector competence and capacity; the epidemiology of the infections; and the effects of climatic and global warming on these viruses, their vectors, and the disease in animal species. In this regard, there are aspects of the virus and the related vectors and environmental changes that can be used as models for other vector-borne diseases.

ENVIRONMENTAL FACTORS INFLUENCE TRANSMISSION OF SIN NOMBRE HANTAVIRUS BETWEEN RODENTS (AND TO HUMANS?)

Charles H. Calisher, Ph.D.[21]
Colorado State University

James N. Mills, Ph.D.[22]
Centers for Disease Control and Prevention[23]

J. Jeffrey Root, Ph.D.[24]
U.S. Department of Agriculture

Jeffrey B. Doty, M.S.[21]
Colorado State University

Barry J. Beaty, Ph.D. [21]
Colorado State University

The factors that condition the transmission and maintenance of zoonotic agents in reservoir and tangential vertebrate hosts are poorly understood. This is particularly true for vector-borne zoonotic agents because of their complex transmission cycles. Risk assessment, prevention, and control of zoonotic diseases would be enhanced by understanding the determinants of emergence of these pathogens into human populations. Unfortunately, in many cases we do not even know what all the variables are and these variables may differ between agents, from time to time, and geographically, at the very least. Hantaviruses, which are transmitted between rodents (and shrews), and thereby to humans, may provide model systems for investigation of these diverse factors. Long-term (longitudinal) studies of Sin Nombre virus in deer mice (*Peromyscus maniculatus*) in Colorado have provided insight into the maintenance and amplification of this virus in nature. Lessons learned may be extrapolated to other zoonotic agents, including those transmitted by arthropod vectors.

[21]Arthropod-borne and Infectious Diseases Laboratory, Department of Microbiology, Immunology & Pathology, College of Veterinary Medicine and Biomedical Sciences, Fort Collins, CO 80523. Phone: (970) 491-2987; Fax: (970) 491-8707; E-mail: calisher@cybersafe.net.

[22]Special Pathogens Branch, National Center for Infectious Diseases, Atlanta, GA 30333. E-mail: jum0@cdc.gov.

[23]The findings and conclusions in this report are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.

[24]U.S. Department of Agriculture, Wildlife Services, National Wildlife Research Center, 4101 La Porte Avenue, Fort Collins, CO 80521. E-mail: jeff.root@aphis.usda.gov.

Natural Cycles of Arthropod-Borne and Rodent-Borne Viruses

The classical definition of an arthropod-borne virus ("arbovirus") is that it is a virus maintained in nature through biological transmission between susceptible vertebrate hosts by hematophagous arthropods (mosquitoes, psychodids, ceratopogonids, and ticks). That is, these viruses replicate both in an arthropod host and a vertebrate host; vertebrate infection occurs when the infected arthropod takes a blood meal. Most human, livestock, and wild animal diseases occur when the arbovirus is transmitted to these hosts from the enzootic vertebrate host by the arthropod vector. Few arboviruses are transmitted directly from human to human by arthropod vectors; for example, dengue viruses, yellow fever virus, and Chikungunya virus are among these exceptions. The life cycles of these viruses are very complex, given that these viruses have the ability to replicate in both an arthropod and a vertebrate. The arthropod is either unaffected or minimally affected and usually is infected for life, whereas the vertebrate may be unaffected, mildly affected, or severely affected. Although the arthropod host has little effect on the virus, other than serving to amplify the virus, the vertebrate host responds to infection with viremia and by manufacturing antibody, cytokines, chemokines, and other products with antiviral activities.

Viruses that are strictly rodent-borne (i.e., without arthropod components to their life cycles) are transmitted directly and biologically (not mechanically) between rodents or from rodents to vertebrates of other taxa, including humans. The natural cycles of both arboviruses and rodent-borne viruses are conditioned by features of the ecology, environment, host, and virus, factors which vary temporally and geographically, perhaps in a complex and ephemeral interrelationship that Yates et al. (2002) called a "trophic cascade" (*vide infra*).

Among the exclusively rodent-borne viruses are hantaviruses (family *Bunyaviridae*, genus *Hantavirus*) and arenaviruses (family *Arenaviridae*, genus *Arenavirus*), both of which include serious human pathogens. These viruses appear to replicate in their rodent hosts with some, usually minor, effects but do not cause disease in them. Hantaviruses may cause persistent infections, with or without virus shedding, and antibody to them does not quench those infections. Thus, the presence of antibody to a hantavirus may serve as a surrogate indicator of current, recent, or remote infection with that virus.

Introduction to the Hantaviruses

Hantaviruses (family *Bunyaviridae*, genus *Hantavirus*) are first known from Chinese medical records of 1,000 years ago, describing what is now known as hemorrhagic fever with renal syndrome (HFRS). Reports of this or similar diseases were made during World War I, the Japanese-Chinese war, and among German soldiers during 1941-1942 in Russia and Finland, although the latter likely was a mild form of HFRS called nephropathia epidemica. Korean hemor-

TABLE 2-4 Recognized Hantaviruses (to April 2007)

Virus[a]	Source[b]	Distribution[c]	Disease[d]
Hantaan	*Apodemus agrarius (mantchuricus)*	Asia	HFRS
Seoul	*Rattus norvegicus*	Nearly worldwide	HFRS
Soochong	*Apodemus peninsulae*	Asia	None
Dobrava	*Apodemus flavicollis*	Europe	HFRS
Thai	*Bandicota indica*	Asia	HFRS
Saaremaa	*Apodemus agrarius (agrarius)*	Europe	HFRS
Amur	*Apodemus peninsulae*	Asia	HFRS
Puumala	*Myodes glareolus*	Europe	NE
Prospect Hill	*Microtus pennsylvanicus*	North America	None
Bloodland Lake	*Microtus ochrogaster*	North America	None
Isla Vista	*Microtus californicus*	North America	None
Tula	*Microtus arvalis/M. levis*	Europe	HFRS
Khabarovsk	*Microtus fortis*	Asia	None
Topografov	*Lemmus sibericus*	Asia	None
Sangassou	*Hylomyscus simus*	Africa	None
Sin Nombre	*Peromyscus maniculatus* (several subspecies)	North America	HPS
New York	*Peromyscus leucopus*	North America	HPS
Black Creek Canal	*Sigmodon hispidus (spadicipygus)*	North America	HPS
Bayou	*Oryzomys palustris*	North America	HPS
Catacamas	*Oryzomys couesi*	Central America	None
Muleshoe	*Sigmodon hispidus (texianus)*	North America	HPS
Monongahela	*Peromyscus maniculatus (nubiterrae)*	North America	HPS
Limestone Canyon	*Peromyscus boylii*	North America	None
Blue River	*Peromyscus leucopus*	North America	None
El Moro Canyon	*Reithrodontomys megalotis*	North America	None
Río Segundo	*Reithrodontomys mexicanus*	Central America	None
Caño Delgadito	*Sigmodon alstoni*	South America	None

rhagic fever and Epidemic hemorrhagic fever (China) are other names for HFRS. In 1978, Lee et al. reported that they had isolated the etiologic agent of Korean hemorrhagic fever (Hantaan virus) from striped field mice (*Apodemus agrarius*) captured in South Korea. The discovery of other hantaviruses in other rodents soon followed, and with increasing frequency, each virus was shown to have an association with a principle rodent host, suggesting a coevolutionary relationship. Table 2-4 provides a list of the hantaviruses recognized to date (J. N. Mills, unpublished summary). Hantaviruses may cause persistent infections in their rodent hosts, even in the presence of antibody to the infecting virus.

TABLE 2-4 Continued

Virus[a]	Source[b]	Distribution[c]	Disease[d]
Juquitiba	*Oligoryzomys nigripes*	South America	HPS
Araraquara	*Necromys lasiurus*	South America	HPS
Castelo dos Sonhos	Unknown	South America	HPS
Río Mamoré	*Oligoryzomys microtis*	South America	None
Anajatuba	*Oligoryzomys fornesi*	South America	HPS?
Rio Mearim	*Holochilus sciureus*	South America	None
Laguna Negra	*Calomys laucha*	South America	HPS
Andes	*Oligoryzomys longicaudatus*	South America	HPS
Lechiguanas	*Oligoryzomys flavescens*	South America	HPS
Bermejo	*Oligoryzomys chacoensis*	South America	HPS
Orán	*Oligoryzomys longicaudatus*	South America	HPS
Maciel	*Necromys benefactus*	South America	None
Hu39694	Unknown	South America	HPS
Pergamino	*Akodon azarae*	South America	None
Central Plata	*Oligoryzomys flavescens*	South America	HPS
Choclo	*Oligoryzomys fulvescens (costaricensis)*	Central America	HPS
Calabazo	*Zygodontomys brevicauda (cherriei)*	Central America	None
Maporal	*Oligoryzomys fulvescens*	South America	None
Thottapalayam	*Suncus murinus*	Asia	None
Tanganya	*Crocidura theresae*	Africa	None

[a]Other viruses are known but have not been sufficiently studied to warrant a name; these may be newly recognized viruses or subtypes of recognized viruses.

[b]Principal or only known hosts are listed; other rodents may serve as hosts.

[c]The distribution of these viruses generally parallels the distribution of the principal rodent host. Thus, whereas general locations are given, the virus and its host may be found only in limited areas.

[d]HFRS: hemorrhagic fever with renal syndrome; HPS: hantavirus pulmonary syndrome; NE: nephropathia epidemica; None: no disease recognized.

Discovery of Sin Nombre Virus and of Hantavirus Pulmonary Syndrome

In April 1993, an outbreak of adult respiratory distress syndrome occurred among some residents of the Four Corners area of the southwestern United States (where Colorado, New Mexico, Arizona, and Utah are contiguous). It was soon thereafter shown that the etiologic agent of this disease, called hantavirus pulmonary syndrome (HPS), is a hantavirus hosted by deer mice (*Peromyscus maniculatus*); the virus eventually was named Sin Nombre virus (Nichol et al., 1993; Butler and Peters, 1994; Elliott et al., 1994; Ksiazek et al., 1995; Schmaljohn et al., 1995).

Deer mice, the most common mammal in North America, invade houses, breed prolifically, and are distributed throughout much of North America, with

most of the eastern (Atlantic) coasts of the United States and Canada being an exception. Their populations fluctuate from season to season and from year to year, which is an important epidemiological characteristic.

Longitudinal Studies of Sin Nombre Virus in Colorado

Until recently, most studies of rodent-borne viruses have provided information on changes in abundance and prevalence of viral infection in host populations. While epidemiologically informative, these data do not explain the series of events leading to human disease and comprise, in effect, point prevalence studies, yielding snapshots of the situation at specific time points. Yates et al. (2002) provided data suggesting and supporting the hypothesis that, in the southwestern United States, there is a "trophic cascade"—climatological, ecologic, and demographic events—leading, somehow, from significant occurrences of precipitation to human disease. This trophic cascade is apparently very complex and involves weather, rodent population densities, and many other factors, some, perhaps many, unrecognized to date.

In 1994, under contract with the U.S. Centers for Disease Control and Prevention, research groups in northern and southern Arizona, New Mexico, and Colorado began long-term studies of the prevalence of Sin Nombre virus, the densities of rodent populations, and the environmental factors that may influence both. We terminated the Colorado studies in October of 2006, when funding was no longer available. During those 12 years, however, we studied numerous ecologic aspects of Sin Nombre virus transmission and were able to accumulate a huge database regarding Sin Nombre virus and its deer mouse host. Scores of publications regarding various aspects of this work have been published; references to some of them can be found interspersed below.

Studies were conducted at sites in southwestern (Fort Lewis, La Plata County) and west-central (Molina, Mesa County) Colorado and at the Pinon Canyon Maneuver Site (PCMS) in Las Animas County, southeastern Colorado. For serologic tests (IgG ELISA) we used the nucleocapsid antigen of Sin Nombre virus (Feldmann et al., 1993). For reasons not yet understood, and which may be related to deer mouse genetic differences, the prevalence of antibody to Sin Nombre virus at PCMS was much lower than that at the western Colorado sites. We already had observed a positive association of rodent abundance and prevalence of antibody to Sin Nombre virus at the Fort Lewis site (Calisher et al., 1999b).

We have analyzed in detail many of the specifics of rodent populations, virus (antibody) prevalence, air and ground temperatures, precipitation and ground moisture, vegetational surveys, terrestrial insect biomass, deer mouse genetics, and deer mouse cytokine analyses at PCMS (Calisher et al., 2005a,b), but have not yet done the same for the western Colorado sites. Therefore, the data to be described and discussed here are those from the PCMS.

The PCMS, which comprises more than 1,040 km^2, was acquired by the U.S.

Department of the Army in 1983 and is under the management of the Directorate of Environmental Compliance and Management, Fort Carson, Colorado. Prior to that acquisition, the area had been grazed by domesticated and wild ungulates and had supported small populations of humans since it was pioneered in the late 1870s. PCMS has been described as an area of dry continental climate and with elevation ranges from 1,300 to 1,700 m (Shaw et al., 1989; U.S. Department of the Army, 1980; Anderson et al., 1989). The topography consists of broad, moderately sloping uplands bordered by the Purgatoire River canyon on the east, limestone hills on the west, and a basalt hogback on the south. Vegetation is dominated by short-grass prairie but includes pinyon pine (*Pinus edulis*)-one-seeded juniper (*Juniperus monosperma*) woodland (Costello, 1954); the pinyon-juniper association is concentrated along the Purgatoire River canyon and its side canyons, in the limestone hills, and on parts of the basaltic hogback. The Fort Carson authorities have made concentrated and successful efforts to maintain and improve wildlife habitat, archaeologic sites, roads, and facilities. We trapped rodents at various locations but the results reported here were from two principal sites: one in Red Rocks Canyon and the other about 2 km from there, at the head of Red Rocks Canyon (Figures 2-19 and 2-20).

The data reported herein will be used to exemplify the effects of climatological variations on rodent populations. Our intent was to accrue sufficient data from these longitudinal studies to determine environmental risk factors for transmission of Sin Nombre virus to rodents and to humans.

Major Findings Concerning Sin Nombre Virus Transmission and Maintenance at Colorado Sites

Long-term studies at these varied sites inevitably led to many observations not made previously and revealed many aspects of rodent and virus characteristics and relationships not observed previously:

- We observed an association between gender and antibody prevalence (more males than females infected).
- We determined that infection status was associated positively with observed wounds, which likely were the result of intraspecific aggressive behaviors (Calisher et al., 2007).
- A similar correlation between prevalence of antibody to Sin Nombre virus and wounds has been observed with Limestone Canyon hantavirus and its principle host, the brush mouse (*Peromyscus boylii*), but not between western harvest mice (*Reithrodontomys megalotis*) and El Moro Canyon hantavirus or meadow voles (*Microtus pennsylvanicus*) and Prospect Hill hantavirus, suggesting different transmission mechanisms for the latter two and the former two viruses (unpublished data).
- We observed that antibody to (infection with) Sin Nombre virus is acquired

FIGURE 2-19 Overview of Red Rocks Canyon, Pinon Canyon Maneuver Site, southeastern Colorado. Note shallow canyon, one-seeded juniper, and otherwise arid short-grass prairie.

FIGURE 2-20 Close-up view of rocky area in Red Rocks Canyon, Pinon Canyon Maneuver Site, southeastern Colorado. Note the abundance of grasses, forbs, small one-seeded junipers, and rocky outcroppings.

by males, mostly during the late summer to late fall period (when aggressive behavior peaks) and that antibody to Sin Nombre virus is acquired by females more frequently during the period from winter to early spring (when breeding commences).

- We found that antibody titers are about the same in male and female deer mice (unpublished data).
- Simultaneous multiple captures of rodents of the same species suggest group foraging, which may relate to trafficking of Sin Nombre virus (Calisher et al., 2000).
- Long-lived infected individual deer mice may serve as transseasonal reservoirs of Sin Nombre virus (Calisher et al., 2001a).
- Deer mice have excellent navigational instincts (Calisher et al., 1999a).
- There is a positive association of deer mouse movement, available vegetation, and prevalence of infection with Sin Nombre virus (Root et al., 1999).
- Mammalian habitat diversity is inversely correlated with prevalence of infection of deer mice with Sin Nombre virus (J. N. Mills et al., unpublished data).
- And there is a great deal more we do not know about deer mice and other rodents, about deer mouse genetics, about Sin Nombre virus, and about other viruses (Calisher et al., 1999b, 2001b; Root et al., 2001, 2003, 2004, 2005).

These and other papers focusing on Sin Nombre virus and on other hantaviruses, in other contexts, by us and by others, have made contributions to the body of scientific knowledge on this subject.

Factors That Condition Sin Nombre Virus Transmission and Emergence in Humans

The original and principal intents of our investigations were to acquire information regarding deer mouse populations and Sin Nombre virus prevalence and the factors that influence them, in regard to the premise that this information should be directly relevant to prediction and prevention of HPS in the southwestern United States.

Determining Relative Risk (Incidence of Infection)

At all sites, mark-recapture studies allowed us to track individual rodents over time and to determine incidence, seasonality, and prevalence of Sin Nombre virus infections in deer mice by age, sex, and location. For example, of 792 deer mice at PCMS, we recaptured 116 males and 162 females, some more than 11 months after they were first captured and two more than a year after they were first captured (Table 2-5). The majority, 514/792 (65 percent), were never recaptured; emigration, starvation, age-related deaths, and predation are among

TABLE 2-5 Recaptured Deer Mice (*Peromyscus maniculatus*), by Sex and Maximum Number of Weeks Between First and Last Capture, Pinyon Canyon Maneuver Site, Southeastern Colorado, January 1995-November 2000

		Weeks After First Capture								
Sex	Total	0[a]	6	7-18	19-30	31-42	43-54	55-66	>66	Mean
Female	317	201	29	53	20	10	3	1	0	17.4
Male	475	313	51	55	39	14	2	0	1	17.0

[a]0 = not recaptured.

TABLE 2-6 Incidence of IgG Antibody Reactive with Sin Nombre Virus in Deer Mice (*Peromyscus maniculatus*) Recaptured and Sampled at Least Twice at Pinyon Canyon Maneuver Site, Southeastern Colorado, January 1995-November 2000

Sex	Number at Risk[a]	Number of New Infections	Cumulative Percentage with Antibody	Mouse Months of Observations[b]	Incidence[c]
Male	149	5	3.4	614	0.81
Female	108	1	0.93	430	0.23
Total	257	6		1044	0.57

[a]Number of mice without antibody when first captured.

[b]Total time intervals between successive captures when mice were antibody-negative, plus half the interval between the time when mice changed from antibody-negative to antibody-positive.

[c]New infections per 100 mice per month.

the likely explanations for this. As well, we were able to determine the relative risk (incidence of infection) an individual deer mouse experienced at the site. As shown in Table 2-6, the estimated incidence for male deer mice at PCMS was 0.81 and for female deer mice 0.23 (new infections per 100 deer mice per month from January 1995 to November 2000).

Generalized Risk Factor Associations

Mills (2005) suggested that "prevalence and transmission rates of rodent-borne viruses within host populations vary in time and space and among host-virus systems" and categorized possible regulators of prevalence and transmission as follows: "(1) Environmental regulators such as weather and food supply affect transmission rates through their effect on reproductive success and population densities. (2) Anthropogenic factors, such as disturbance, may lead to ecosystem simplification and decreased diversity. These changes favor opportunistic species,

which may serve as reservoirs for zoonotic viruses. (3) Genetic factors influence susceptibility of mice to infection or capacity for chronic shedding and may be related to population cycling. (4) Behavioral factors, such as fighting, increase risk of transmission of some viruses and result in different patterns of infection between male and female mice. Communal nesting may result in over-winter transmission in colder climates. (5) Physiologic factors control host response to infection and length of time the host remains infectious."

Whereas these regulators may interact and compound one another, predicting risk based on them is far too complex for us to either determine their relative importance or to understand at this time. An excellent beginning to an overall view of these complexities has been made by Glass et al. (2000, 2002) and by Hjelle and Glass (2000). In the former paper the authors reiterated the hypothesis that the 1993 outbreak of HPS was initiated by environmental conditions and amplified rodent populations that were the result of unusual weather the previous 2 years. Glass et al. (2000) tested that premise using rainfall patterns, elevation data, and Landsat Thematic Mapper satellite imagery. Although precipitation at case-patient sites was not higher than it had been in previous years they found an association between environmental conditions (as indicated by elevation and satellite-derived spectral analysis) and HPS risk the following year. Repetition in later years supported those findings and allowed a degree of predictability. Hjelle and Glass (2000) reported results of analyses indicating that increased precipitation resulting from the 1991-1992 El Niño/Southern Oscillation fostered increased rodent population densities and suggested that this indicated a possible increase in transmission of Sin Nombre virus among rodents and from rodents to humans in 1993-1994. Furthermore, they pointed out the strong El Niño/Southern Oscillation of 1997-1998, and that in 1998-1999 the Four Corners states suffered a 5-fold increase in HPS cases over the number of cases expected. These studies are important if we are to understand the basic association between climate, rodent populations, Sin Nombre virus, and HPS, but they cannot provide us with specifics necessary for determining cause and effect.

In the 6-year period from 1995 to 2000 we trapped deer mice and other rodents (total number of rodents 2,798; total captures of these rodents 6,155) at the PCMS in southeastern Colorado, tested them for antibody to Sin Nombre virus, and took numerous climatologic measurements. Population dynamics differed for rodents of different species but had some common characteristics. Deer mice had highest relative population abundances in winters, lowest in summers. Nonetheless, there were clear interannual variations, sometimes associated with meteorologic conditions that similarly affected rodents of most of the 18 species captured. The results indicated that "typical" seasonal population dynamics may occur only under "average" conditions. Divergence from average conditions may occur frequently and result in changes in rodent population dynamics.

While temperature is not extremely variable focally in the American southwest, precipitation can be. We used mean precipitation and temperature data

from three sites near our trapping sites: one where we were trapping (Red Rocks Canyon), one about 24 km from the trapping site, and one 48 km from the trapping site; available data were comparable (Figure 2-21). As shown in Figure 2-22, there was an interaction effect between precipitation and temperature. Low rodent population abundances were associated with high precipitation during cold periods and low precipitation during warm periods (Calisher et al., 2005a). Cold, wet fall/winter conditions and hot, dry spring/summer conditions were associated with negative effects on populations of most species, including deer mice. For example, the cold and wet fall of 1997 coincided with an El Niño/Southern Oscillation event with high winter precipitation and abrupt declines in relative abundance of rodents.

Of importance to rodent populations is not only the amount of precipitation that occurs, but when it occurs. An abundance of precipitation in September or October, for example, is not the same as a uniformly distributed precipitation occurring in spring. Precipitation affects vegetation and insects, both of which are dietary resources for deer mice, so that the timing of precipitation during the growing season is important. When it occurs outside the growing season it may not contribute to resource availability, but it may negatively impact deer mouse survivorship. Our data also indicate that the timing of rainfall is an important determinant of breeding success and recruitment of juveniles into the population. For example, although juvenile recruitment likely peaked in the autumn (Figure 2-23), the only period during our study when juvenile recruitment appeared to

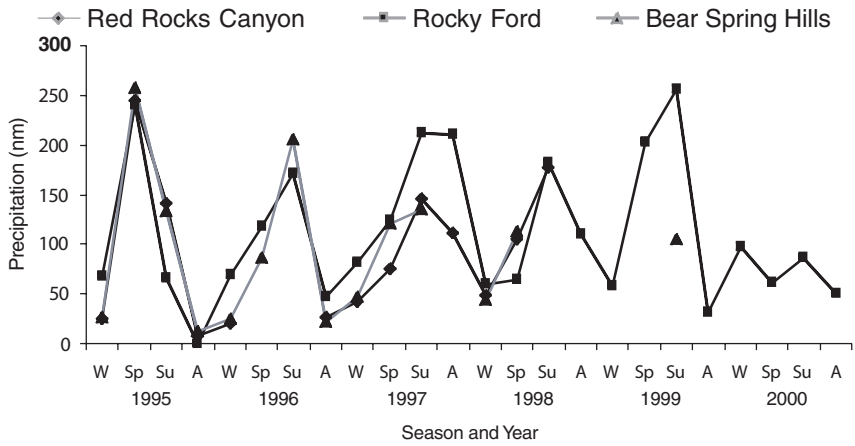

FIGURE 2-21 Quarterly precipitation as recorded at three weather stations in or near the Pinon Canyon Maneuver Site, southeastern Colorado, 1995-2000.
SOURCE: Reprinted with permission from Calisher et al. (2005a).

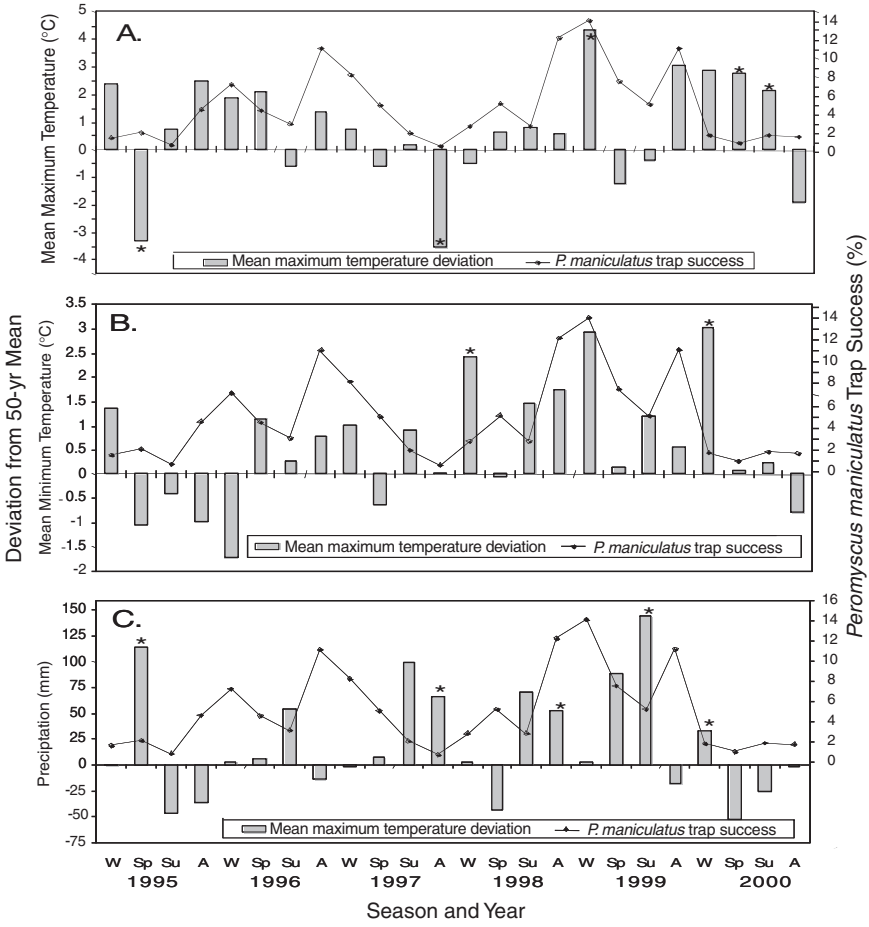

FIGURE 2-22 Deviations from the 50-year mean (1951-2000) for quarterly (A) mean maximum and (B) mean minimum temperatures and quarterly precipitation at Rocky Ford, Colorado, weather station. Asterisks indicate deviations that are at least two standard deviations from the 50-year mean. The line shows quarterly trap success (number of individuals captured per 100 trap nights) for deer mice.
SOURCE: Reprinted with permission from Calisher et al. (2005a).

be zero was the wet, cold El Niño autumn of 1997 (Figures 2-22 and 2-23). Conversely, the highest juvenile recruitment was observed in the unusually wet summer of 1999. Because rainfall in the American southwest can be remarkably focal, and because we did not monitor for diseases or predation, we cannot determine with certainty exactly what caused these population declines and surges but the

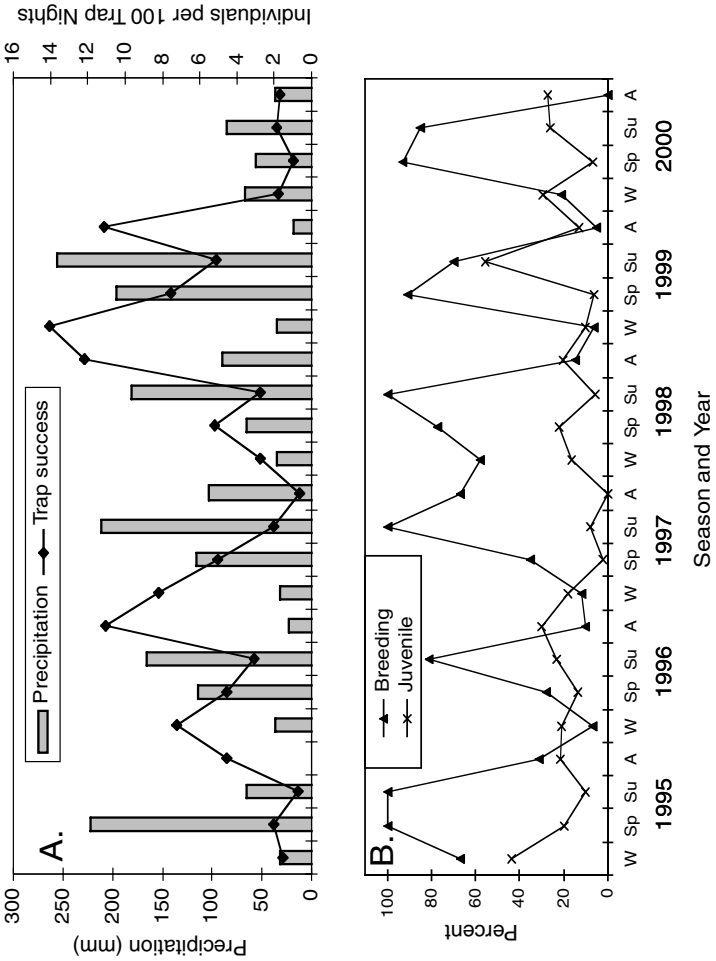

FIGURE 2-23 (A) Quarterly trap success for deer mice and total quarterly precipitation; (B) percent of adults in reproductive condition and percent of captures consisting of juveniles, at two mark-recapture sites in southeastern Colorado, 1995-2000.
SOURCE: Reprinted with permission from Calisher et al. (2005a).

weather patterns we have monitored suggest that they have an essential effect on relative abundance of rodent populations. Consequently, we caution that predicting rodent populations based on data from one site cannot be made with accuracy based on data from another, even nearby, site. Nonetheless, at the PCMS we found that precipitation during cold periods or lack of precipitation during warm periods each was associated with declines of populations of deer mice.

What Data Are Necessary and Sufficient to Establish Predictive Models?

Central to determining predictive models for Sin Nombre virus and HPS are observations suggesting delayed density-dependency. Niklasson et al. (1995), Mills et al. (1999), Yates et al. (2002), and Madhav et al. (2007) have hypothesized that prevalence of antibody to hantaviruses in host rodents was delayed density-dependent. That is, increasing and peaking host populations consist predominantly of uninfected juveniles that are likely not to have antibody (i.e., not infected). In the case of Sin Nombre virus, antibody prevalence will rise most quickly in declining populations in which reproduction has ended and the juvenile dilution effect (the consequence of there being more seronegative juveniles in the population) also has ended. Because the rate of intraspecific encounters and, therefore, virus transmission events are likely to be positively correlated with population density, the prevalence of antibody in those declining or low-density populations may be proportional to the peak population density from the previous reproductive season (i.e., prior to the decline). We have demonstrated clearly that deer mouse population abundances vary among sites and are positively and statistically correlated with prevalence of infection, an association that others, who have done shorter-term studies, failed to demonstrate (Calisher et al., 2007). Accordingly, high rodent population densities may not be directly predictive of an immediate rise in antibody prevalence, indicative of an increasing incidence of infection, but rather may be a longer-term predictor of such an increase. Common sense suggests that reducing contact with infected rodents is a critical first step in the prevention of human disease caused by Sin Nombre virus and other rodent-borne viruses. For example, having 10 deer mice in a residence, with 1 of them infected (10 percent), is not as great a risk as having 100 deer mice in that residence, with 10 of them infected (10 percent). Temporizing efforts, such as rodent exclusion, are important but beg the question of prevention in the long term (Glass et al., 1997). Until we have determined the fundamental relationships between meteorological events and plant productivity and quality, the dynamics of persistence and shedding of virus in Sin Nombre virus-infected deer mice, the effects of diet on urinary, fecal, and salivary pH, and the effects caused by changes in diet due to the aforementioned meteorological events, we will not be able to fully appreciate the complex sequence of events in the trophic cascade leading from precipitation to HPS. Figures 2-24 and 2-25 summarize the associations between meteorological events of 1991-1993 and 1997-1998, rodent

population abundances, and HPS in New Mexico (Parmenter et al., 1993) and between the 1997-1998 El Niño and rodent population densities in New Mexico and Colorado (Yates et al., 2002; Mills and Calisher, unpublished data).

Complicating our understanding of this moving target is climate change. Should mean temperatures and precipitation patterns continue to deviate upward from the current norms, increases in rodent population densities, the geographic distribution of rodents, and the prevalence of the viruses they harbor are likely to increase significantly, to the detriment of humans (Anyamba et al., 2006b). What is needed is a great deal more effort and funding invested in basic studies of the biology of both virus and vertebrate host—on their interactions, on the relative interactions of environmental variables, and on the variables that account for meaningful deviations from the norm.

Conclusions

The data accumulated during these and associated longitudinal studies of hantaviruses, specifically Sin Nombre virus, suggest that longitudinal studies may be the only current means available to identify predictors of risk for rodent acquisition of this virus and for subsequent transmission to humans.

We know that rodent populations fluctuate, sometimes considerably, but we do not know all the variables that impact those fluctuations. We know that virus (antibody) prevalence fluctuates, sometimes from 0 to 40 or 50 percent, but we do not know all the variables that impact those fluctuations. Nonetheless, these data suggest that the "trophic cascade" hypothesis is an innovative and acceptable one to test further. A simple and obviously correct hypothesis is not yet within our grasp but we seem to be intriguingly close.

It has long been accepted that certain ecologic and/or environmental conditions are associated with emergent transmission of agents causing zoonotic diseases. Recent development of predictive models for plague in the American southwest (Enscore et al., 2002; Eisen et al., 2007) are an example. In addition, Linthicum et al. (1999) offered a predictive model for Rift Valley fever in Kenya, and Anyamba et al. (2006b) predicted Rift Valley fever and malaria in East Africa, dengue fever and respiratory illnesses in specific areas of Asia, malaria in South America, cholera in Bangladesh and coastal India, southwestern United States for increased risk for HPS and plague, southern California for increased West Nile virus transmission, and northeast Brazil for increased dengue fever and respiratory illness. The recent extensive epizoodemic of Rift Valley fever, recognized in Kenya in December 2006, spread to Sudan, Tanzania, Somalia, and Burundi by May 2007 (ProMED-Mail, 2007). This disease outbreak alone indicates the utility of such predictive models.

It is possible that the trophic cascade hypothesis is a conceptual umbrella, and that using key elements of the predictive modeling systems mentioned earlier, and of other systems, might be useful in establishing models of other emerging

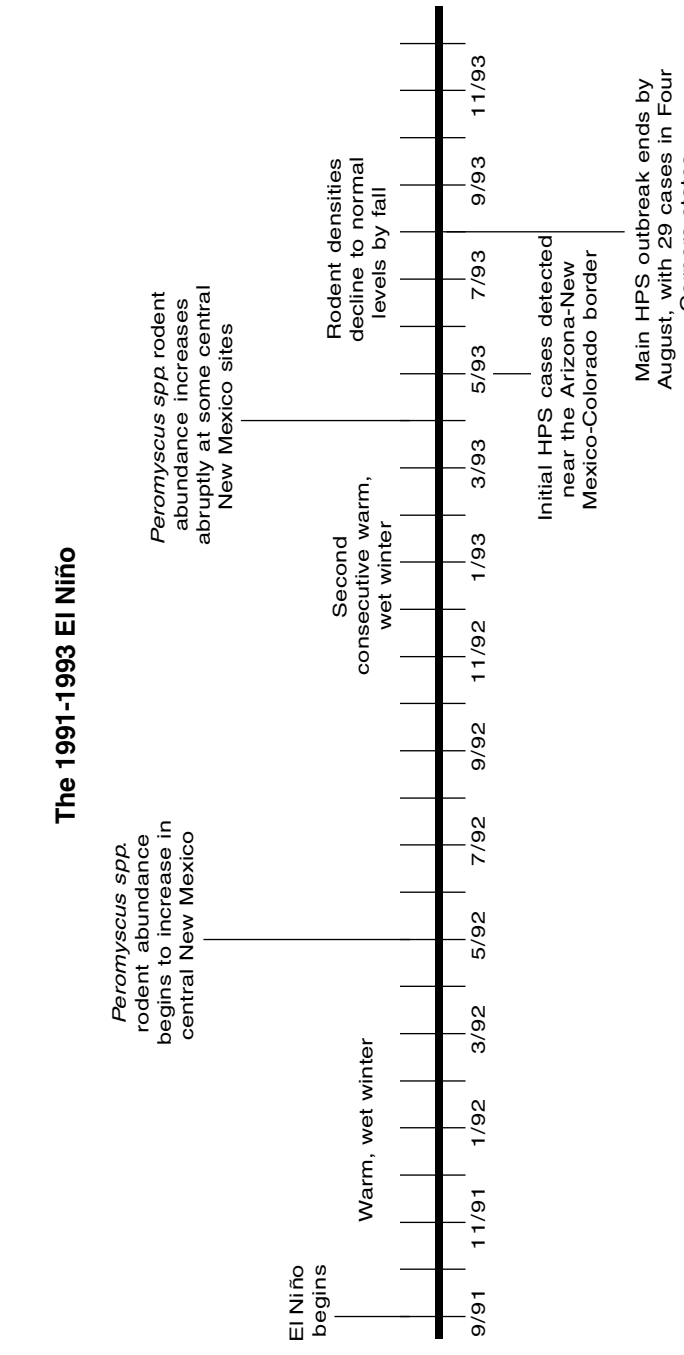

FIGURE 2-24 The 1991-1993 El Niño and some of its consequences in the southwestern United States.

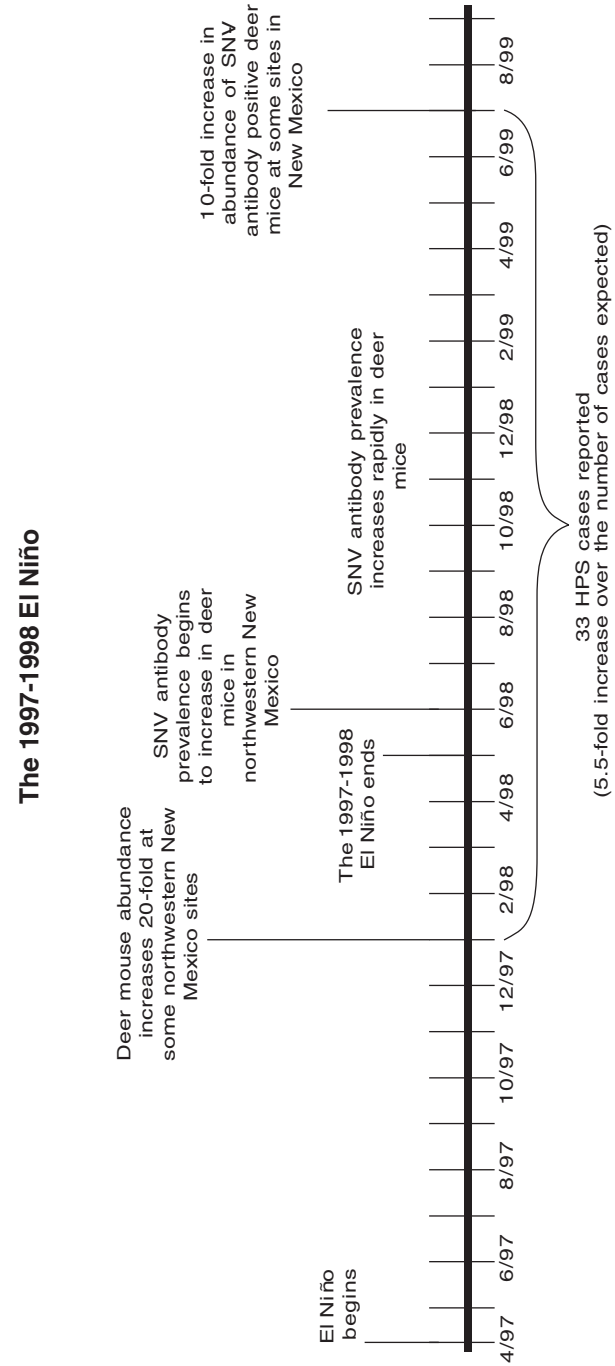

FIGURE 2-25 The 1997-1998 El Niño and some of its consequences in the southwestern United States.

and recurrent zoonoses, vector-borne and non-vector-borne, such as for arenaviruses. The important point is that, although particular zoonotic diseases have particular etiologic agents, the controlling conditions for each may have enough similarities to provide us with predictors of risk for acquisition and, therefore, with bases for prevention and control measures.

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3

Integrating Strategies to Address Vector-Borne Disease

OVERVIEW

Vector-borne diseases, among the general class of emerging infectious diseases, entail a host of needs and opportunities that have been characterized in numerous reviews and reports. A core report of the Institute of Medicine, *Microbial Threats to Health* (2003), recommended several actions related to the prediction, prevention, and control of vector-borne diseases; these are reviewed in this chapter's first paper by presenter Barry Beaty (a member of the Institute of Medicine committee that produced the *Microbial Threats to Health* report) and Lars Eisen of Colorado State University. In an additional contribution in Chapter 1, these authors describe how researchers and public health policy makers have responded to specific recommendations, including efforts by the Innovative Vector Control Consortium (IVCC) to develop new pesticides and formulations, as well as novel tools and management approaches, in order to advance vector control in and around the house.

In the chapter's second and third papers, Roger Nasci of the Centers for Disease Control and Prevention (CDC), and Sherrilyn Wainwright, of the U.S. Department of Agriculture's (USDA's) Animal and Plant Health Inspection Service (APHIS), offer their perspectives on issues discussed by the workshop panel on integrating strategies for vector-borne disease surveillance, diagnosis, and response. Topics included the need for, and challenges of, creating multidisciplinary teams to study and respond to vector-borne disease outbreaks; opportunities to integrate the surveillance and diagnosis of vector-borne disease with outbreak response; funding opportunities; research directions; and the training of vector biologists.

Based on his experience at CDC, Nasci notes both the successes and challenges of training and fielding multidisciplinary teams for outbreak response and to conduct basic research. Using the ArboNET surveillance network as an example (see also Petersen in Chapter 2), he also explores the creation and expansion of integrated information systems to monitor disease transmission and risk factors and argues for the development of comprehensive, testable predictive models based on input from a diversity of scientific fields. APHIS also uses multidisciplinary teams to monitor and detect infectious disease outbreaks in animals and plants, often in collaboration with the U.S. Departments of Health and Human Services and Fish and Wildlife Services, state agencies, affected industries, and diagnostic laboratories. Wainwright notes that these efforts, while largely successful, have on occasion "exposed weaknesses in communication and coordination between human public health and animal health agencies." Through the Agricultural Research Service (ARS), APHIS is involved in a number of studies of vector-borne disease, many of which are being addressed through a "multidisciplinary systems approach," involving other government agencies.

The subsequent paper by panelist David Morens of the National Institute of Allergy and Infectious diseases (NIAID) identifies several overarching scientific and logistical obstacles presented by vector-borne disease and compares them with challenges faced by the founders of tropical medicine. "The question of how to foster generalist training and team approaches to problem-solving, in which team members cross disciplinary lines regarded as being remote from each other . . . is no more impossible than the challenges faced and met successfully in the first 50 years of the 20th century, in which science and public health worked to produce a yellow fever vaccine [and] discovered and developed effective treatments for many vector-borne diseases," he observes. In order to begin to meet today's challenges, Morens explains, scientific and political leaders must recognize the complex problems posed by vector-borne diseases, and a cadre of multidisciplinary scientists and public health workers must be trained to address these problems in innovative and integrative ways.

Workshop panelist Adriana Costero, vector biology program officer for NIAID's Division of Microbiology and Infectious Diseases, describes the variety of funding mechanisms and projects supported by that agency in her contribution to this chapter. These include grants for basic studies and the initial phases of translational research, training grants, and career awards.

As noted in the Summary and Assessment (see section entitled "Needs and Opportunities"), response to the workshop panel presentations was both deep and wide-ranging. In his manuscript, included in Chapter 1 of this volume, Durland Fish offers a vision of "a new interdisciplinary approach to the understanding of vector-borne diseases" firmly grounded in ecology—a discipline historically central to the control of vector-borne diseases, but now at considerable remove from the biomedical sciences. He argues that the shift in studies of vector biology away from ecology and toward molecular biology, which began in the 1970s,

has produced "reductionistic and narrowly focused research agendas [that] have contributed very little to a broader understanding of interactions between vectors and their physical or biological environment."

There is a need to create a balanced, integrated, basic and applied research agenda to address the challenges and opportunites associated with vector-borne disease control efforts. Fish advocates a repositioning of the field of vector biology as a collaboration of environmental sciences and infectious disease epidemiology, supported by technologies such as remote sensing and geographic information systems. Among infectious diseases, Fish concludes, "vector-borne diseases have the greatest potential for advancing the integration of ecology and environmental science into the mainstream of infectious disease epidemiology."

NEEDS AND OPPORTUNITIES TO CONTROL VECTOR-BORNE DISEASES: RESPONSES TO THE IOM MICROBIAL THREATS TO HEALTH COMMITTEE RECOMMENDATIONS

Barry J. Beaty, Ph.D.[1]
Colorado State University

Lars Eisen, Ph.D.[1]
Colorado State University

Summary

Vector-borne diseases (VBDs) remain major threats to human health and well-being, and, as an epidemiological group, inflict a terrible and unacceptable public health burden on humankind. The developed world has been fortunate to have escaped much of the terrible burden that mosquitoes and their arthropod allies inflict on humans in countries endemic for diseases such as malaria and dengue, but the introduction and rapid spread of West Nile virus in the western hemisphere demonstrated that we can no longer be complacent in the face of emerging and resurging VBDs. Unfortunately as the burdens and threats of VBDs have increased, the U.S. and international public health capacity to address them has decreased.

The Institute of Medicine (IOM) report entitled *Microbial Threats to Health* (IOM, 2003) reviewed and identified factors leading to the resurgence and emergence of infectious diseases, including VBDs, and made recommendations to address the needs and opportunities for the prediction, prevention, and control of infectious diseases. The factors contributing to resurgence and emergence of

[1]Arthropod-borne and Infectious Diseases Laboratory, Department of Microbiology, Immunology, and Pathology, College of Veterinary Medicine and Biomedical Sciences.

VBDs and the recommendations made to address these issues will be reviewed here. Much of the information is excerpted directly from the Committee on Emerging Microbial Threats to Health in the 21st Century's 2003 report. This provides a context for the issues, needs, and opportunities in addressing the emergence and resurgence of VBDs—topics that are directly relevant to many of the chapters in this current report.

Despite the seemingly intractable nature of many VBDs, significant progress and new initiatives are underway to address their prediction, prevention, and control. New computer-based tools, novel approaches, and new knowledge being provided in the vector post-genomics era all provide new opportunities and targets for vector control and disease prevention. Rebuilding the human resource capacity to exploit the new tools and information to address VBDs remains a critical need to address.

The Extraordinary Burden of Vector-Borne Diseases

Resurgence and Emergence of Vector-Borne Diseases

In the 20th century, extraordinary advances were made in the diagnosis, treatment, and control of many infectious diseases. These successes were not uniform, and, unfortunately, the medical, veterinary, and economic importance of many VBDs has continued and indeed increased. VBDs have proven to be unusually refractory to control or eradication programs. When considered as an epidemiological group, VBDs, such as malaria, leishmaniasis, filariasis, onchocerciasis, trypanosomiasis, dengue, West Nile virus (WNV) disease, Lyme disease, and other vector-borne viral, bacterial, and parasitic diseases, put billions of people at risk for infection, infect hundreds of millions of humans annually, and cause millions of deaths and inestimable morbidity each year. Malaria and dengue are most important in this regard. Approximately 40 percent of humankind is at risk for malaria; up to 500 million cases occur annually with 2.7 million deaths. More than 2.5 billion people are at risk for dengue virus infection, and 100 million cases are estimated to occur annually. Ominously, the incidence of life-threatening dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) has increased rapidly throughout the tropics over the past 20 years. The burdens imposed by VBDs can be impediments to social and economic development in the areas of the world least able to afford them. Indeed, VBDs account for 7 of 10 neglected infectious diseases that are considered to disproportionally affect poor and marginalized populations and therefore have been targeted by the World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases (TDR) for special control programs.[2]

It is very frustrating that a number of VBDs were controlled to a certain

[2]See http://www.who.int/tdr/index.html.

extent in some regions but are now resurgent in these areas. For example, malaria was virtually eradicated from Sri Lanka by the mid-1960s; only 17 cases were recorded in 1963. Over 2 million cases now occur there annually. In India, 50,000 cases were reported in 1961; 35 million are now reported there annually (Gratz, 1999). Epidemic dengue fever and DHF-DSS have emerged as major public health problems in the Americas mirroring what happened in Southeast Asia several decades ago (Beaty, 2000; Gubler, 2002a,b). Other VBDs have emerged in or trafficked to new or previously endemic areas (e.g., Lyme disease, plague, Japanese encephalitis, WNV disease, and Rift Valley fever), resulting in significant morbidity and mortality. Lyme disease is now the most reported VBD of humans in the United States, followed by WNV disease (Gubler, 2002b).[3] The recent resurgence of chikungunya in many parts of the world, including a local outbreak in Italy, is testimony to the ongoing emergence potential of VBDs (Charrel et al., 2007).

Agricultural and Economic Impact of Vector-Borne Diseases

VBDs also cause significant economic impact in agriculture. Many of the List A diseases of the Office des International Epizooties (OIE), for example, bluetongue and vesicular stomatitis, are VBDs. Worldwide economic losses due to bluetongue are estimated at $3 billion per year, principally due to non-tariff barriers to international trade. Vesicular stomatitis virus epizootics in the western United States in 1995 and 1997 resulted in losses of approximately $50 million. International trade agreements (e.g., General Agreement on Tariffs and Trade [GATT] and North American Free Trade Agreement [NAFTA]) and globalization provide opportunities as well as threats for agriculture. The importation of vectors and pathogens would seem to be the inevitable result of increased movement of animals and products, and increased trade in general (USAHA, 1998).

Vector-Borne Diseases and Biodefense

Finally, many VBDs (e.g., plague, tularemia, certain equine encephalitis, and VB hemorrhagic fevers) are potential bioterroism agents and some have been weaponized. A natural (or purposeful) introduction of a bioterrorism agent, such as Rift Valley fever virus, would have enormous agricultural and public health consequences (LaBeaud et al., 2007). The emergence of WNV in New York in 1999 and its subsequent spread across the country (Lanciotti et al., 1999; Hayes et al., 2005) clearly demonstrated the vulnerability of the United States to emerging diseases, whether resulting from natural or purposeful events. Such dramatic emergences, the resurgence of diseases such as malaria and dengue, and the failure to control Lyme disease, even with the economic resources available to

[3]See http://www.cdc.gov/ncidod/dvbid.

the United States and northern Europe, highlight the deficits in human resources and infrastructure needed to address VBDs, and the critical needs to augment the armamentarium of tools and approaches to predict, prevent, and control VBDs.

Factors Contributing to the Resurgence and Emergence of Vector-Borne Diseases

The IOM report entitled *Microbial Threats to Health* (2003) listed a number of factors that have contributed to and exacerbated the emergence of infectious diseases (Table 3-1). In the "convergence" model used in the report, these factors were then placed into larger groupings—Physical Environmental Factors, Social, Political, and Economic Factors, Ecological Factors, Genetic and Biological Factors—all of which converged with the microbe and human to condition emergence of diseases (IOM, 2003).

The emergence of VBDs is clearly conditioned by many if not all of these factors, which have been reviewed elsewhere (Gratz, 1999; Beaty, 2000; Gubler, 2002b). In this paper, the focus will be on selected factors that are particularly relevant to the emergence of VBDs (Table 3-2). Brief examples will be discussed to provide insight into the needs, difficulties, and complexities of controlling VBDs. The lack of vaccines and therapeutics for many tropical and orphan diseases, and the economic and public health issues that are associated with the development and deployment of vaccines and therapeutics are described in detail in *Microbial Threats to Health* (IOM, 2003). This issue will not be discussed further here except to say that enhanced vector control will complement and enhance vaccine deployment for disease control (see paper by Scott in Chapter 2).

Clearly, many of the factors listed in Table 3-2 condition the emergence of all

TABLE 3-1 Factors in Emergence of Infectious Diseases

- Microbial adaptation and change
- Human susceptibility to infection
- Climate and weather
- Changing ecosystems
- Economic development and land use
- Human demographics and behavior
- Technology and industry
- International travel and commerce
- Breakdown of public health measures
- Poverty and social inequality
- War and famine
- Lack of political will
- Intent to harm

SOURCE: IOM (2003), pp. 4-7.

TABLE 3-2 Factors Conditioning the Resurgence and Emergence of Vector-Borne Diseases

- Population growth and unplanned urbanization
- Poverty, social inequalities, and the emergence of the throw-away society
- Globalization and trafficking of humans, pathogens, vectors, and genes
- Erosion of public health infrastructure, including human resource capacity in medical entomology and vector biology
- Lack of new targets and approaches to control vectors and VBDs
- Loss of pesticides for real and perceived environmental issues, development of pesticide resistance in vectors, and economic disincentives to new pesticide and formulation development
- Lack of robust models and information systems to predict, prevent, and control VBDs

SOURCE: Adapted from IOM (2003).

infectious diseases, not just VBDs. There is little recourse for Microbial Threats to Health Committee recommendations to address major factors such as population growth, poverty, unplanned urbanization, and social inequalities. Other behavioral factors such as the throw-away society and the dramatic increases in human, vector, and pathogen trafficking in this era of globalization complicate greatly the control of VBDs. Nonetheless, each of these is a major driver for the resurgence of VBDs and will be briefly discussed herein to illustrate the problems involved with controlling these important diseases.

Explosive population growth is a major determinant of the emergence and resurgence of VBDs. Dramatic increases in urbanization are frequently associated with little or no civic planning, and sanitation may be limited or nonexistent (Gratz, 1999; Gubler, 2002a; IOM, 2003). The lack of wastewater and refuse removal provides plentiful breeding sites for mosquitoes. Many newly urbanized areas do not have piped water, and stored water provides plentiful breeding sites for *Aedes* and *Culex* vectors. Even when piped water is available, it may be so only sporadically or unreliably. Thus, residents still store water, and paradoxically there may be more water, breeding sites, and mosquitoes than before piped water was available. Population growth and other socioeconomic factors also frequently result in humans migrating into undeveloped areas. There they impinge upon sylvatic or jungle cycles of VBDs and/or perturb the natural environment, making it more conducive to vectors and to pathogen transmission, potentially leading to the emergence of new diseases (Monath, 2001).

Poverty, social inequalities, and behavioral issues not only condition emergence of VBDs but also exacerbate their prevention and control. There are too many of these factors to enumerate; only a few will be discussed to provide insights into the problems. Clearly, the most important VBDs in tropical regions are diseases of poor people. One recent epidemiological and entomological

investigation of dengue in "sister" cities in Mexico and Texas illustrates this very well (Reiter et al., 2003). In the U.S. city, *Ae. aegypti* immatures were relatively abundant in the peridomestic environment, but there was very little dengue. In contrast, the Mexican city was characterized by lower abundances of *Ae. aegypti* immatures but higher numbers of dengue cases. The investigators attributed this to numerous factors, one of the most important being the quality of housing (window screens and air conditioners were common in the U.S. city). Poverty is directly linked to the dramatic growth in human populations, unplanned urbanization, and movement of humans, all of which can condition VBDs (Gubler, 2002b; IOM, 2003).

Globalization and rapid dissemination of pathogens and vectors has contributed greatly to the resurgence and emergence of VBDs. The global economy, which is predicated upon commerce and rapid and efficient transport of goods and people, provides unprecedented capability for emergence and rapid dissemination of pathogens and their vectors throughout the world (IOM, 2003). The recent emergence of WNV in the New World (Roehrig et al., 2002) is testimony to the ability of VBDs to traffic rapidly into new areas. The many reports of airport and railroad malaria also illustrate the continual trafficking of pathogens (Lounibos, 2002). Fortunately, in most cases the components necessary for establishment of a transmission cycle are not present, and the pathogen does not become established. Obviously, when WNV was introduced into New York, all of the necessary ingredients for establishment and spread were present, and it will be many years before the epidemiologic consequences of this emergence in the New World are determined (Roehrig et al., 2002; Hayes et al., 2005).

Vectors themselves can also traffic to and become established in new areas. One of the most notable examples was the dissemination of *Ae. aegypti* throughout the world (Tabachnick et al., 1985). The ancestral form of *Ae. aegypti* is found in central Africa and is a sylvatic mosquito. After domestication and adaptation to humans and human environments, *Ae. aegypti* apparently disseminated to coastal areas of Africa, and was then transported throughout the world in sailing ships. Presumably both *Ae. aegypti* and yellow fever virus (YFV) were introduced into the New World on slave ships. *Aedes albopictus*, the Asian tiger mosquito, and *Ae. japonicus* presumably entered the United States via shipping (Moore, 1999; Fonseca et al., 2001). *Aedes spp.* eggs can easily be transported in tires, containers, and so on to new areas and hatch upon exposure to water in new settings. Adult mosquitoes can be spread much more quickly throughout the world in airplanes (Lounibos, 2002). Indeed, mosquitoes have become the ultimate frequent fliers, spreading themselves and their genes and perhaps pathogens throughout the world. Such transport has been postulated as the mechanism for the rapid dissemination of an esterase mutation conferring pesticide resistance to organophosphates through *Culex pipiens* populations throughout the world (Raymond et al., 1998). Unfortunately, U.S. public health programs to disinfect aircraft were

disbanded as a cost-saving measure in the 1960s; such a program could conceivably have prevented the introduction of WNV into the western hemisphere.

Human behavioral changes and societal trends can also potentially exacerbate VBDs. Certainly, the advent of the "throw-away society" has had major implications in terms of breeding sites for vector mosquitoes. Even in the poorest of societies, breeding sites are now ubiquitous because of the proliferation of bottles, cans, old tires, and so on in the environment, which then provide a plethora of breeding sites for container-breeding mosquitoes and which dramatically complicate source reduction and larviciding control programs (IOM, 2003).

The Committee on Emerging Microbial Threats to Health in the 21st Century Recommendations to Address Vector-Borne Diseases

The Committee report proposed a number of actions to national agencies to address major needs in emerging diseases (IOM, 2003), many of which were directly applicable to VBDs. The Committee recommended that (1) the human resource capacity in medical entomology, vector biology, and zoonoses (from academia to public health practitioner) be rebuilt, expanded, and sustained; (2) the armamentarium for vector control be enhanced and expanded, by developing (a) new and improved environmentally sound pesticides, (b) novel strategies to prolong the use of existing pesticides by mitigating the evolution of resistance, (c) new biopesticides and biocontrol agents to augment chemical pesticides, (d) safe, efficacious repellants and attractants, and (e) by investigating novel strategies to interrupt vector-borne pathogen transmission to humans; and (3) that appropriate federal and state agencies expand their efforts to exploit geographic information systems (GIS) and robust models to predict and prevent VBDs.

Human Resource Capacity

The Recommendation: The Centers for Disease Control and Prevention (CDC), Department of Defense (DoD), National Institutes of Health (NIH), and U.S. Department of Agriculture (USDA) should work with academia, private organizations, and foundations to support efforts at rebuilding the human resource capacity at both academic centers and public health agencies in the relevant sciences—such as medical entomology, vector and reservoir biology and ecology, and zoonoses—necessary to control vector-borne and zoonotic diseases.

Background Erosion in the human resource capacity to address VBDs is linked to the erosion of overall public health infrastructure for VBDs. Surveillance and control programs for VBDs are expensive. These programs are especially vulnerable to reductions or elimination when budget shortfalls occur and when VBD activity is incorrectly perceived to be controlled. Both of these issues have led to decreased support for and deterioration of public health surveillance and control

capacity throughout the world. For example, the sporadic and epidemic nature of many VBDs resulted in the closure of state programs and in the demise of university training programs in medical entomology and vector biology (NRC, 1983). In the developing world, where resources are much more limited, the consequences of such reductions can be even more dramatic. For example, in the 1950s and 1960s the Pan American Health Organization (PAHO) and participating western hemisphere countries established a remarkably effective program to control *Ae. aegypti* to preclude the emergence of sylvatic YFV into urban populations (Gratz, 1999; Monath, 2001; Gubler, 2002a). Overall, the program was quite effective, but success led to demise of the programs, and the resources to support these efforts were shifted to other priorities. Now *Ae. aegypti* is resurgent and essentially hyperabundant throughout much of tropical and subtropical America. Concomitantly all four dengue virus serotypes including American/Asian genotypes are cocirculating in Latin America (Beaty, 2000; Gubler, 2002a). High mosquito abundance and intensive virus transmission have resulted in a state of dengue hyperendemnicity, resulting in the emergence of DHF-DSS as a major public health problem in the Americas. In addition, YFV has recently caused epidemics in South America and Africa (Monath, 2001; Gubler, 2002b). With *Ae. aegypti* resurgent in metropolitan areas in the Americas, it seems to be only a question of when urban yellow fever will reemerge or chikungunya (Charrel et al., 2007) will emerge in these areas with disastrous consequences.

Concomitant with the erosion of VBD control infrastructure has been the dramatic decline in medical entomology/vector biology expertise. Indeed, it was difficult to identify local medical entomologists, vector biologists, and arbovirologists to respond to the WNV emergency in the initially affected states. There has been a reduction in the numbers of medical entomologists, vector biologists, and vector control personnel. This unfortunate trend and its public health implications were first described in a U.S. National Academy of Sciences report (NRC, 1983). The emergence of WNV and the paucity of human resources available to address that emergency were ample testimony to the prescience of the authors of that report. The critical needs in this area have also been addressed in other publications and books (e.g., Spielman, 1994). However, these reports did little to change attitudes in academic departments across the nation. Medical entomology positions were invariably lost when occupants retired or left and when entomology departments combined with plant pathology and related departments.

Responses With the emergence of Lyme disease, human granulocytic anaplasmosis, human monocytic erlichiosis, and WNV disease in the United States and the resurgence of VBDs throughout the world (Gratz, 1999; Gubler, 2002b), organizations such as the NIH, the World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO-TDR), and a number of foundations began to promote research in vector biology. With increased funding and program development opportunities, there has been an increase in the number

of scientists entering the field, many of whom are now assuming faculty positions in universities. Indeed, there has been a renaissance in vector biology, which is providing not only new knowledge and targets for vector control but also a new generation of vector biologists capable of applying modern molecular and quantitative approaches to control VBDs. Hopefully, as the scientific excitement in and public health importance of the field is recognized, and the opportunities for program development in vector biology increase, student demand will increase and previously lost positions will be regained in entomology departments. This will provide a renewed stream of students to replenish the depleted ranks of medical entomologists at all levels.

Training Training of a new generation of vector biologists/medical entomologists capable of applying modern molecular and information technology approaches to prevent and control emerging and resurging VBDs is critical. A number of agencies, including WHO-TDR, PAHO, NIH, CDC, and private foundations, recognized this situation and initiated training programs for vector biologists and medical entomologists in the United States and other countries. Frequently, however, such programs only address urgent needs. For example, the emergence of WNV resulted in a major effort by CDC to train individuals in mosquito identification, arbovirology, and mosquito control. WHO provides workshops devoted to specific important issues concerning vectors and VBDs in disease-endemic areas. Such programs, however, typically do not provide personnel with in-depth training in molecular, biological, epidemiological, and information technology techniques or permit trainees to exploit these techniques effectively in real-world situations.

Efficient training strategies are necessary to address the human resource needs in all areas of VBDs, from identification and processing of vectors to gene identification and characterization, and to development of GIS and other information technology-based approaches for control of vectors and VBDs. Web-based training programs, courses, and texts would seem to be a robust enough venue to address critical short-term needs. However, alternate approaches are necessary to provide quickly a new generation of VBD specialists and leaders. The Biology of Disease Vectors course was notable in this regard. This intensive 2-week course, which was supported by the MacArthur Foundation, WHO-TDR, and other agencies, was developed to catalyze the use of modern molecular and quantitative approaches into medical entomology and vector biology. The course also provided exceptional learning and networking opportunities for vector biologists. Many of the students emerged as leaders, trainers, and program initiators in their respective countries. Internationally recognized faculty provided invaluable networking and career opportunities.

Similar courses should be offered to provide a new generation of leaders in critical and emerging disciplines. For example, the renaissance of vector biology/medical entomology at NIH and the new vector biology study section

has been very laboratory associated; field-oriented and control programs have not kept pace. Training programs and research focusing on the biological, behavioral, entomological, and environmental determinants of pathogen emergence and persistence, and that incorporate the most modern and robust molecular and information technology tools, are desperately needed. These would be powerful incentives to translate the explosion of new information concerning vectors into field-relevant tools and management strategies, and to train vector biologists capable of incorporating the new methodologies into daily vector and disease control operations. Indeed, the cadre of molecular vector biologists trained in the laboratories contributing to the renaissance of vector biology would be excellent candidates for such a course.

There have been some very notable successes in programs to promote field-oriented VBD research. CDC has established major extramural efforts to partner with state and university scientists to address important vector-borne and rodent-borne diseases such as Lyme disease, WNV disease, and hantavirus pulmonary syndrome. This leverages CDC monies and talents to address emerging disease issues, provides support for applied epidemiological research and training in disease endemic sites, and greatly enhances communication and partnering between CDC and state and local institutions. In addition, CDC launched a Fellowship Training Program (FTP) in Vector-Borne Infectious Diseases in direct response to the introduction of WNV into the United States. The purpose of the FTP was to provide training in arbovirology, microbiology, entomology, and epidemiology relating to VBDs. The goal was to improve the ability of the U.S. public health system to respond to the problem of VBDs by increasing the number of specialists with demonstrated skills in the public health aspects of VBDs and to provide them with the essential, pertinent field and research skills. Programs such as the NIH International Collaborations in Infectious Disease Research (ICIDR) and Tropical Medicine Research Units also provide excellent training and research opportunities in field-oriented vector biology and control programs. The NIH ICIDR grants with the companion ABC Fogarty Center training programs are well conceived in this regard and emphasize epidemiological research and training in disease-endemic areas in the context of NIH-funded research programs. Scientists not only are trained in cutting-edge scientific methodology but also apply new discoveries and approaches in disease-endemic countries.

These types of programs need to be continued and expanded upon in the future, especially to transfer scientific and technical know-how to the developing world where improved vector and disease control is a matter of life and death. Unfortunately, funding for the CDC FTP in Vector-Borne Infectious Diseases has been terminated after one funding cycle, despite the productivity and popularity of this program, which was such a well-conceived approach to address human resource needs in field-oriented vector biology and VBD control.

Training opportunities in disease-endemic countries Long-term presence of sustainable laboratories in selected disease-endemic countries is critical (IOM, 2003). Such laboratories are invaluable for research, training, and surveillance for tropical and emerging diseases and for training vector biologists. Historically, the U.S. Naval Medical Research Unit, U.S. Army, and WHO laboratories have provided outstanding opportunities for trainees to obtain experience in tropical disease research. Such programs also initiate long-term interactions with collaborators in tropical regions and yield long-term benefits by establishing public health infrastructure, training and research opportunities, and listening posts in areas of the world where many pathogens emerge.

Innovative approaches for rebuilding and sustaining medical entomology/vector biology Some very innovative approaches to augment proposals to address national and international needs in medical entomology/vector biology and to sustain the expertise were proposed by the Committee (IOM, 2003). Some of these are listed in Table 3-3. For example, CDC could establish a medical entomology/vector biology program to complement the existing Epidemic Intelligence Service (EIS) program, and the officers emerging from the new program could provide support to national and international jurisdictions requesting entomological expertise. The USDA and DoD should establish a similar program devoted to vectors of animal diseases. Such programs would bring great visibility and prestige to the field. In addition, Regional Centers of Excellence (RCEs) in medical entomology/vector biology should be established, which would provide service, training, and research in medical entomology/vector biology at the regional level, thereby replacing many of the programs lost at the state and local levels. Such an effort would also bring visibility to the field, would provide positions for medical entomologists, and would provide training opportunities for VBD specialists. These RCEs would preferably be incorporated into larger Interdisciplinary and Zoonotic Infectious Disease Centers (IOM, 2003), which

TABLE 3-3 Innovative Approaches to Restoring Human Resource Capacity in Vector-Borne Diseases

- Establish a medical entomology/vector biology program to complement the existing CDC EIS program
- Establish RCEs in medical entomology/vector biology, preferably incorporated into larger interdisciplinary comprehensive infectious disease centers
- New training initiatives (e.g., Biology of Disease Vectors course) for targeted areas for training new leaders and advancing the field scientifically
- Targeted RFAs for field-oriented research using modern molecular and quantitative tools and approaches
- Long-term sustainable laboratories in disease-endemic countries for training, research, and surveillance of VBDs

SOURCE: Adapted from IOM (2003).

would be sustainable and would be invaluable resources to the regions, states, nation, and the world in issues involving vector-borne and other emerging diseases and bioterrorism.

Summary The efforts and programs outlined and proposed would bring visibility and prestige to medical entomology/vector biology, would educate public and professional groups concerning the importance of vectors and VBDs, and would provide incentives for discipline development and sustainability. These actions would undoubtedly increase student demand and would be of great value in increasing the number of faculty positions and programs in medical entomology/vector biology in the United States.

Increase the Armamentarium for Vector Control

The Recommendation: DoD and NIH should develop new and expand upon current research efforts to enhance the armamentarium for vector control. The development of safe and effective pesticides and repellents, as well as novel strategies for prolonging the use of existing pesticides by mitigating the evolution of resistance, is paramount in the absence of vaccines to prevent most VBDs. In addition, newer methods of vector control—such as biopesticides and biocontrol agents to augment chemical pesticides, and novel strategies for interrupting vector-borne pathogen transmission—should be developed and evaluated for effectiveness.

Background There is a critical need to increase the armamentarium for vector control both in terms of new pesticides and formulations, and new targets and approaches for control. Complicating control of VBDs has been a lack of knowledge of fundamental genetic, biological, and environmental determinants of vector pesticide resistance, vectorial capacity, and vector competence. Indeed, the vector has frequently been viewed as a black box, with little knowledge of the molecular bases of pesticide resistance or pathogen transmission. Similarly, there was a paucity of information concerning critical components of vector biology such as vector immunity, development, diapause, longevity, and so forth, all of which could lead to novel targets and interventions.

For the foreseeable future, traditional approaches based on pesticides to reduce vector populations or to repel vectors will remain the first line of defense against emerging and resurging VBDs. Development of new pesticides and formulations is critical because of emerging resistance to existing pesticides in vector populations and removal of other pesticides from the armamentarium of vector control (Hemingway et al., 2002, 2006). Societal aversion to the use of pesticides, because of perceived environmental and health effects, is of great concern. This has led to resistance to pesticide application even in the face of ongoing epidemics, such as WNV disease epidemics in New York and Colorado, and the removal of pesticides from control programs. In this regard, the discovery

and subsequent use of DDT to control VBDs was a major achievement in public health (Attaran et al., 2000). However, indiscriminant DDT usage associated with agricultural practices led to detrimental effects in nontarget organisms, and DDT was banned even for public health use in indoor residual spraying (IRS) programs. New pesticides have proven to be more expensive, less stable, and less efficacious than DDT. Unfortunately, the widespread termination of DDT usage coincided with a resurgence in malaria, leishmaniasis, dengue, and other diseases that are transmitted principally indoors (Roberts et al., 1997; Gratz, 1999; Attaran et al., 2000). IRS of DDT disrupts the close association between the human host and important anthropophilic and endophilic vectors, such as *Ae. aegypti* and *Anopheles gambiae,* thereby reducing transmission and disease. Clearly, development of environmentally sensitive insecticides and formulations with the efficacy of DDT is a public health imperative.

Unfortunately, no new public health pesticides for adult mosquitoes have been developed in more than 30 years (Hemingway et al., 2006). Pyrethroids are the cornerstone of vector control, whether for use in spraying, IRS, or bednets (Hawley et al., 2003). Knockdown resistance (*kdr*) as well as metabolic resistance to pyrethroids has emerged in *An. gambiae* populations in Africa. The effect that *kdr* in *Anopheles* populations may have on the efficacy of bednets and other control measures of this disease remains to be determined (Guillet et al., 2001; N'Guessan et al., 2007). Numerous studies are now documenting resistance in *Ae. aegypti* to commonly used pesticides targeting immatures and adults, potentially removing these from the armamentarium used by mosquito control officials to control dengue (see Eisen and Beaty in Chapter 2). For example, increasing resistance to temephos, which is widely used for control of *Ae. aegypti*, is of great concern (e.g., Lima et al., 2003). Resistance in vectors is a major problem and one that will undoubtedly worsen without the development of new, environmentally sensitive resistance-breaking pesticides.

Responses The Innovative Vector Control Consortium (IVCC) (Hemingway et al., 2006) was founded to address this and other needs and opportunities identified in the 2003 IOM report. The major objectives of the IVCC are to partner with industry to develop new pesticides and formulations and to develop new tools and approaches to manage vector control programs and mitigate pesticide resistance, focusing upon vector control in and around the house. The IVCC and a number of its projects are reviewed in papers by Coleman and Hemingway, Eisen and Beaty, and Scott in this report.

Pesticides The Committee recognized the public health imperative to develop new environmentally sensitive insecticides and formulations with the efficacy of DDT. The IVCC (Hemingway et al., 2006) is addressing this in a very unique and potentially powerful way. The first objective of the IVCC is to develop new insecticides and formulations for vector control. The loss of DDT and the poten-

tial loss of pyrethroids for vector control due to emerging resistance would be a public health catastrophe. The most expeditious way to develop new pesticides and formulations is to partner with the agrochemical industry. Unfortunately, as noted previously, no new adulticides have been developed in more than 30 years. This is partially due to perceived limited market size for public health pesticides and the costs and opportunity losses associated with bringing a public health pesticide product to market. The IVCC is partnering with industry to develop and deploy new public health pesticides and/or formulations for vector control. The cost of developing a new insecticide is in the range of $70 million. The IVCC will help address issues involving market failure by removing some of the risk associated with bringing a product forward. Partnering companies will revisit existing pesticide libraries with the intent of repurposing products, participate in the development of resistance-breaking pesticides, and even develop new active ingredients. The IVCC will provide the vector and disease expertise as well as field sites to conduct proof of concept and WHO Pesticide Evaluation Scheme (WHOPES) trials, which would be difficult for industrial partners to do. Indeed, the latter issue is a major disincentive to companies becoming involved in public health pesticide development, which will be alleviated by partnerships with IVCC consortium institutions. Such private-public partnerships seem to be an excellent way to address critical needs in developing new public health pesticides.

The Committee recognized the public health needs for continued use of DDT in the face of VBD epidemics. Since domicile treatment with DDT has not been associated with major adverse environmental consequences, this practice should be allowed for vector control in public health emergencies until equally effective and inexpensive substitutes for DDT are developed. Care will be needed to ensure that availability of DDT for public health uses does not result in its use in agricultural applications. DDT controls VBDs, such as dengue and malaria, not only by killing vectors but also by repelling them (Roberts et al., 1997), thereby disrupting the close association between the human host and anthropophilic and endophagic vectors (e.g., *An. gambiae* and *Ae. aegypti*) and dramatically reducing opportunities for pathogen transmission. Clearly, development of efficacious and environmentally sensitive alternatives to DDT needs to become a major research objective, and one in which the issues of repellency receive equal attention with killing capacity.

The Committee also recommended using pesticides in Integrated Pest Management (IPM) programs, which incorporate established agricultural practices to mitigate the evolution of resistance (e.g., rotation of pesticide usage, inclusion of refugia with no pesticide applications), to provide better stewardship of pesticides, thereby extending their useful life. Incorporation of new molecular tools to diagnose pesticide resistance into routine control program activities would result in more effective and efficient pesticide usage. Development of novel strategies to prolong pesticide efficacy, such as negative cross-resistance, should be possible in this era of high-throughput screening (Pittendrigh and Gaffney, 2001).

Determining the effect of pesticide resistance prevalence on control of VBDs would be of great value for risk assessment.

The renaissance in vector biology described below has also provided unprecedented information concerning pesticide resistance in vectors. Indeed, the publication of the genomes of the two major VBD vectors *An. gambiae* and *Ae. aegypti* (Holt et al., 2002; Nene et al., 2007) has provided dramatic insight into the molecular bases of resistance (Hemingway et al., 2002). This information can be exploited for developing new tools and approaches for monitoring and mitigating resistance (e.g., David et al., 2005), and for developing new pesticides for vector control.

New biopesticides and biocontrol agents to augment chemical pesticides The Committee also recommended renewed effort in developing a new generation of biocontrol agents, such as viruses and bacteria, which could augment chemical pesticides and be incorporated into IPM approaches for vector control. New formulations of *Bacillus thuringiensis* and *B. sphaericus* exhibit promise for vector control, even in tropical regions (Fillinger et al., 2003; Frederici, 2005). Baculoviruses (Becnel, 2006) or parvoviruses (Carlson et al., 2006) from mosquitoes may be useful for vector control. Other biopesticide agents could now be improved using molecular genetic approaches to make them more effective control agents. For example, viruses can be used to transduce effector molecules to enhance vector knockdown or manipulate vector phenotypes.

Innovative interventions As noted earlier, for many years the vector was essentially viewed as a black box. Little was known about the molecular bases of vector competence, vector biology, vector immunology, and other vector phenotypes critical to pathogen transmission. Such information is essential for developing new interventions for VBD control.

The field of vector biology is currently experiencing a renaissance. Efforts of the MacArthur Foundation's Network on the Biology of Parasite Vectors, as well as other agencies, institutions, and investigators, to infuse modern molecular and genetic approaches into vector research has led to the emergence of a new field of vector molecular biology and the resultant explosion of information on vectors. The genomes of two of the most important vectors of diseases to humankind—*An. gambiae* and *Ae. aegypti*—have now been sequenced (Holt et al., 2002; Nene et al., 2007), and other culicine and tick vector genomes are currently being sequenced. Major advances in vector transformation, genetics, and molecular biology have occurred, including the development of effective transformation strategies for culicine and anopheline mosquitoes (Coates et al., 1998; Catteruccia et al., 2000); new tools such as virus-based transducing systems and RNAi for gene expression and characterization in vectors (e.g., Johnson et al., 1999; Levashina et al., 2001); robust population genetic approaches for characterizing gene flow in vector populations (e.g., Lanzaro et al., 1995; Besansky et al.,

1997; Gorrochotegui-Escalante et al., 2000); molecular taxonomic approaches for identifying vectors and cryptic species (e.g., Ballinger-Crabtree et al., 1992; Collins and Paskewitz, 1996); new insight into the vector immune system and the development of the field of vector immunology (Christophides et al., 2002; Bartholomay et al., 2003; Keene et al., 2004; Blandin et al., 2004; Waterhouse et al., 2007); new immunization strategies that incorporate vector salivary protein antigens to reduce pathogen transmission or other antigens for vector killing vaccines (e.g., Titus and Ribiero, 1988; Kamhawi et al., 2000); new insights and understanding of vector olfaction and host seeking (e.g., Fox et al., 2001; Pitts et al., 2004), which provides opportunities for developing new repellents and attractants for vector traps; new understanding of the infection, development, and transmission of pathogens by vectors (e.g., Dimopoulos et al., 1998; Sanders et al., 2005); new insights into the molecular biology of vectors (e.g., Barillas-Mury et al., 1995; Valenzuela et al., 2003; Hansen et al., 2004); and the molecular manipulation of vectors to make them resistant to pathogen (dengue virus and malaria) transmission (e.g., Ito et al., 2002; Franz et al., 2006; Olson et al., 1996).

The accumulation of new knowledge of vector biology has been stunning. Indeed, the field moved from one mosquito gene in 1989 (James et al., 1989) to more than 14,000 genes with the publication of the *An. gambiae* genome in 2002 (Holt et al., 2002). *In silico* approaches have revolutionized gene identification and research in vector biology, and the post-genomics era in vector biology offers great promise for identifying new targets and approaches for control of vectors and VBDs. This renaissance in vector biology is reflected by the dramatic increase in vector grants at NIH, the development of a new vector biology study section at NIH, a dramatic increase in the number of publications in leading journals, and a dramatic increase in vector biology presentations and sessions at scientific society meetings. There is now unprecedented accumulation of information concerning vector biology, population genetics, genomics, immunity, and so forth. The task is to translate this research and knowledge into tools and approaches to combat VBDs.

The Committee also recommended continued or expanded research in areas pertinent to VBD control, including the following:

New repellents and attractants Repellents remain a first line of defense against emerging or resurging VBDs. Development of new personal and spatial repellents for prevention of VBDs was highly recommended by the committee as a potentially very fruitful area of research. Modern high-throughput and genomic approaches may permit identification of new molecules with repellent activity similar to that of DEET (and DDT), but without adverse effects. Understanding the molecular basis of vector olfaction and host seeking (Hill et al., 2002) may lead to new repellents and attractants to control vectors (Day et al., 2001).

Novel immunization strategies for vector-borne diseases Insights into the

molecular basis of vector-pathogen-host interactions provide new strategies to control VBDs (Willadsen, 2001; Foy et al., 2003). Immunizing hosts to vector-specific determinants of pathogen transmission (e.g., salivary effector proteins that enhance pathogen infection [Titus and Ribeiro, 1988]) could provide broad-spectrum protection against multiple pathogens or strains (Kamhawi et al., 2000; Valenzuela et al., 2003). Other critical determinants of pathogen infection of and transmission by vectors (e.g., vector proteolytic enzymes, which process arbovirus proteins and condition vector infection) could be targeted for transmission-blocking vaccines (Carter, 2001). Immunizing vertebrate hosts to immunologically-privileged vector antigens could kill or impair blood-feeding mosquitoes, a strategy that works for ticks (Willadsen, 2001), and may also be useful against mosquito vectors (e.g., *An. gambiae* and *Ae. aegypti*), which feed frequently on humans (Foy et al., 2002). Theoretically, these vectors would feed on other hosts (zooprophylaxis), thereby reducing pathogen transmission.

Novel genetic approaches to the control of vector-borne diseases Genetic approaches in which vector populations are manipulated to become incompetent vectors also offer the potential to interrupt pathogen transmission. Such approaches would minimize potential environmental issues associated with pesticide usage and would not create an ecological vacuum that other vectors could occupy. The vector population could theoretically be genetically immunized to make it nonpermissive to pathogen transmission. The "immunogens" could be driven into vector populations by harnessing naturally occurring arthropod systems, such as transposable elements, symbionts (e.g., *Wolbachia*), or transducing viruses, which would be vector specific (Beaty, 2000). RNAi was recently documented as a robust immune response to arboviruses in vectors (Keene et al., 2004), and was quickly exploited to develop transgenic mosquitoes immunized to prevent dengue infection (Franz et al., 2006). Proof of principle has been provided that vectors can be molecular manipulated to make them refractory to arboviruses and trypansome and malaria parasites (Olson et al., 1996; Beard et al., 2002; Ito et al., 2002; Franz et al., 2006). Considering the amazing amount of recent progress in vector molecular biology, continued research in this area may well provide dramatically new approaches for VBD control.

Summary The renaissance in vector biology is providing unprecedented information concerning the molecular basis of vector biology and critical vector phenotypes that could be exploited for vector control. Testimony to the growth of the field from the black box of the vector to the renaissance in vector molecular biology is the formation of VectorBase (Lawson et al., 2007)—a critical resource for collecting and making available the explosion of information concerning vectors that has emerged in recent years from investigations of vector molecular biology, genomics, population genetics, and pathogen-vector-host interactions, etc. Undoubtedly, this information can be exploited to develop alternate, novel

strategies for vector control, for disrupting host-vector interactions, and for interrupting pathogen transmission.

Geographic Information Systems and Robust Models for Predicting and Preventing Vector-Borne Diseases

The Recommendation: CDC, DoD, and NIH should work with state and local public health agencies and academia to expand efforts to exploit geographic information systems and robust models for predicting and preventing the emergence of VB and zoonotic diseases.

Background Because biological and environmental factors condition transmission of pathogens from vectors or vertebrate amplification or reservoir hosts to humans, temporal models based on climate data to predict outbreaks of sporadically occurring diseases and GIS-based models to predict spatial risk patterns have great potential for providing predictive capability for vector-borne and zoonotic diseases. A GIS spatial backbone can also be incorporated into a computer-based decision support system as a tool for analysis and presentation of relevant environmental, entomological, or epidemiological data (e.g., presence of larval habitat for anopheline mosquitoes, areas with especially high vector abundance, or locations of human disease cases). This type of system can revolutionize surveillance, risk assessment, and prevention strategies for vector-borne and zoonotic diseases, manage and mitigate pesticide resistance, and permit focusing of resources and talents on prevention efforts in the areas at greatest risk.

Responses In the United States, climate-based models to predict outbreaks of rare but severe vector-borne or zoonotic diseases have been developed for hantavirus pulmonary syndrome and plague (Glass et al., 2000, 2002; Hjelle and Glass, 2000; Enscore et al., 2002). GIS- and/or remote sensing-based models predicting the presence of vector breeding habitat, acarological or entomological risk of exposure to vectors (vector abundance or density), or risk of pathogen exposure (presence or abundance of infected vectors or vertebrates, presence or incidence of human disease) have been developed for a variety of diseases including hantavirus pulmonary syndrome, Lyme disease, plague, and WNV disease in the United States, and dengue and malaria in tropical areas (e.g., Kitron et al., 1991; Glass et al., 1995, 2000, 2002; Boone et al., 2000; Hay et al., 2000; Brownstein et al., 2002; Rogers et al., 2002; Peterson et al., 2005; Diuk-Wasser et al., 2006; Eisen et al., 2006, 2007a,b). GIS-based modeling approaches also have been used to study spatial patterns of gene flow in key mosquito vectors such as *Ae. aegypti* (e.g., Gorrochetegui-Escalante et al., 2000; Bosio et al., 2005; da Costa-Ribeiro et al., 2007) and rodent reservoirs of Sin Nombre virus (Root et al., 2003). Incorporation of GIS into computer-based decision support systems for management of VBDs is described in the paper by Eisen and Beaty in this report.

To date, there has been a tendency in the research community to stovepipe GIS-based risk modeling approaches for VBDs to either vector data or epidemiological data. This is highly unfortunate because these two types of data have weaknesses but also complementary strengths. For example, although the location of sampling sites for vector data readily can be georeferenced, human behavior may strongly impact risk of vector and pathogen contact. On the other hand, a human disease case, which unequivocally demonstrates contact with an infected vector, often is accompanied by questionable information regarding the pathogen exposure site. To overcome these issues, models combining independently derived estimates for vector risk and epidemiological risk are needed (Eisen et al., 2006).

In the case of GIS-derived risk models for vector-borne and zoonotic diseases based on epidemiological data in the United States, plague and hantavirus pulmonary syndrome models are most reliable because probable sites of pathogen exposure are determined through comprehensive case investigations carried out by state health agencies or CDC (Eisen et al., 2007a,b). The more common but less severe Lyme disease and WNV disease are far more problematic in this regard because the quality of information from case files regarding probable sites of pathogen exposure is highly variable, which can compromise the output model. Simply put, the tremendous potential for using GIS modeling approaches in spatial epidemiology and ecoepidemiology currently is severely compromised for many VBDs based on poor quality of information regarding pathogen exposure site (Eisen and Eisen, 2007).

Advances in GIS technology and the ever-increasing use of the Internet as a primary knowledge resource present tremendous but currently largely untapped possibilities for disseminating information regarding spatially explicit risk of exposure to VBDs. Using a web mapping approach, static risk maps can readily be converted to a dynamic web-based information delivery system where selecting an area of interest provides a close-up view showing risk patterns for labeled spatial units (e.g., counties, zip codes, or census tracts) and the location of major roads, population centers, and other easily recognizable features. This approach will facilitate information transfer regarding VBD risk to both the medical community and the public at large.

Indeed, web-based delivery of research information is a sadly neglected field that in the future can help to bridge the gap between the research community, the public health community, and the public. Much information of immediate interest and practical use to public health practitioners and the U.S. public now languishing in scientific journals could be effectively broadcast through web-based information delivery systems developed by academic or public health institutions. Positive examples from the academic side are scarce but include the University of Rhode Island web-based Tick Encounter Resource Center[4] and the

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

Iowa State University Medical Entomology Laboratory website for mosquito- and tick-borne disease.[5]

Summary There has been an explosion in information technology solutions to prediction, prevention, and control of VBDs in recent years. This includes implementation of computer-based VBD surveillance systems (e.g., CDC's ArboNET and WHO's DengueNet), development of decision support systems for VBD management, a plethora of GIS-based models predicting risk of exposure to vectors or VBDs, and movement toward web-based delivery of GIS-based risk maps and other pertinent and evidence-based information related to prevention and control of VBDs. One main task ahead is to adapt the technological solutions now being incorporated into routine surveillance and control activities in developed countries for use in resource-poor countries in desperate need of VBD management solutions.

Discussion

Overall, there is considerable excitement in vector biology and vector control. Progress in understanding the molecular biology of vectors has been extraordinary, and indeed the actual vectors of the respective pathogens are now becoming the models for studying these processes. Model organisms, such as *Drosophila* and *Manduca,* which have contributed enormously to our understanding of the molecular biology and physiology of arthropods and arthropod vectors, are now being supplanted by epidemiologically-relevant organisms.

The major advances in understanding the biology and molecular biology of vectors and vector–pathogen interactions provides promise for the development of new targets and opportunities for control, whether by new pesticides, repellents, or even more innovative approaches, especially in the post-genomics era of vector biology. Decision support systems exploiting advances in information technology and robust models provide exciting opportunities for predicting, preventing, and controlling emerging and resurging diseases.

The task is now to translate this explosion of information as quickly as possible into field programs for surveillance and control of VBDs and to train a generation of VBD specialists capable of deploying and refining these tools to control these important diseases.

Acknowledgments

This paper is dedicated to Robert E. Shope, who was a friend, mentor, and role model for us all. Support was provided by the Innovative Vector Control

[5]See http://www.ent.iastate.edu/medent.

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INTEGRATION OF STRATEGIES: SURVEILLANCE, DIAGNOSIS, AND RESPONSE

Roger S. Nasci, Ph.D.[6]
Centers for Disease Control and Prevention[7]

The panel convened as part of this workshop on vector-borne diseases was charged with discussing the following questions:

- Are multidisciplinary teams and collaborative responses required to deal with emerging vector-borne diseases?
- How can systems be integrated to enhance surveillance, diagnosis, and response?
- How can vector-borne disease be linked to a broader public health agenda to increase support?
- What research directions should be promoted to enhance prediction and control of vector-borne diseases?
- Are we effectively training research and operational professionals for the future?

I would like to summarize my comments from the panel discussion regarding each of the preceeding points, describing some of the relevant Centers for Disease Control and Prevention's (CDC's) activities and recommendations.

Multidisciplinary Teams and Collaborative Responses

One of the historical strengths of CDC programs in general, and specifically in vector-borne diseases, is the ability to field multidisciplinary teams to respond to outbreaks and to address basic public health research. CDC subject matter experts in epidemiology, medical entomology, vertebrate ecology, virology, immunology, pathology, diagnostics, human behavior, public communication, and so forth readily work as teams to address specific outbreak events and to formulate comprehensive approaches to further public health programs. In addition, CDC frequently works closely with a variety of government, academic, and

[6]Research Entomologist; Chief of the Arboviral Diseases Branch, Division of Vector-Borne Infectious Diseases. 3150 Rampart Road, Fort Collins, CO 80521. Phone: (970) 221-6400; E-mail: rnasci@cdc.gov.

[7]The findings and conclusions in this report are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.

private agencies and organizations to address specific problems. The complexity of zoonotic, vector-borne diseases demands this multidisciplinary response. The West Nile virus outbreak during 1999 in New York is an excellent example of this broad networking among agencies and has been described in detail in numerous reports (e.g., GAO, 2000). Similar responses and networks are functional internationally as well. The recent (2006-2007) epidemic of Rift Valley fever virus in East Africa and the multiagency international response (CDC, 2007) demonstrated how multidisciplinary teams and collaborative responses are essential to dealing with these events.

Though the multidisciplinary teams within CDC generally assemble quickly and respond efficiently, the ad hoc formation of larger collaborations involving many agencies is often accompanied by inefficiencies and complications. The Government Accountability Office (GAO) 2000 report on the 1999 West Nile virus response identifies many of the problems encountered during the initial event, makes recommendations for resolving them, and outlines a number of actions taken by CDC and other agencies to achieve that end. Similarly, the 2006-2007 Rift Valley fever response by numerous U.S. federal agencies was followed by an effort coordinated by U.S. Department of Agriculture (USDA) to take a priori steps to plan multidisciplinary, multiagency responses (Britch et al., 2007). While large, multiagency emergency responses will always be accompanied by some degree of confusion, communication among the agencies, planning, and network development can significantly decrease these problems and should be actively promoted.

Integration of Systems

Surveillance systems are the foundations of public health. Surveillance for human disease is well developed in the United States and is a primary function of health programs from the local to the national level. Because vector-borne zoonotic diseases involve nonhuman components (e.g., mosquitoes and birds amplify West Nile virus), monitoring enzootic/epizootic transmission activity may provide early warning of conditions that result in epidemic transmission. An example of a system designed to capture enzootic/epizootic arbovirus transmission activity as well as human case data is the ArboNET arbovirus surveillance system (CDC, 2004) that was developed and implemented in response to the introduction of West Nile virus into the United States in 1999. This system was expanded to capture information about all mosquito-transmitted arboviral zoonoses in 2004. ArboNET exemplifies the integration of systems because it allows capture of arbovirus prevalence information from numerous agencies (e.g., mosquito-based surveillance from local mosquito control programs, horse deaths from state public health veterinary programs, dead birds from local/state wildlife health agencies), as well as information about human case reports from the traditional health surveillance networks. These data are compiled weekly at

the state health department level and submitted to the CDC Division of Vector-Borne Infectious Diseases. The data are summarized and disseminated through a variety of avenues; prominent among them is the U.S. Geological Survey (USGS) Disease Maps program,[8] which provides graphic representations of the weekly data summaries. There are likely additional data sources that could be integrated into a more comprehensive ArboNET system. For example, the USDA National Animal Health Monitoring and Surveillance equine arbovirus monitoring program captures data on arboviruses in horses that are reported independently of the CDC ArboNET system.[9] Currently, it is difficult to determine if these cases duplicate or supplement data provided to ArboNET.

The ArboNET arbovirus surveillance system is structured to provide a flexible data capture portal at the state health department level that may be modified to capture similar environmental surveillance data for other zoonotic vector-borne diseases. It may also be used to capture and disseminate weather/climate information that may provide better prediction of regional risk patterns. An example of such a program is the still experimental ArboNET/plague surveillance system.[10] This system, a partnership between the CDC Division of Vector-Borne Infectious Diseases and the NASA Science Mission Directorate, Earth-Sun System Division Applied Sciences Program, is designed to evaluate and verify models as early warning tools for plague. There are likely a number of complementary systems and developing models that may be formulated into better, integrated surveillance programs.

Linking Vector-Borne Disease to a Broader Public Health Agenda

In a previous report, the Institute of Medicine (IOM) did an excellent job describing the global importance of zoonotic diseases (IOM, 2002), producing a comprehensive report that unequivocally linked vector-borne disease to core public health issues. Similarly demonstrating the link between vector-borne disease and a broad health agenda is the fact that several of the disease agents recognized to be of high health impact and with the potential to impact national security are vector-borne (e.g., plague, tularemia, alphavirus, and flavivirus viral encephalitides such as Venezuelan equine encephalitis, eastern equine encephalitis, and Japanese encephalitis).[11] Increased support for research should logically flow to these programs due to the apparent association of vector-borne diseases with the high-profile, national security health agenda. In fact, the National Institutes of Health (NIH) does provide substantial support for research addressing a variety of vector-borne disease topics (see paper by Adriana Costero in this chapter). Addi-

[8]See http://diseasemaps.usgs.gov.

[9]See http://nsu.aphis.usda.gov/nahss_web/faces/arbovirus_summary.jsp.

[10]See http://aiwg.gsfc.nasa.gov/esappdocs/projplans/arbonet_plague_ProjectPlan.pdf.

[11]See http://www.bt.cdc.gov/agent/agentlist.asp.

tional needed support may be obtained by explicitly publicizing the importance of these diseases to a broader audience, and by developing targeted requests for proposals by the nation's research funding agencies.

Research Directions to Enhance Prediction and Control of Vector-Borne Diseases

There is a large number of critical research directions related to vector-borne diseases, many of which have been previously described in earlier reports by this Forum (IOM, 2002). Much of the discussion about research directions in the current Forum centered on climate change and the impact global warming may have on vector-borne zoonotic diseases. This issue has been the subject of numerous speculative publications, as well as a number of publications describing the influence of climate and weather on transmission dynamics. The complexity of the topic and the difficulty in deriving simple answers is reviewed admirably by Sutherst (2004). In this article, Sutherst states the following:

> Adaptation (to the impact of climate change) must be based on a sound understanding of the causes of changed transmission patterns in each situation, in other words on an understanding of the whole vector-pathogen-host-environment system. This calls for a systems approach with comprehensive and testable predictive models to remove the subjectivity from qualitative judgments.

Only through application of "systems analysis" research, combining input from a diversity of fields like epidemiology, vector biology, quantitative ecology, spatial modeling, and meteorology/climatology will we be able to develop a knowledge base leading to predictive models and operational decision support systems for use in public health.

A second research direction that should be pursued is related to the development of public health pesticides (PHPs). For most vector-borne diseases there are no vaccines or effective medical therapies. As a result, vector control is the primary strategy for disease prevention and pesticides are integral to pest management programs designed to manage vector populations. Pesticides to control mosquitoes target larvae with a variety of modes of action (e.g., insect growth regulators, oils, microbial-produced insecticides like *Bacillus thuringiensis israelensis* or *B. sphaericus*). However, the alternatives available to control adult mosquitoes, which often is required for rapid control during disease outbreaks and emergencies, are limited to two modes of action represented by the pyrethroids and organophosphates. Unfortunately, development of resistance and growing concerns about human exposure and environmental safety restrict how and where these pesticides can be used. There is an urgent need not only to maintain the PHPs currently registered for vector control, but also to develop new pesticides with novel modes of action to increase safety and to allow us to better manage vector resistance. This is a global concern recognized by the World Health Orga-

nization (WHO) Global Collaboration for Development of Pesticides for Public Health, which recognized the serious public health risk incurred because of the reduction in available PHPs. This body noted that the development of alternative pesticide products and technologies is a high priority for the WHO (2004). The United Nations also called upon the international community to support investment in new insecticides and delivery modes as part of the Roll Back Malaria plan (United Nations General Assembly, 2005).

Effective Training of Research and Operational Professionals for the Future

> The recent introduction of West Nile virus into the United States has resulted in an unprecedented demand for expertise in mosquito surveillance and control operations throughout much of the country. Not only are there not enough trained medical entomologists to fill these new positions, but there are very few academic institutions still capable of providing such training (Fish, 2001).

This quote succinctly summarizes the situation regarding operational scientists in the United States, and I suspect it is representative of the global situation. Fish goes on to describe prior reports highlighting this problem going back to 1983. The topic of ensuring an adequate public health entomology workforce is discussed in the broader context of education and training needs in the IOM report *Ensuring an Infectious Disease Workforce: Education and Training Needs for the 21st Century* (IOM, 2006). In my position at the CDC, I interact regularly with public health entomologists in health departments at the state and local levels. While it is laudable that many of these jurisdictions have chosen to add such staff to deal with the problems stemming from the West Nile virus introduction, in my experience many of the positions are being filled by entomologists lacking public health training or experience. Many are highly skilled, professional entomologists, but many come from fields like insect ecology, forest entomology, or crop entomology and are responding to changes in the current job market.

In prior years, the NIH supported topical training grants (e.g., parasitology and vector biology) to partially address these needs in the public health community. Currently, training grants are rare and most training is done under the auspices of NIH's Research Project Grant Program (R01). In 2002, CDC's Division of Vector-Borne Infectious Diseases solicited proposals from universities to develop multidisciplinary masters and doctoral programs in public health entomology in an effort to improve the ability of the U.S. public health system to effectively respond to the problem of vector-borne infectious diseases and to increase the number of specialists with demonstrated field- and laboratory-based skills. Tuition, stipend, and research support were provided for 5 years in four university programs. However, this training grant program is not being continued beyond the initial 5-year cycle due to shifts in public health funding priorities.

It is apparent that more training programs must be developed at the nation's universities to meet the growing needs of public health entomology and the global health community.

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Numerous colleagues in the Division of Vector-Borne Infectious Diseases and the Public Health Pesticide Consortium contributed to the programs described above and provided comment in the development of this discussion.

SURVEILLANCE, DIAGNOSIS, AND RESPONSE: INTEGRATION OF STRATEGIES[12]

Sherrilyn Wainwright, D.V.M., M.P.H.[13]
U.S. Department of Agriculture

During the Forum on Microbial Threats "Vector-Borne Diseases" workshop, a panel of experts convened to discuss the following questions pertaining to vector-borne disease surveillance, diagnosis, and response strategies:

- Are multidisciplinary teams and collaborative responses required to deal with emerging vector-borne diseases?
- How can systems be integrated to enhance surveillance, diagnosis, and response?
- How can vector-borne disease be linked to a broader public health agenda to increase support?
- What research directions should be promoted to enhance prediction and control of vector-borne diseases?
- Are we effectively training research and operational professionals for the future?

I would like to summarize my comments from the panel discussion regarding each of these points and describe some of the relevant Animal and Plant Health Inspection Service (APHIS) activities related to the aforementioned topics.

[12]The findings and conclusions in this report are those of the author and do not necessarily represent the views of the U.S. Department of Agriculture, Animal and Plant Health Insepction Service, Veterinary Services, Centers for Epidemiology and Animal Health (CEAH).

[13]Animal and Plant Health Inspection Service (APHIS), Center for Epidemiology and Animal Health, Center for Animal Disease and Information Analysis, Risk Analysis Team, 2150 Centre Ave., Building B, 2W75, Fort Collins, CO 80526. Phone: (970) 494-7318; E-mail: Sherrilyn.H.Wainwright@aphis.usda.gov.

Multidisciplinary Teams and Collaborative Responses

The U.S. Department of Agriculture (USDA) APHIS, Veterinary Services (VS) plays a leading role in animal health outbreak responses by using multidisciplinary teams to expand current national and international monitoring and surveillance programs, support early detection of threats to animal and plant resources, including wildlife disease threats, and coordinate with congress and other government agencies.[14] The Food and Agriculture Incident Annex (July 2006) describes how the USDA and HHS (the "coordinating agencies") should respond to incidents involving the U.S. food and agriculture system, with the help of several other federal agencies (DHS, 2006). The Annex lists the following objectives of a coordinated federal response:

- Detect the event through the reporting of illness, disease/pest surveillance, routine testing, consumer complaints, and/or environmental monitoring
- Establish the primary coordinating agency
- Determine the source of the incident or outbreak
- Control and contain the distribution of the affected source
- Identify and protect the population at risk
- Assess the public health, food, agriculture, and law enforcement implications
- Assess the extent of residual biological, chemical, or radiological contamination and decontaminate and dispose as necessary

A collaborative effort between USDA APHIS VS, HHS, Agriculture Research Service (ARS), U.S. Fish and Wildlife Services, state agencies, affected animal industries, and diagnostic laboratories is essential in the response to a vector-borne disease outbreak. APHIS has worked successfully with these agencies on national and international vector-borne disease outbreak responses, such as in the case of responses to West Nile virus (GAO, 2000) and vesicular stomatitis virus. However, West Nile virus outbreaks have exposed weaknesses in communication and coordination between human public health and animal health agencies, as described in a Government Accountability Office (GAO) 2000 report:

> Links between public and animal health agencies are becoming more important. Many emerging diseases, including West Nile, affect both animals and humans. So do many viruses or other disease-causing agents that might be used in bioterrorist attacks. The length of time it took to connect the bird and human outbreaks of the West Nile virus signal a need for better coordination among public and animal health agencies.

[14]Department of Homeland Security (DHS), Health and Human Services (HHS), Environmental Protection Agency (EPA), and Department of the Interior (DoI).

APHIS has addressed vector-borne disease VBD challenges through initiatives such as the creation of a new biological threat awareness capacity, the development of mitigation strategies for critical production and processing node vulnerabilities, and the enhancement, integration, and protection of its science and technology infrastructure.

Within APHIS, multiple scientific and technical disciplines are represented.[15] Working together, they coordinate with the other agencies and manage communications to address the multiple issues associated with a zoonotic vector-borne disease outbreak response.

APHIS's operational program units mobilized to participate in multidisciplinary teams include Animal Care, Biotechnology Regulatory Services, International Services and Trade Support Team, Plant Protection and Quarantine, Wildlife Services, and Veterinary Services. Each team contributes its vast experience, knowledge, and expertise to collaborative responses. For example, in 2003 the Centers for Disease Control and Prevention (CDC) collaborated with the Food and Drug Administration (FDA) and APHIS in response to the multistate outbreak of monkeypox (CDC, 2003). In this case, APHIS's Animal Care program assisted FDA in obtaining information from pet store distributors of prairie dogs and African rodents, including Gambian giant rats and dormice. The investigation concluded that prairie dogs were likely infected by Gambian giant rats and dormice at an Illinois animal distributor in April and May 2003. At least 35 human cases of monkeypox were linked to contact with prairie dogs from this distributor. APHIS's Wildlife Services also assisted by trapping and testing prairie dogs, Gambian giant rats, and dormice for surveillance and control.

Internationally, the multidisciplinary responses and collaborations have also functioned well. In May 2000, a joint CDC-USDA APHIS team investigated a Q-fever and Brucellosis outbreak in Bosnia and Herzegovina (Nicholson et al., 2003). The team included human and animal health epidemiologists and laboratorians who worked closely with in-country counterparts and ultimately assisted in capacity building for Bosnia and Herzegovina.

There is a real need for proactive, rather than reactive, planning for outbreak responses involving multiagency collaborations. Multidisciplinary teams should prepare in advance to minimize inefficiencies and complications. Actions identified by the GAO (2000) report to resolve such issues have been initiated by a number of agencies, including USDA APHIS and CDC, though more work is needed for essential communication, coordination for planning, operations, logistics, administration, and diagnostics for an effective outbreak response.

[15]Including veterinarians, epidemiologists, entomologists, virologists, pathologists, laboratory diagnosticians, geographic information specialists, information technologists, economists, diagnostic laboratories, and legislative and public affairs specialists.

Integration of Systems

Integration of information management surveillance, laboratory, emergency, and other systems is essential for the efficiency of a multidisciplinary multiagency outbreak response. The exchange of information, especially during a zoonotic vector-borne disease response, is vitally important. Within APHIS, the National Surveillance Unit (NSU) coordinates animal health surveillance activities in the United States through evaluation, design, analysis, prioritization, and integration (USDA, 2007a). The National Animal Health Surveillance System (NAHSS) combines animal health monitoring and surveillance activities into a comprehensive, coordinated system. The NSU coordinates, implements, and distributes information about the NAHSS (USDA, 2007a). The Center for Emerging Issues (CEI) was created in the early 1990s to work on emerging animal health problems. Today, CEI also explores surveillance approaches and examines open source information for signs of international animal health events using advanced information technology tools (USDA, 2007b). Adding to this surveillance network are reports from APHIS International Services (IS). Nationally, APHIS VS has developed the Veterinary Services Process Streamlining System to capture the interstate movement and transportation of animals, both imports and exports, that when combined with other surveillance systems will assist in identifying the potential transmission of diseases. Much of the detailed information gathered for the aforementioned information systems is collected and electronically entered and transmitted to centralized databases by trained field USDA APHIS VS and state veterinary medical officers located in every state throughout the United States.

APHIS is currently integrating state and the National Veterinary Services Laboratory resources into a nationwide laboratory network, the National Animal Health Laboratory Network (NAHLN), for veterinary and plant health; standardizing diagnostic protocols and procedures; and working in concert with HHS, CDC, and the Department of Justice (DoJ) to develop and implement processes and procedures for monitoring and tracking the possession and use of select agents and toxins. The NAHLN is a state and federal partnership currently consisting of 58 laboratories in 45 states (USDA, 2007c).

It is critical to evaluate the accuracy and compatibility of the multiple, complicated, and varied reporting systems, to identify any duplication or gaps, as well as to gather and analyze appropriate information for an effective, coordinated multiagency, multidisciplinary outbreak response.

The integration of multiagency, multidisciplinary surveillance systems is essential because the epidemiology of vector-borne diseases involves not only human and animal hosts, but also vectors (i.e., mosquitoes, ticks, etc.) and often wild animal hosts. The outbreak of West Nile virus is an example of the need to integrate the varied animal, human, and entomological surveillance and laboratory systems. By monitoring an outbreak and anticipating the potential transmis-

sion variables that could indicate favorable outbreak conditions, multiagency prevention and intervention measures can be set up in advance. For example, the U.S. Geological Survey (USGS), CDC, and DoI created Disease Maps[16] to document wild bird testing and results for West Nile virus. Together with APHIS Wildlife Services, these systems also monitor wild birds for highly pathogenic avian influenza (HPAI). The National Animal Health Monitoring and Surveillance (NAHMS) system reports all equine arbovirus cases to CDC ArboNET.[17] Additionally, the USDA APHIS VS, Centers for Epidemiology and Animal Health (CEAH), CEI, Spatial Epidemiology Team (SET), utilizing geographic information systems (GIS) supports VS's spatial analysis needs in animal disease surveillance, incident management, and epidemiological analysis. The SET provides this support to many customers in VS.[18]

Linking Vector-Borne Disease to a Broader Public Health Agenda

A number of reports have linked vector-borne disease to the broader public health agenda, including the IOM (2002) report on the global importance of zoonotic diseases. Effective historical and ongoing links between vector-borne disease and the broader public health agenda have involved public health, animal health, and entomology experts, such as in the cases of equine encephalitides, West Nile virus, and Rift Valley fever. HHS, CDC, DHS, and APHIS have identified many agents and diseases that could be used for bioterrorism, many of which are zoonotic. A number of these agents are on the Select Agents list.[19]

Research Directions to Enhance Prediction and Control of Vector-Borne Diseases

ARS, the research arm of APHIS, has extensive expertise in the area of vector-borne diseases. It is currently working on a number of research projects to enhance prediction and control of vector-borne diseases and has worked with other agencies to coordinate a multidisciplinary method. Current vector-borne disease research projects include the following:

[16]See http://diseasemaps.usgs.gov.

[17]See http://nsu.aphis.usda.gov/nahss_web/faces/arbovirus_summary.jsp.

[18]These customers include the following: CEAH, National Animal Health Policy and Program, Emergency Management, National Veterinary Services Laboratory, VS area offices, VS regional offices, VS deputy administrator's office; and customers outside Veterinary Services, including the GIS user community, ARS, CDC, Food Safety Inspection Service, state departments of animal agriculture, colleges and universities, International Services, Wildlife Services, Plant Protection and Quarantine, Animal Care, Planning and Program Development, and the World Organization for Animal Health (OIE) (USDA, 2007d).

[19]See http://www.bt.cdc.gov/agent/agentlist.asp.

- "Use of Geographic Information System (GIS) methods to understand spatial patterns of mosquito vectors of West Nile virus," to predict areas and conditions of high and low risk for WNV
- "Evaluation of operator safe diagnostic reagents for Rift Valley fever virus," to develop diagnostic reagents and vaccines for Rift Valley fever that can be safely produced and distributed in North America
- "Genetic studies of Rift Valley fever virus vectors in Kenya," to study the genetics of known Rift Valley fever virus (RVFV) vectors in Kenya
- "Remotely sensed satellite climate and environmental data to detect elevated populations of mosquito vectors of emerging arboviruses in the U.S.," to develop an early warning system to detect elevated populations of potential vectors of RVF and other mosquito-borne emerging virus threat in the United States, providing decision support for agricultural and public health officials to implement improved agricultural and medical planning for potential containment and control operations
- "Vector competence of North American mosquitoes for Rift Valley fever," to assess and determine epidemiological and entomological factors to facilitate/develop effective RVFV control measures
- "Countermeasures to control and eradicate RVF," through diagnostics

Addressing questions through a multidisciplinary systems approach, including predictive modeling, is an essential component of the research that is needed. Research related to prevention and control measures, as well as effective vaccines for viral diseases in both humans and animals, is also needed.

Effective Training of Research and Operational Professionals for the Future

There is a recognized demand for trained and skilled vector-borne disease experts, especially entomologists; however, the available financial and human resources are currently limited. Academic training programs need to increase capacity for field veterinary and entomology emergency response programs, as well as laboratory, policy, and emergency response management programs. Training grants from the National Institutes of Health provide some opportunities to address these needs; but they are not on the scale needed to fill the gaps. The efforts of the multidisciplicary agencies with vested and mutual interests to mount effective emergency responses to incursions of vector-borne diseases of public and animal health significance, potentially threatening U.S. national security, can jointly promote the need to provide incentives and financial support for interdisciplinary studies towards the development of experts to work in the area of vector-borne diseases at the national level through funding sources, including NIH and DHS.

CONFRONTING VECTOR-BORNE DISEASES IN AN AGE OF ECOLOGIC CHANGE

David M. Morens, M.D.[20]
National Institutes of Health

Introduction

The human-inhabited world has been changing dramatically since before recorded time. Such change has inevitably created new microbial opportunities to exploit ecosystem dynamism, including the ability to find, infect, and adapt to human hosts. In man's hunter-gatherer days, from about 2 million years ago until about 10,000 years ago, infectious diseases were substantially limited to those caused by colonizing skin and gut organisms because person-to-person spread was unsustainable beyond small roving kinship groups.

Crop domestication and animal husbandry (revolutions occurring about 10,000 years ago) led to geographic stability, the establishment of populous cities, and in consequence the first era of disease emergence, in which animal organisms switched and adapted to human populations, being sustained by now-unimpeded human-to-human transmission. It was in this era that many of the world's great epidemic diseases emerged as zoonoses, including tuberculosis, smallpox, measles, and possibly some of the human arboviruses. This era of newly emerging diseases was eventually followed by disease reemergences as existing but localized diseases spread geographically with expanding trade and travel (e.g., the movement of plague from China to Europe in the 14th century; syphilis from the New World to Europe in 1493; and smallpox back from Europe to the Americas in 1520). It was in this same reemergence era that exploration and the slave trade spread African mosquitoes around the world, along with some of the diseases they carried (e.g., *Aedes aegypti* carrying yellow fever, dengue, and chikungunya).

The idea that once having emerged, such vector-borne diseases would settle down and become endemic background problems has, in the past 50 years, been shattered by tens of millions of deaths from increasingly drug-resistant falciparum malaria, by a 30-fold increase in the incidence of dengue associated with the emergence and global spread of dengue hemorrhagic fever, and by the emergences and reemergences of many other important vector-borne diseases, such as Lyme disease, West Nile virus disease, Rift Valley fever, and others (Gubler, 1998).

There are now hundreds of vector-borne diseases associated with hundreds of vectors and intermediate hosts. Each of them is a product of interrelated determinants operating within complex and dynamic ecosystems that are poorly

[20]National Institute of Allergy and Infectious Diseases, Building 31, Room 7A-10, 31 Center Drive, Bethesda, MD 20892. Phone: (301) 496-7453; E-mail: dm270q@nih.gov.

understood. It is also clear that many changes of modern life, such as population growth, urbanization, climate changes, and environmental perturbation, are creating new opportunities for the global expansion of vector-borne diseases (Gubler, 1998; Watson et al., 2005). They are clearly on the move and all evidence suggests that we are not well prepared to deal with them.

The Scope of the Problem

Vector-borne diseases have killed more humans in the past three centuries than all other diseases combined (Gubler, 1998). After a brief respite (a half-century; roughly from 1900 to 1950), in which public health and scientific advances either stopped or slowed down the relentless advance of these diseases, many are now aggressively reemerging by expanding into new geographic territory (e.g., dengue, West Nile virus, and Japanese encephalitis), becoming resistant to drugs or insecticides (e.g., malaria), developing genetic mutations that favor spread (e.g., Venezuelan equine encephalitis [Anischenko et al., 2006]), or adapting to new vector hosts (e.g., West Nile virus). New vector-borne diseases are also emerging (e.g., Lyme disease and dengue hemorrhagic fever).

At the same time, the decay of public health infrastructure in developed countries, and the inability to create and sustain them in developing ones, leaves us largely helpless at a time of belated recognition that vector-borne diseases have straddled the two worlds (developed and developing) to such an extent that solutions can no longer be compartmentalized or reduced to localized responses.

Moreover, earth and the human environments within it are also rapidly changing. Largely rural only a century ago, the world is now becoming decidedly urban and periurban. Within the next century, most humans will live in large cities surrounded by periurban environments directly connected to ecosystems harboring nonurban pathogens (e.g., tick-borne encephalitis virus), and directly interconnected to each other by international air routes; even now, it is possible for a microorganism in any place to reach almost any other place in the world within 1-2 days. While it has long been the notion that vector-borne diseases are largely rural, there has been an increasing tendency for many of the major vector-borne causes of morbidity and mortality to be urban and periurban. For example, yellow fever, dengue, and chikungunya are largely urban diseases; the first emergence of West Nile virus in the western hemisphere occurred in New York City; and the resurgence of tick-borne encephalitis in the former Soviet Union has been fueled by the building of dachas in periurban fringes of large cities, placing millions of urbanites in direct contact with rural microorganisms (Morens et al., 2004).

Determinants of vector-borne diseases include not only urbanization and periurbanization, but also population growth, travel and transportation, deforestation, and environmental perturbation, the existence of multiple vector hosts, or intermediate or alternative reservoir hosts, climate change (e.g., El Niño/Southern Oscillation, global warming, expanding vector mosquito distributions), govern-

mental policy and public funding patterns, professional training and support, and many others (Benedict et al., 2007; Gubler, 1998; Morens et al., 2004; Watson et al., 2005). Ironically, some of these same determinants have led to the emergence of non-vector-borne tropical diseases (e.g., HIV/AIDS) that now compete for limited funds that might otherwise go to maintaining general public health infrastructure and vector-borne disease control.

Balancing somewhat these critical determinants of vector-borne disease emergence, we are also experiencing an explosion in scientific knowledge that promises new approaches and tools to fight them, including genomics and proteomics. In the past decade, for example, the genes of all three "players" in the global tragedy of falciparum malaria have been fully sequenced—the parasite, the vector *Anopheles gambiae*, and the human host—and that information is now beginning to be exploited in search of new disease-fighting tools. Thus, there is hope that with an additional emphasis on translational and applied research, seemingly insurmountable problems of vector-borne diseases can be met with new solutions.

But this can only happen if we look beyond the old approaches that have emphasized limited responses and fatalistic outlooks. That responding to vector-borne diseases is now recognized as not only difficult but also a challenge mired in complexities suggests a need to escape the constraint of "biomedical models" to place them in a larger ecological context. This obviously requires inter- and multidisciplinary approaches. But who can take these approaches? Who has the training, experience, and perspective, and how do they acquire it? How do we initiate and support the necessary interactions? If complex problems require complex solutions, what are they, and how do we put the pieces together?

While these questions are not easily answered, and little consensus has yet formed around them, the many experts who have begun to address them seem to agree on a few fundamental deficiencies that inhibit our ability to implement any solution to the vector-borne disease problem:

- Deterioration of public health infrastructure
- Lack of adequate funding
- Lack of adequate training and training models
- Overspecialization in the biomedical sciences driven by the explosions of technology and basic science information
- Bureaucratization

While many other deficiencies can be cited, these five are among the most fundamental. There is a general consensus that fixing them is an essential prerequisite to further progress.

Deterioration of Public Health Infrastructure

In the early 20th century, when epidemiology was strongly allied with microbiology, local health departments were well funded to deal with some of the most important infectious diseases (e.g., tuberculosis, water-borne and milk-borne diseases, and epidemic childhood diseases, such as measles and poliomyelitis). But the phenomenal rise in developed countries of institutionalized hospital-based curative medicine, coupled with the development first of passive immunotherapy (diphtheria antitoxin in 1890), followed by vaccines in the 1920s and antibiotics in the 1940s, led to a gradual and then a rapidly accelerating decline in public health infrastructure. When the AIDS pandemic was noticed in the early 1980s, tuberculosis control programs were so deeply eroded in the United States that none were able to respond adequately to the AIDS-related tuberculosis resurgence. When West Nile virus was imported into the United States in 1999, it was learned that some states had abandoned their vector control capacities entirely. Some states had no vector control personnel at all.

That basic public health infrastructure needs to be strengthened in the United States and in many other developed countries is almost universally agreed. That it has not happened is difficult to attribute to any one cause but may reflect a combination of the difficulty in securing and sustaining long-term commitment to substantial funding, competing priorities, and a psychological reluctance to spend money on things that have not happened yet but might happen in the future. In some countries, such as the United States, there is an ingrained preference for fire-fighting approaches to problem solving, rather than fire-prevention approaches. All of these deficiencies are magnified by problems like vector-borne diseases, which require integrated multidisciplinary approaches. It is enough of a problem to face insufficient personnel to staff unmanned and deteriorated facilities; it is quite another to be faced with creating new models for and mechanisms to train and support diverse professionals and to bring them together into working teams.

Infrastructure deterioration is of course a problem specific to the developed world. The challenge for the developing world, where the burden of morbidity and mortality from vector-borne diseases is much higher, is substantially greater because there has generally been little vector control infrastructure to begin with, and no funding to support it even if created. In much of the world the infrastructure gap cannot be filled by nongovernmental organizations (NGOs) or by monies from donor nations. It will probably require sustained economic development over many decades, if not longer. Thus both the developed and the developing world are destined, for the foreseeable future, to rely on the resources and expertise of developed nations to control vector-borne diseases.

Lack of Adequate Funding

Establishing and supporting public health infrastructures is expensive, but it is only a part of the funding challenge. In recent decades, philanthropic sources like the Bill and Melinda Gates Foundation have stepped up to provide substantial new monies for disease control in developing countries, but these foundations must work through existing structures rather than build new ones. Infrastructure and funding problems are therefore codependent. Moreover, the orientation of these philanthropic programs is necessarily toward support of existing approaches (e.g., bringing vaccines to populations with a high burden of vaccine-preventable diseases), rather than supporting basic or translational research to develop new tools, or even to purchase and maintain expensive equipment or train cadres of technical personnel.

Much the same can be said of national programs such as the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) program. The successes of such programs in developing countries are threatened by the same forces that impede local efforts and traditional research partnerships with wealthy nations, such as lack of trained personnel, lack of roads, bridges, and cold chains, climate and weather challenges, and so on. Researchers and field workers in developing countries repeatedly claim that funders do not understand these basic realities. This observer recalls an incident that occurred almost 30 years ago in which, after several days of travel, he caught up with a tropical disease research colleague in a remote African village. "The last thing I need is another epidemiologist," she observed, not entirely in jest. "What I really need is a Revco repairman, a diesel generator, and someone to fix the broken axle on the Land Rover." No amount of philanthropy or scientific ardor can bring all of the benefits of the developed to the developing world.

Moreover, direct support from wealthy nations, however motivated by humanitarian concerns, is unlikely to have any substantial impact because there is limited coordination between wealthy donor nations and because the funds are typically inadequate to address problems so large, so complex, and so deeply rooted. Models for funding national and international vector control were never fully established and are now largely forgotten or no longer relevant. *Aedes aegypti* and malaria eradication programs are remembered only by senior experts, most of them retired. To the average citizen, DDT is more likely to evoke cartoon images of poison labels and dead eagles than of effective pesticides that could potentially save millions of human lives. In addition, there is a long history of donor nations picking up ambitious projects to benefit the developing world only to drop them once problems or unexpected resistance—sometimes from vectors, other times from interest groups—arise. On the other hand, there is little history of such benevolence expressed in long-term commitment to solving a problem no matter what level of effort is required. While the situation has been slowly improving, large-scale funding from wealthy donor nations has clearly

suffered from a variety of ills that include inadequate resources, lack of coordination between donors, lack of commitment to solving problems that have been addressed, and lack of long-range vision.

Lack of Adequate Training and Training Models

The past 50 years have seen revolutions in medical, biomedical, and public health training, which have pulled apart many of the shared values and approaches that once formed the basis of natural interdisciplinary alliances. Throughout the 1930s epidemiology and microbiology were closely allied fields within biomedicine. When the United States began its experiment with schools of public health in the 1920s, they were located within medical schools because of the obvious importance of the medical arts and basic biomedical sciences, but were also established with the conscious intent to forge interdisciplinary partnerships with the social sciences (Fee and Acheson, 1991).

Whether or not this was an idea doomed to failure from the beginning, as many Europeans seem to believe, it has worked poorly with respect to the particular question of vector-borne diseases. Few schools of public health are found outside the United States; of the 33 American schools, most are now free-standing (i.e., not within, and in general not closely allied with, medical schools). Indeed, it is customary to view the two as being in competition. Infectious disease epidemiology, so recently the bedrock of most schools of public health, has been marginalized in all but a few. Public health laboratory programs, long required for accreditation, have been dropped. Most graduates of public health masters programs have had no infectious disease experience beyond an epidemiology survey course; in most schools, students desiring solid infectious disease epidemiology training have difficulty acquiring it.

Even epidemiology departments have been largely abandoned to the study of chronic and behavioral disorders, fueled by the "massaging" of large data sets with sophisticated computer programs rather than "hands-on" or "real-world" experiences. American-born physicians have also become something of an endangered species within public health schools, most of which have become focused on social sciences, as well as health services administration and health education. Even maternal and child health programs have often tilted toward program administration. With the exception of a few excellent schools, prominent among them the London School of Hygiene and Tropical Medicine, and the Johns Hopkins School of Public Health, public health schools seem incapable of making substantial contributions to the creation of a professional and scientific workforce engaged in interdisciplinary approaches to vector-borne diseases in their current configurations.

Beyond schools of public health, the picture remains grim. Nearly a century after the "Flexner report" (1910), American medical schools have been gradually squeezing out the basic sciences in favor of courses in ethics, intercultural

sensitivity, doctor–patient relationships, and so forth. In some schools anatomy is now an elective. In others, resident physicians, whose counterparts three decades ago would have been delivering babies and assisting at major surgeries, now stand waiting at the bedside to have procedure cards signed for drawing 10 cc of blood from an arm vein. Medical education is expensive, and the public wants doctors with whom they can empathize. At the same time, the biomedical sciences have become increasingly complex and technical, and thus less accessible to medical students and medical graduates with generalist educations that include only survey courses in the basic sciences. Some medical schools (e.g., Duke) have experimented with aggressive programs that emphasize scientific training (O'Connor et al., 2007), but most of these, however excellent, are not oriented toward tropical medicine, epidemiology, or vector-borne diseases.

Two approaches that have worked extremely well, as judged by the quality and output of scientific work and the record of professional development of vector-borne disease and tropical medicine researchers, have been those of the U.S. Department of Defense (DoD) and the U.S. Centers for Disease Control and Prevention (CDC). The DoD has long maintained sophisticated overseas labs in partnership with scientists from host countries (e.g., the Armed Forces Research Institute of Medical Science [AFRIMS] in Bangkok, Thailand; and the Naval Medical Research Unit No. 3 [NAMRU-3] in Masr-el-Gedida, Egypt). These and a number of other overseas laboratories have been leaders in interdisciplinary and international tropical medicine research. They have also trained several generations of leaders in tropical medicine/vector-borne diseases, including researchers based in preventive medicine, microbiology, entomology, and other allied fields. Unfortunately, however, these programs are "one of a kind," may be difficult to duplicate outside the military environment, and are expensive to operate. In recent years, the military emphasis on the "warfighter" mission, as well as the outside contracting of many medical services, has led to concerns that continued existence of the overseas research programs may be imperiled.

The CDC has for decades been involved in national and international vector-borne disease research and investigation. In recent years, these activities have been sustained even though strained by losses of key scientists. A different challenge has been a greater emphasis for young Atlanta-based scientists on program management, with fewer opportunities to do hands-on work, including overseas field work, in part a result of the growing expertise of state health departments and foreign ministries of health who are less dependent on the once unique outbreak investigative skills of the CDC. While historically successful in supporting solid research and training a cadre of leaders, the ability of relevant CDC programs to expand seems limited; like the DoD programs, the CDC vector-borne and international programs may be "one of a kind," resistant to duplication, and easily saturated.

Overspecialization in the Biomedical Sciences Driven by Explosions of Technology

The increasing schism between generalist training for physicians and specialist training for biomedical scientists in doctoral programs is being widened by an explosion of technology and basic science information that is increasingly backlogged and untranslated into medical advances, creating the dual problems of insufficient progress and interdisciplinary alienation that further impedes such progress. A similar phenomenon occurred in England 125 years ago when the new and highly technical field of microbiology, which required microscopes, expensive laboratory equipment, and much nontraditional study, was largely passed over by the British medical profession, to its great detriment (Worboys, 2000).

The other side of the coin is that graduates of doctoral programs in fields like microbiology or entomology have often become so narrowly focused that they lack any practical orientation toward diseases associated with the microbes or vectors they have studied. Several decades ago, for example, graduates of microbiology programs would generally have been well grounded in bacteriology, virology, parasitology, immunology, and pathology. Nowadays, in the genomics era, the traditional distinction between bacteriology, parasitology, and virology has become almost anachronistic. It is probably possible to obtain a Ph.D. degree in molecular biology studying one molecule, or even one gene, but having had little or no exposure to a disease or to an interdisciplinary problem, let alone any experience working with colleagues or students from different disciplines, or in international settings.

Bureaucratization

We live in an increasingly bureaucratized world, in which governments and other authoritative entities believe that order and progress is best served by increasing layers of oversight. For researchers in tropical and vector-borne diseases, the impediments to accomplishing the most basic tasks have become so great that it is apparently driving prospective students and junior faculty out of the field. The flow of biological materials, the life blood of vector-borne disease research, is now impeded, and often times stopped entirely, by air transport regulations (International Air Transport Association [IATA] and Air Transport Association [ATA]), the USDA, and "select agent" rules associated with the U.S. Patriot Act, which also restricts foreign scientists from working on U.S.-funded research even in their own countries, where the diseases, vectors, and microbial agents are widely prevalent.

In other cases, nations experiencing disease outbreaks have refused to let biological specimens outside their borders for fear of losing patent rights or, more ominously, to blackmail developed nations who they believe will use the

materials to develop vaccines they will not be able to purchase because of cost or unavailability. At the same time, clinical studies conducted by Western researchers have been greatly impeded by regulations and paperwork, often surrounding issues of informed consent and recordkeeping practices, and despite pleas from the nations where the studies are being conducted that they meet all of their own ethical and documentary requirements.

Looking Backward in Time

Although it would be easy to lose heart at the challenges noted earlier and at the lack of easy or obvious solutions, it may be worthwhile to look back at an earlier time in which the challenges were even greater, but were met with foresight, commitment, and considerable success. Tropical medicine as an idea and discipline arose during the colonial era when European powers began sending their citizens abroad to administer new colony-nations. Realizing that they were among the most important and deadly challenges, these nations turned their scientific attention to tropical diseases. While it is popular today to characterize these efforts as exploitative, since colonialism itself was exploitative, the historical records suggests otherwise; in any case, advances that benefited one group benefited others. For example, the efforts of Gorgas to eliminate yellow fever from Havana saved mostly the local poor, while overseas tropical disease research by Kitasato, Koch, Yersin, and others led to advances against diseases that predominantly affected native peoples (e.g., cholera and plague).

Advances within the first three decades of the microbiology era (beginning in 1876) led to subsequent decades of startling successes in tropical medicine in general, and in vector-borne diseases in particular. By the first few years of the 20th century, the agents of malaria and dengue had been discovered, and the transmission of yellow fever worked out. By 1899, the London School of Hygiene and Tropical Medicine had been set up, followed by an explosion of public health and tropical disease research in the United States. The U.S. Public Health Service Hygienic Laboratory was set up under the leadership of a physician trained in tropical medicine (under both Koch and Pasteur); eventually it became the U.S. National Institutes of Health. Internationally, agencies like the Pan-American Health Organization (PAHO) and the Office International d'Hygiène Publique (OIHP) grew out of the sanitary movements of the 19th century to develop programs based on the breakthroughs from microbiology and tropical medicine. After World War I, the League of Nations Health Office initiated its own tropical disease programs.

In the 1940s, the CDC evolved out of a war-related malaria control program. In the middle years of the 20th century, as NIH and CDC grew in the United States, the Rockefeller Foundation, long active in tropical diseases, moved forward to establish a number of overseas research centers (e.g., in Bahia, Entebbe, and Trinidad). It was the influential work of these centers that largely created the

field of arbovirology. Most of the major arboviruses were discovered, characterized, studied, and placed in the *Arbovirus Catalog* during this era. It is surprising and painful to reflect that most of our knowledge of tropical medicine, and most of the tropical medicine pharmacopeia still in use, derives from the body of scientific work undertaken in the first five decades of the 20th century (Hotez, 2004), now relegated to seldom-read history books and increasingly distanced from modern science and practicing scientists.

It would probably be a mistake to try to recreate these golden days of tropical medicine by returning to the formulae that worked then. The problem of vector-borne diseases is a complex one that goes beyond simple "bug and drug" solutions. One expert has opined that we need a North American tropical disease training and research center (Hotez, 2004), but however timely and powerful the idea, one senses it would not be sufficient to meet a challenge so broad, so deep, and so complicated.

While there seem to be no easy or obvious solutions, a first step must be recognition of the problem in all its challenges and complexities by policy makers, government scientists, and academic leaders. A next step is surely to find new and innovative ways to train and co-train key scientists and public health workers taken from a variety of disciplines—medicine, nursing, biomedical sciences, entomology, veterinary sciences, ecological sciences, wildlife management, and many others—in interdisciplinary approaches to these complex problems, and then to provide them job opportunities to apply their new skills in interdisciplinary settings. There are few if any models for how to achieve this—perhaps the closest are the DoD and CDC models—and there is also a need for models that work in academic settings where advanced training has become increasingly compartmentalized and narrowly focused, rather than multidisciplinary. A greater emphasis on applied research in overseas settings is required, and an attempt to solve bureaucratic and regulatory impediments to such work is crucial.

The vector-borne disease problem will not go away nor will it simplify itself. We can expect accelerating problems and a substantial start-up time for any new solution destined to work. Among the greatest challenges to innovation is nostalgia for old approaches that once worked but are now outdated. In an era in which scientific and technical advances drive narrowly focused research and training, the question of how to foster generalist training and team approaches to problem solving, in which team members cross disciplinary lines regarded as being remote from each other, is a difficult challenge. But it is no more impossible than the challenges faced and met successfully in the first half of the 20th century, in which science and public health worked to produce a yellow fever vaccine, discovered and developed effective treatments for many vector-borne diseases, and rolled back some of the deadliest among them in the direction of, if not quite up to, eradication.

THE VECTOR BIOLOGY PROGRAM AT THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Adriana Costero, Ph.D.[21]
National Institute of Allergy and Infectious Diseases

Introduction

The Division of Microbiology and Infectious Diseases (DMID), part of the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), supports a wide variety of vector biology research projects mainly through its Vector Biology Program, but also through other programs within the Division. Projects range from basic research to studies on the ecology and epidemiology of vector-borne diseases of human importance.

The overall purpose of the Vector Biology Program is to advance our understanding of vectors of pathogens responsible for human disease by supporting research projects on a wide scope of topics and vectors. A variety of funding mechanisms exist that support different facets of the research process, from basic studies of vector biochemistry and physiology to the initial phases of translational research in the form of proof-of-concept or target validation studies.

DMID is also committed to providing career development opportunities to new investigators through training grants and career awards. In addition, conference grants are available to provide financial support to students, postdocs, and new investigators attending and participating in scientific meetings.

Vector Biology Portfolio

The Vector Biology portfolio comprises approximately 140 grants and cooperative agreements for fiscal year 2007. Most of these are studies on mosquitoes; the remainder deal with snails, ticks, sandflies, triatomine bugs, tsetse flies, lice, and scabies mites.

Many grants encompass different aspects of research related to vector control. These include target identification; development of improved larvicides; understanding of insecticide resistance mechanisms; development of improved traps for mosquitoes, ticks, and triatomine bugs; and studies on effectiveness of bednets in preventing malaria transmission. Numerous projects are looking at the ecology and epidemiology of vector-borne diseases, including biochemistry, control, genetics, genomics, immunology, interaction, modeling, pathogenesis, physiology, surveillance, proteomics, transgenics, and vaccines.

Research on a variety of vectors and their associated pathogens is supported by different funding mechanisms. Grant applications in the Vector Biology portfolio come in mostly as unsolicited grants, and occasionally in response to NIAID

[21]Vector Biology Program Officer, Division of Microbiology and Infectious Diseases.

solicitations (requests for applications [RFAs] or program announcements [PAs]). The cornerstone of NIH-funded extramural programs is the peer-review process, carried out by study sections stationed at the Center for Scientific Review. Several study sections review grants for the Vector Biology Program, but most applications go through peer review in the Vector Biology Study Section.

This reflects the support for well-established investigators as well as for highly innovative/high-risk projects that may move the field forward. DMID also supports small research projects to generate hypotheses and data, as well as support for undergraduate-prevalent institutions, which are primarily designed for training new investigators. Cooperative agreements have facilitated translation of basic science into products, and small business grants (SBIRs/STTRs) have allowed for the development of short-term vector control technologies and approaches. Conference grants support new investigators in their participation in scientific meetings.

The great majority of grants in the portfolio are supported by the Research Grant (R01) mechanism. This mechanism supports research with strong preliminary data and hypotheses. R01 grants can be as short as 3 years or as long as 5 years. This mechanism is the cornerstone of scientific research at NIH and supports a high percentage of investigators in the United States and abroad.

The second most represented mechanism in the Vector Biology portfolio is the Exploratory/Developmental Research Grant mechanism (R21). The purpose of this funding mechanism is to support research that is considered high risk/high pay-off. Preliminary data are not required for submission of an application, and projects are supported for 2 years with a moderate level of funding. This mechanism enables investigators with highly innovative ideas or approaches to determine if their approach may be feasible and allows for the generation of preliminary data that can later be included in an R01.

The Small Research Grant mechanism (R03) is also represented in the portfolio. This mechanism typically supports 2-year projects with a small budget. Research projects supported as R03s are designed to generate preliminary data and/or hypotheses that can later be tested in an R01 application.

NIH Academic Research Enhancement Award (AREA) grants are also represented and are valuable in providing funding to investigators in undergraduate-prevalent institutions, allowing them to perform 3-year projects and train the next generation of investigators. This funding mechanism is very valuable in allowing investigators in small institutions to contribute to the scientific knowledge being generated about vectors.

As a result of the NIAID's Partnerships initiative, several cooperative agreements have been funded that address translational aspects of vector management strategies. These projects have resulted in new insights and potential products for improved control of vector-borne diseases.

Several mechanisms are available for postdocs and new investigators (F32, F33, K22) to enable them to start designing and writing small-grant applications.

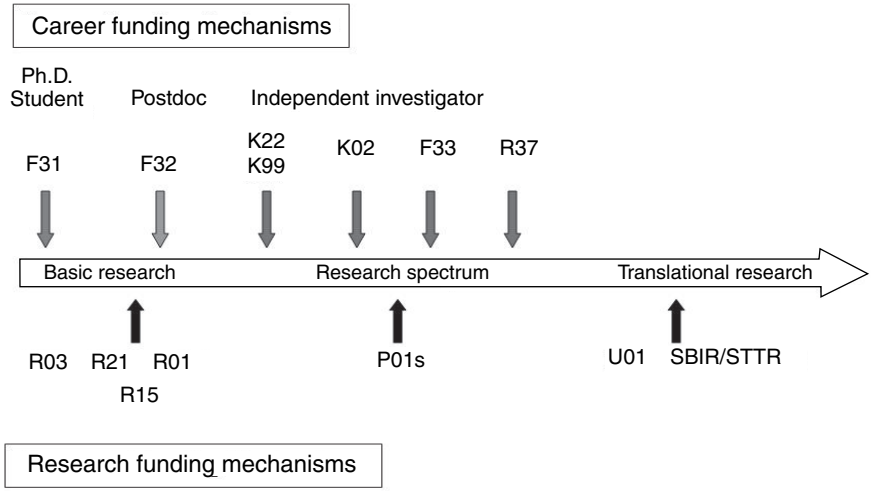

FIGURE 3-1 Available funding mechanisms for research.

These mechanisms involve a new investigator and a mentor/institution where the transition from student to independent investigator can be made, providing an invaluable experience for those transitioning into independent careers.

Small business grants (SBIRs, STTRs) are also represented in the portfolio and represent short-term investments into technologies and devices that may develop into vector control strategies. This mechanism encourages small businesses to become involved in research on novel mechanisms to better control and/or prevent vector-borne diseases.

The Vector Biology portfolio is well rounded in terms of the mechanisms represented and the type of research being supported, ranging from basic to translational. Figure 3-1 demonstrates different funding mechanisms available during these research phases.

Numerous projects headed by U.S. investigators contain foreign components. Some DMID initiatives, such as the International Research in Infectious Diseases (IRID) Program, and the Tropical Medicine Research Centers (TMRCs) are designed for investigators in foreign institutions. This is very important to the program as many vector-borne diseases occur in tropical and subtropical areas of the world and not in the United States. Foreign investigators are encouraged to take advantage of these initiatives whenever possible to fund their research projects.

Challenges

The Vector Biology Program at NIAID is vibrant and strong, with research on many aspects of the field and a wide variety of organisms. The Program uses a broad range of funding mechanisms that support new as well as more experienced investigators. The Program encourages interdisciplinary projects and collaboration among field- and lab-based investigators in order to help to elucidate the complex interactions among vectors, their hosts, the pathogens they transmit, and the ecological environment in which these interactions take place. Only by understanding these complex networks of interactions can we achieve sound, comprehensive, and sustainable vector management and disease prevention.

The training and retention of new investigators must continue to be a priority; not only as part of the regular research mechanisms (R15, R01, etc.) but also through training grants such as the Ruth L. Kirschstein National Research Service Awards (NRSAs) (F32, F33), the Career Development Awards (K22), and the Institutional Research Training grants (T32). In addition, Conference Grants (R13) can help fund participation of students and new investigators in scientific meetings.

Communication and collaboration among federal agencies involved in vector research will enable the resources of all agencies to be used more effectively in supporting the research community.

Conclusion

The vector biology field is at an exciting juncture. With great potential for novel vector management strategies underway and exciting cutting-edge research being performed, there is great promise ahead. Our challenge is to work together as a group, with open communication channels, to achieve the promise of the future to improve people's health.

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Appendix A

Agenda

Vector-Borne Diseases: Understanding the Environmental, Human Health, and Ecological Connections

Hilton Hotel
425 W. Prospect Road
Ft. Collins, Colorado
June 19-20, 2007

Tuesday, June 19, 2007

8:30 a.m.	Continental Breakfast
9:00 a.m.	Welcome and Opening Remarks • Stanley M. Lemon, M.D., Chair Forum on Microbial Threats • Lyle Petersen, M.D., M.P.H. Centers for Disease Control and Prevention
9:15 – 10:15 a.m.	Keynote Address Duane Gubler, Sc.D. University of Hawaii
10:15 – 10:45 a.m.	Discussion
10:45 – 11:00 a.m.	Break

Session I:
The Importance of Vector-Borne Diseases

Moderator: Lonnie King, D.V.M., Centers for Disease Control and Prevention

11:00 – 11:30 a.m.	What are the common denominators in vector-borne disease outbreaks? Ned Hayes, M.D. Centers for Disease Control and Prevention
11:30 a.m. – 12:00 p.m.	Emergence of epidemic dengue and dengue hemorrhagic fever in Mexico: Lessons learned and toward better vector and disease control Barry Beaty, Ph.D. Colorado State University
12:00 – 12:30 p.m.	What are the unique issues and challenges associated with vector-borne diseases? Thomas W. Scott, Ph.D. University of California, Davis
12:30 – 1:00 p.m.	Discussion of Session I
1:00 – 1:45 p.m.	Lunch/Continuing discussion of Session I

Session II:
Factors of Emergence:
The Biology and Ecology of Vector-Borne Diseases

Moderator: Col. George Korch, Ph.D., U.S. Army Medical Research Institute for Infectious Diseases

1:45 – 2:15 p.m.	Ecology of disease: The intersection of human and animal health Ken Linthicum, Ph.D. USDA, Agricultural Research Service
2:15 – 2:45 p.m.	What role(s) do anthropogenic factors play in the biology and ecology of vector-borne disease? Durland Fish, Ph.D. Yale University

2:45 – 3:00 p.m.	Break
3:00 – 3:30 p.m.	The effects of anthropogenic environmental change and emerging diseases Jonathan A. Patz, M.D., M.P.H. University of Wisconsin, Madison
3:30 – 4:00 p.m.	Vector-borne plant diseases: Factors driving the emergence and spread of pathogens Rodrigo Almeida, Ph.D. University of California, Berkeley
4:00 – 4:30 p.m.	Discussion of Session II
4:30 – 5:00 p.m.	Open Discussion of Day 1
6:00 p.m.	Meeting adjourns

Wednesday, June 20, 2007

8:00 a.m.	Continental Breakfast
8:30 – 8:45 a.m.	Summary of Day 1 P. Frederick Sparling, M.D., Vice Chair Forum on Microbial Threats

Session III:
Detection and Control of Vector-Borne Diseases

Moderator: Stanley M. Lemon, Chair, Forum on Microbial Threats

8:45 – 9:15 a.m.	West Nile virus Lyle Petersen, M.D., M.P.H. Centers for Disease Control and Prevention
9:15 – 9:45 a.m.	Rift Valley fever C. J. Peters, M.D. University of Texas Medical Branch, Galveston
9:45 – 10:15 a.m.	Malaria Michael Coleman, Ph.D. Medical Reseach Council, South Africa

10:15 – 10:30 a.m.	Break
10:30 – 11:00 a.m.	Sudden Oak death David Rizzo, Ph.D. University of California, Davis
11:00 – 11:30 a.m.	Vector-borne zoonotic diseases and their ecological and economic implications: Bluetongue disease in Europe Bennie Osburn, Ph.D., D.V.M. University of California, Davis
11:30 a.m. – 12:00 p.m.	Environmental factors influence transmission of Sin Nombre hantavirus between rodents (and to humans?) Charlie Calisher, Ph.D. Colorado State University
12:00 – 12:30 p.m.	Open discussion of Session III
12:30 – 1:15 p.m.	Lunch/Continued discussion of Session III

Session IV:
Integration of Strategies: Surveillance, Diagnosis, and Response

Moderator: Carole Heilman, Ph.D., National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIAID/NIH)

1:15 – 5:00 p.m.	Panelists • Roger Nasci, Ph.D., Centers for Disease Control and Prevention • Adriana Costero, Ph.D., NIAID/NIH • David Morens, M.D., NIAID • Sherrilyn Wainwright, D.V.M., M.P.H., U.S. Department of Agriculture, Animal and Plant Health Inspection Service
5:00 p.m.	Wrap-up and concluding remarks
5:15 p.m.	Adjourn

Appendix B

Acronyms

AIDS	Acquired Immune Deficiency Syndrome
AFRIMS	Armed Forces Research Institute of Medical Science
ALS	almond leaf scorch
APHIS	Animal and Plant Health Inspection Service
AREA	Academic Research Enhancement Award
ARMA	Malaria Atlas Project
ARS	Agricultural Research Service
ATA	Air Transport Association
AVHRR	Advanced Very High Resolution Radiometer
BI	Breteau index
BSE	bovine spongiform encephalopathy
BTV	bluetongue virus
CDC	Centers for Disease Control and Prevention
CEAH	Center for Epidemiology and Animal Health
CEI	Center for Emerging Issues
CGDM2	Coupled Global Climate Model version 2
CI	container index
CJD	Creutzfeldt-Jakob disease
CVC	citrus variegated chlorosis
DALY	disability-adjusted life-years
DDSS	Dengue Decision Support System
DENV	dengue virus

DF	dengue fever
DHF	dengue hemorrhagic fever
DHS	Department of Homeland Security
DMID	Division of Microbiology and Infectious Diseases
DoD	Department of Defense
DoJ	Department of Justice
DSS	dengue shock syndrome; decision support system
DTP	dengue transmission potential
DV	dengue virus
EIP	extrinsic incubation period
EIR	entomological inoculation rate
EIS	Epidemic Intelligence Service
ELISA	enzyme-linked immunosorbent assay
EMPRES	Emergency Prevention System for the Transboundary Animal Diseases
ENSO	El Niño/Southern Oscillation
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FTP	Fellowship Training Program
GAO	Government Accountability Office
GATT	General Agreement on Tariffs and Trade
GCM	global climate model
GHG	greenhouse gas
GIS	geographic information system
HadCM3	Hadley Centre Coupled Model version 3
HCV	hepatitis C virus
HFRS	hemorrhagic fever with renal syndrome
HHS	Department of Health and Human Services
HI	house index
HIV	Human Immunodeficiency Virus
HPAI	highly pathogenic avian influenza
HPS	hantavirus pulmonary syndrome
IATA	International Air Transport Association
ICIDR	International Collaborations in Infectious Disease Research
IOM	Institute of Medicine
IPCC	Intergovernmental Panel on Climate Change
IPM	Integrated Pest Management
IRID	International Research in Infectious Diseases

IRS	indoor residual spray
IS	International Services
ITM	insecticide-treated materials
ITN	insecticide-treated bednets
IVCC	Innovative Vector Control Consortium
JEV	Japanese encephalitis virus
kdr	knockdown resistance
LD	lethal dose
LL-ITM	long-lasting insecticide-treated materials
LSDI	Lubombo Spatial Development Initiative
MARA	Mapping Malaria Risk in Africa project
MAUP	modifiable areal unit problem
MP-NAT	mini-pool nucleic acid amplification test
NAFTA	North American Free Trade Agreement
NAHLN	National Veterinary Services Laboratory Network
NAHMS	National Animal Health Monitoring and Surveillance
NAHSS	National Animal Health Surveillance System
NAMRU	Naval Medical Research Unit
NDVI	normalized difference vegetation index
NE	nephropathia epidemica
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NMCP	National Malaria Control Programme
NRSA	National Research Service Award
NS	nonstructural proteins
NSU	National Surveillance Unit
OIE	Office International des Epizooties
OIHP	Office International d'Hygiène Publique
OLR	outgoing longwave radiation
OLS	oleander leaf scorch
PA	program announcement
PAHO	Pan American Health Organization
PCMS	Pinon Canyon Maneuver Site
PCR	polymerase chain reaction
PD	Pierce's disease of grapevines
PDI	power dissipation index

PEPFAR	President's Emergency Plan for AIDS Relief
PHP	public health pesticide
PRNT	plaque reduction neutralization test
PTSD	post-traumatic stress disorder
RCE	Regional Centers of Excellence
RDT	rapid diagnostic test
RFA	requests for applications
RNA	ribonucleic acid
RNAi	RNA interference
RREDS	Ross River virus Early Detection and Surveillance
RVF	Rift Valley fever
RVFV	Rift Valley fever virus
SEIR	susceptible-exposed-infected-resistant
SLE	St. Louis encephalitis
SLEV	Saint Louis encephalitis virus
SNV	Sin Nombre virus
SOI	Southern Oscillation Index
SST	sea surface temperature
TDR	Special Programme for Research and Training in Tropical Diseases
TMRC	Tropical Medicine Research Center
ULV	ultra low volume
UN	United Nations
USDA	U.S. Department of Agriculture
USGS	U.S. Geological Survey
VBD	vector-borne disease
VEEV	Venezuelan equine encephalitis virus
VP	viral structural protein
VS	Veterinary Services
WHO	World Health Organization
WHOPES	World Health Organization Pesticide Evaluation Scheme
WNV	West Nile virus
YF	yellow fever
YFV	yellow fever virus

Appendix C

Forum Member Biographies

Stanley M. Lemon, M.D. (*Chair*), is the John Sealy Distinguished University Chair and director of the Institute for Human Infections and Immunity at the University of Texas Medical Branch (UTMB) at Galveston. He received his undergraduate A.B. degree in biochemical sciences from Princeton University summa cum laude and his M.D. with honors from the University of Rochester. He completed postgraduate training in internal medicine and infectious diseases at the University of North Carolina at Chapel Hill and is board certified in both. From 1977 to 1983 he served with the U.S. Army Medical Research and Development Command, followed by a 14-year period on the faculty of the University of North Carolina School of Medicine. He moved to UTMB in 1997, serving first as chair of the Department of Microbiology and Immunology, then as dean of the School of Medicine from 1999 to 2004. Dr. Lemon's research interests relate to the molecular virology and pathogenesis of the positive-stranded RNA viruses responsible for hepatitis. He has had a long-standing interest in antiviral and vaccine development and has served previously as chair of the Anti-Infective Drugs Advisory Committee of the U.S. Food and Drug Administration (FDA). He is the past chair of the Steering Committee on Hepatitis and Poliomyelitis of the World Health Organization (WHO) Programme on Vaccine Development. He is past chair of the Board of Scientific Councilors of the National Center for Infectious Diseases (NCID) of the Centers for Disease Control and Prevention (CDC), and currently serves as a member of the U.S. Delegation of the U.S.–Japan Cooperative Medical Sciences Program. He was co-chair of the Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats for the National Academy of Sciences (NAS), and he recently chaired an Institute of Medicine (IOM) study committee

related to vaccines for the protection of the military against naturally occurring infectious disease threats.

Margaret A. Hamburg, M.D. (*Vice Chair*), was the founding vice president for Biological Programs at the Nuclear Threat Initiative, a charitable organization working to reduce the global threat from nuclear, biological, and chemical weapons and ran the program for many years. She currently serves as senior scientist for the organization. She completed her internship and residency in internal medicine at the New York Hospital/Cornell University Medical Center and is certified by the American Board of Internal Medicine. Dr. Hamburg is a graduate of Harvard College and Harvard Medical School. Before taking on her current position, she was the assistant secretary for planning and evaluation, U.S. Department of Health and Human Services (HHS), serving as a principal policy advisor to the secretary of health and human services with responsibilities including policy formulation and analysis, the development and review of regulations and legislation, budget analysis, strategic planning, and the conduct and coordination of policy research and program evaluation. Prior to this, she served for nearly 6 years as the commissioner of health for the city of New York. As chief health officer in the nation's largest city, her many accomplishments included the design and implementation of an internationally recognized tuberculosis control program that produced dramatic declines in tuberculosis cases, the development of initiatives that raised childhood immunization rates to record levels, and the creation of the first public health bioterrorism preparedness program in the nation. She currently serves on the Harvard University Board of Overseers. She has been elected to membership in the IOM, the New York Academy of Medicine, and the Council on Foreign Relations and is a fellow of the American Association for the Advancement of Science (AAAS) and the American College of Physicians.

P. Frederick Sparling, M.D. (*Vice Chair*), is the J. Herbert Bate Professor Emeritus of Medicine, Microbiology, and Immunology at the University of North Carolina (UNC) at Chapel Hill, and Professor of Medicine, Duke University. He is director of the North Carolina Sexually Transmitted Infections Research Center and also the Southeast Regional Centers of Excellence in Biodefense and Emerging Infections. Previously he served as chair of the Department of Medicine and chair of the Department of Microbiology and Immunology at UNC. He was president of the Infectious Diseases Society of America (IDSA) from 1996 to 1997. He was also a member of the IOM Committee on Microbial Threats to Health (1990-1992) and the IOM Committee on Emerging Microbial Threats to Health in the 21st Century (2001-2003). Dr. Sparling's laboratory research has been on the molecular biology of bacterial outer membrane proteins involved in pathogenesis, with a major emphasis on gonococci and meningococci. His work helped to define genetics of antibiotic resistance in gonococci, and the role of iron scavenging systems in pathogenesis of human gonorrhea.

David W. K. Acheson, M.D., F.R.C.P., is assistant commissioner for food protection within the U.S. Food and Drug Administration. Dr. Acheson graduated from the University of London Medical School in 1980, and following training in internal medicine and infectious diseases in the United Kingdom, moved to the New England Medical Center and Tufts University in Boston in 1987. As an associate professor at Tufts University, he undertook basic molecular pathogenesis research on foodborne pathogens, especially Shiga toxin-producing *E. coli*. In 2001, Dr. Acheson moved his laboratory to the University of Maryland Medical School in Baltimore to continue research on foodborne pathogens. In September 2002, Dr. Acheson accepted a position as chief medical officer at the Food and Drug Administration's (FDA) Center for Food Safety and Applied Nutrition (CFSAN). In January 2004, he also became the director of CFSAN's Food Safety and Security Staff and in January 2005, the staff was expanded to become the Office of Food Safety, Defense and Outreach. In January 2007, the office was further expanded to become the Office of Food Defense, Communication and Emergency Response. On May 1, 2007, Dr. Acheson assumed the position of FDA assistant commissioner for food protection to provide advice and counsel to the commissioner on strategic and substantive food safety and food defense matters. Dr. Acheson has published extensively and is internationally recognized both for his public health expertise in food safety and his research in infectious diseases. Additionally, Dr. Acheson is a fellow of both the Royal College of Physicians (London) and the Infectious Disease Society of America.

Ruth L. Berkelman, M.D., is the Rollins Professor and director of the Center for Public Health Preparedness and Research at the Rollins School of Public Health, Emory University, in Atlanta. She received her A.B. from Princeton University and her M.D. from Harvard Medical School. Board certified in pediatrics and internal medicine, she began her career at the CDC in 1980 and later became deputy director of NCID. She also served as a senior advisor to the director, CDC, and as assistant surgeon general in the U.S. Public Health Service. In 2001 she went to her current position at Emory University, directing a center focused on emerging infectious disease and other urgent threats to health, including terrorism. She has also consulted with the biologic program of the Nuclear Threat Initiative and is most recognized for her work in infectious diseases and disease surveillance. She was elected to the IOM in 2004. Currently a member of the Board on Life Sciences of The National Academies, she also chairs the Board of Public and Scientific Affairs at the American Society of Microbiology (ASM).

Enriqueta C. Bond, Ph.D., is president of the Burroughs Wellcome Fund. She received her undergraduate degree from Wellesley College, her M.A. from the University of Virginia, and her Ph.D. in molecular biology and biochemical genetics from Georgetown University. She is a member of the Institute of Medicine, the American Association for the Advancement of Science, the American

Society for Microbiology, and the American Public Health Association. Dr. Bond chairs the Academies' Board on African Science Academy Development and serves on the Report Review Committee for the Academies. She serves on the board and executive committee of the Research Triangle Park Foundation, on the board of the National Institute for Statistical Sciences, on the board of the Northeast Biodefense Center and the New England Center of Excellence in Biodefense and Emerging Infectious Diseases, and on the council of the National Institute of Child Health and Human Development. Prior to being named President of the Burroughs Wellcome Fund in 1994, Dr. Bond served on the staff of the Institute of Medicine since 1979, becoming the Institute's Executive Officer in 1989.

Roger G. Breeze, Ph.D., received his veterinary degree in 1968 and his Ph.D. in veterinary pathology in 1973, both from the University of Glasgow, Scotland. He was engaged in teaching, diagnostic pathology, and research on respiratory and cardiovascular diseases at the University of Glasgow Veterinary School from 1968 to 1977 and at Washington State University College of Veterinary Medicine from 1977 to 1987, where he was professor and chair of the Department of Microbiology and Pathology. From 1984 to 1987 he was deputy director of the Washington Technology Center, the state's high-technology sciences initiative, based in the College of Engineering at the University of Washington. In 1987, he was appointed director of the U.S. Department of Agriculture's (USDA's) Plum Island Animal Disease Center, a biosafety level 3 facility for research and diagnosis of the world's most dangerous livestock diseases. In that role he initiated research into the genomic and functional genomic basis of disease pathogenesis, diagnosis, and control of livestock RNA and DNA virus infections. This work became the basis of U.S. defense against natural and deliberate infection with these agents and led to his involvement in the early 1990s in biological weapons defense and proliferation prevention. From 1995 to 1998, he directed research programs in 20 laboratories in the Southeast for the USDA Agricultural Research Service before going to Washington, DC, to establish biological weapons defense research programs for USDA. He received the Distinguished Executive Award from President Clinton in 1998 for his work at Plum Island and in biodefense. Since 2004 he has been chief executive officer of Centaur Science Group, which provides consulting services in biodefense. His main commitment is to the Defense Threat Reduction Agency's Biological Weapons Proliferation Prevention program in Europe, the Caucasus, and Central Asia.

Steven J. Brickner, Ph.D., is a research fellow in antibacterials chemistry at Pfizer Global Research and Development in Groton, CT. He graduated from Miami University (Ohio) with a B.S. in chemistry with honors, and received his M.S. and Ph.D. degrees in organic chemistry from Cornell University. He was a National Institutes of Health postdoctoral research fellow at the University of Wisconsin, Madison. Dr. Brickner is a medicinal chemist with 25 years of

research experience in the pharmaceutical industry, all focused on the discovery of novel antibacterial agents. He is an inventor/co-inventor on 21 U.S. patents, and has published numerous scientific papers within the areas of oxazolidinones and novel azetidinones. Dr. Brickner has been a member of the Forum on Microbial Threats at the Institute of Medicine (National Academy of Sciences) since 1997, and is a member of the editorial advisory board for *Current Pharmaceutical Design*. Dr. Brickner initiated the oxazolidinone research program at Upjohn, led the team that discovered Zyvox® (linezolid), and is a co-inventor of this antibiotic used to treat multi-drug resistant Gram-positive infections. Zyvox® is the first member of *any* entirely new class of antibiotics to reach the market in over 35 years since the quinolones. He is a co-recipient of the 2007 American Chemical Society Team Innovation Award and the Pharmaceutical Research and Manufacturers of America's 2007 Discoverers Award. He was named the 2002-2003 Outstanding Alumni Lecturer, College of Arts and Science, Miami University (Ohio).

Gail H. Cassell, Ph.D., is currently vice president, Scientific Affairs, and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company in Indianapolis, Indiana. She is the former Charles H. McCauley Professor and Chairman of the Department of Microbiology at the University of Alabama Schools of Medicine and Dentistry at Birmingham, a department which ranked first in research funding from the National Institutes of Health during the decade of her leadership. She obtained her B.S. from the University of Alabama in Tuscaloosa and in 1993 was selected as one of the top 31 female graduates of the 20th century. She obtained her Ph.D. in microbiology from the University of Alabama at Birmingham and was selected as its 2003 Distinguished Alumnus. She is a past president of the American Society for Microbiology (the oldest and single largest life sciences organization with a membership of over 42,000). She was a member of the National Institutes of Health Director's Advisory Committee and a member of the Advisory Council of the National Institute of Allergy and Infectious Diseases of NIH. She was named to the original Board of Scientific Councilors of the Center for Infectious Diseases, Centers for Disease Control and served as chair of the Board. She recently served a 3-year term on the Advisory Board of the Director of the Centers for Disease Control and as a member of the Secretary of Health and Human Services Advisory Council of Public Health Preparedness. Currently she is a member of the Science Board of the Federal Food and Drug Administration Advisory Committee to the Commissioner. Since 1996 she has been a member of the U.S.–Japan Cooperative Medical Science Program responsible for advising the respective governments on joint research agendas (U.S. State Department/Japan Ministry of Foreign Affairs). She has served on several editorial boards of scientific journals and has authored over 250 articles and book chapters. Dr. Cassell has received national and international awards and an honorary degree for her research in infectious diseases. She is a member of the

Institute of Medicine (IOM) of the National Academy of Sciences and is currently serving a 3-year term on the IOM Council, the governing board. Dr. Cassell has been intimately involved in establishment of science policy and legislation related to biomedical research and public health. For 9 years she was chairman of the Public and Scientific Affairs Board of the American Society for Microbiology; has served as an advisor on infectious diseases and indirect costs of research to the White House Office of Science and Technology Policy, and has been an invited participant in numerous congressional hearings and briefings related to infectious diseases, anti-microbial resistance, and biomedical research. She has served two terms on the LCME, the accrediting body for U.S. medical schools, as well as other national committees involved in establishing policies in training in the biomedical sciences. She has just completed a term on the Leadership Council of the School of Public Health of Harvard University. Currently, she is a member of the Executive Committee of the Board of Visitors of Columbia University School of Medicine, the Board of Directors of the Burroughs Wellcome Fund, and the Advisory Council of the School of Nursing of Johns Hopkins.

Bill Colston, Ph.D., is the Division Leader for the Chemical and Biological Countermeasures (CB) Division for the Global Security (GS) Principal Directorate at Lawrence Livermore National Laboratory. The newly formed CB Division is comprised of about 190 scientists from a variety of disciplines. The mission of this division is to provide national policy support, threat characterization, biological detection, chemical and explosives detection, instrumentation and systems development, decontamination and restoration, forensics and attribution, Biodefense Knowledge Center products, and incident response support operations. Prior to this assignment he held the positions of founding director of the Department of Homeland Security Biodefense Knowledge Center (BKC) and deputy program leader for the Chemical and Biological Security Program. Dr. Colston holds a Ph.D. from the University of California, Davis in biomedical engineering. He has published over 40 publications in scientific literature, holds over 15 patents related to medical diagnostics and imaging devices, and has received three different R&D 100 Awards. His research interests are mainly focused on molecular characterization of infectious disease, with direct relevance to new diagnostic devices.

Col. Ralph (Loren) Erickson, M.D., M.P.H., Dr.P.H., is the director of the Department of Defense Global Emerging Infections Surveillance and Response System (DoD-GEIS) headquartered in Silver Spring, Maryland. He holds a B.S. degree in chemistry from the University of Washington, an M.D. from the Uniformed Services University of the Health Sciences, an M.P.H. from Harvard, and a Dr.P.H. from Johns Hopkins. Residency trained and board certified in preventive medicine, Dr. Erickson has held a number of leadership positions within the Army Medical Department including: director of the General Preventive

Medicine Residency Program, Walter Reed Army Institute of Research; director of Epidemiology and Disease Surveillance, U.S. Army Center for Health Promotion and Preventive Medicine; commander of the U.S. Army Center for Health Promotion and Preventive Medicine (Europe); and specialty leader for all U.S. Army preventive medicine physicians.

Mark Feinberg, M.D., Ph.D., is vice president for medical affairs and policy in global vaccine and infectious diseases at Merck & Co., Inc., and is responsible for global efforts to implement vaccines to achieve the greatest health benefits including efforts to expand access to new vaccines in the developing world. Dr. Feinberg's received a bachelor's degree *magna cum laude* from the University of Pennsylvania in 1978, and his M.D. and Ph.D. degrees from Stanford University School of Medicine in 1987. His Ph.D. research at Stanford was supervised by Dr. Irving Weissman and included time spent studying the molecular biology of the human retroviruses—HTLV-I and HIV—as a visiting scientist in the laboratory of Dr. Robert Gallo at the National Cancer Institute. From 1985 to 1986, Dr. Feinberg served as a project officer for the Committee on a National Strategy for AIDS of the Institute of Medicine and the National Academy of Sciences. Following receipt of his M.D. and Ph.D. degrees, Dr. Feinberg pursued postgraduate residency training in internal medicine at the Brigham and Women's Hospital of Harvard Medical School and postdoctoral fellowship research in the laboratory of Dr. David Baltimore at the Whitehead Institute for Biomedical Research. From 1991 to 1995, Dr. Feinberg was an assistant professor of medicine and microbiology and immunology at the University of California, San Francisco, where he also served as an attending physician in the AIDS/oncology division and as director of the virology research laboratory at San Francisco General Hospital. From 1995 to 1997, Dr. Feinberg was a medical officer in the Office of AIDS Research in the Office of the Director of the National Institutes of Health, the chair of the NIH Coordinating Committee on AIDS Etiology and Pathogenesis Research, and an attending physician at the NIH Clinical Center. During this period, he also served as executive secretary of the NIH Panel to Define Principles of Therapy of HIV Infection. Prior to joining Merck in 2004, Dr. Feinberg served as professor of medicine and microbiology and immunology at the Emory University School of Medicine, as an investigator at the Emory Vaccine Center and as an attending physician at Grady Memorial Hospital. At UCSF and Emory, Dr. Feinberg and colleagues were engaged in the preclinical development and evaluation of novel vaccines for HIV and other infectious diseases, and in basic research studies focused on revealing fundamental aspects of the pathogenesis of AIDS. Dr. Feinberg also founded and served as the medical director of the Hope Clinic of the Emory Vaccine Center—a clinical research facility devoted to the clinical evaluation of novel vaccines and to translational research studies of human immune system biology. In addition to his other professional roles, Dr. Feinberg has also served as a consultant to, and a member of, several committees of the

Institute of Medicine and the National Academy of Sciences. Dr. Feinberg currently serves as a member of the National Vaccine Advisory Committee (NVAC) and is a member of the Board of Trustees of the National Foundation for Infectious Diseases (NFID). Dr. Feinberg has earned board certification in internal medicine, is a fellow of the American College of Physicians, a member of the Association of American Physicians, and the recipient of an Elizabeth Glaser Scientist Award from the Pediatric AIDS Foundation and an Innovation in Clinical Research Award from the Doris Duke Charitable Foundation.

J. Patrick Fitch, Ph.D., is laboratory director for the National Biodefense Analysis and Countermeasures Center (NBACC) and the president of Battelle National Biodefense Institute, LLC (BNBI). BNBI manages and operates the NBACC national laboratory for the Department of Homeland Security as a Federally Funded Research and Development Center established in 2006. The NBACC mission is to provide the nation with the scientific basis for awareness of biological threats and attribution of their use against the American public. Dr. Fitch joined Battelle in 2006 as vice president for Biodefense Programs after more than 20 years of experience leading multidisciplinary applied-science teams at the University of California's Lawrence Livermore National Laboratory (LLNL). From 2001 to 2006, he led the LLNL Chemical and Biological National Security Program (CBNP), with applied science programs from pathogen biology to deployed systems. CBNP accomplishments include performing more than 1 million assays on national security samples; setting up and operating 24/7 reach-back capabilities; setting up a nationwide bioalert system; receiving three R&D 100 awards; designing signatures for validated assays in the CDC Laboratory Response Network and the National Animal Health Laboratory Network; and designing. His advisory board activities have included the U.S. Animal Health Association, Texas A&M University DHS Center of Excellence, Central Florida University (College of Engineering), Colorado State University (College of Engineering), California State Breast Cancer Research Program, and *Biomolecular Engineering*. Dr. Fitch was a fellow of the American Society for Laser Medicine and Surgery and an associate editor of *Circuits, Systems and Signal Processing*. He has received two national awards for medical devices, a technical writing award for an article in *Science*, and an international best paper award from the Institute of Electrical and Electronics Engineers. He also coinvented the technology, developed the initial business plan, and successfully raised venture investments for a medical device start-up company. Dr. Fitch received his Ph.D. from Purdue University and B.S. from Loyola College of Maryland.

Capt. Darrell R. Galloway, M.S.C., Ph.D., is chief of the Medical Science and Technology Division for the Chemical and Biological Defense Directorate at the Defense Threat Reduction Agency. He received his baccalaureate degree in microbiology from California State University in Los Angeles in 1973. After

completing military service in the U.S. Army as a medical corpsman from 1969 to 1972, Captain Galloway entered graduate school and completed a doctoral degree in biochemistry in 1978 from the University of California, followed by 2 years of postgraduate training in immunochemistry as a fellow of the National Cancer Institute at the Scripps Clinic and Research Foundation in La Jolla, California. Captain Galloway began his Navy career at the Naval Medical Research Institute in Bethesda, Maryland, where from 1980 to 1984 he served as a research scientist working on vaccine development. In late 1984 Captain Galloway left active service to pursue an academic appointment at Ohio State University, where he is now a tenured faculty member in the Department of Microbiology. He also holds appointments at the University of Maryland Biotechnology Institute and the Uniformed Services University of Health Sciences. He has an international reputation in the area of bacterial toxin research and has published more than 50 research papers on various studies of bacterial toxins. In recent years Captain Galloway's research has concentrated on anthrax and the development of DNA-based vaccine technology. His laboratory has contributed substantially to the development of a new DNA-based vaccine against anthrax that has completed the first phase of clinical trials. Captain Galloway is a member of the ASM and has served as president of the Ohio branch of that organization. He received an NIH Research Career Development Award. In 2005 Captain Galloway was awarded the Joel M. Dalrymple Award for significant contributions to biodefense vaccine development.

S. Elizabeth George, Ph.D., is deputy director, Biological Countermeasures Portfolio Science and Technology Directorate, Department of Homeland Security (DHS). Until merging into the new department in 2003, she was program manager of the Chemical and Biological National Security Program in the Department of Energy's National Nuclear Security Administration's Office of Nonproliferation Research and Engineering. Significant accomplishments include the design and deployment of BioWatch, the nation's first civilian biological threat agent monitoring system, and PROTECT, the first civilian operational chemical detection and response capability deployed in the Washington, DC.area subway system. Previously, she spent 16 years at the U.S. Environmental Protection Agency (EPA), Office of Research and Development, National Health and Ecological Effects Research Laboratory, Environmental Carcinogenesis Division, where she was branch chief of the Molecular and Cellular Toxicology Branch. She received her B.S. in biology in 1977 from Virginia Polytechnic Institute and State University and her M.S. and Ph.D. in microbiology in 1979 and 1984, respectively, from North Carolina State University. From 1984 to 1986, she was a National Research Council fellow in the laboratory of Dr. Larry Claxton at EPA. Dr. George is the 2005 chair of the Chemical and Biological Terrorism Defense Gordon Research Conference. She has served as councilor for the Environmental Mutagen Society and president and secretary of the Genotoxicity and Environmental Mutagen

Society. She holds memberships in the ASM and the AAAS and is an adjunct faculty member in the School of Rural Public Health, Texas A&M University. She is a recipient of the EPA Bronze Medal and Scientific and Technological Achievement Awards and DHS Under Secretary's Award for Science and Technology. She is author of numerous journal articles and has presented her research at national and international meetings.

Jesse L. Goodman, M.D., M.P.H., is director of the FDA's Center for Biologics Evaluation and Research (CBER), which oversees medical, public health, and policy activities concerning the development and assessment of vaccines, blood products, tissues, and related devices and novel therapeutics, including cellular and gene therapies. He moved full-time to the FDA in 2001 from the University of Minnesota, where he was professor of medicine and director of the Division of Infectious Diseases. A graduate of Harvard College, he received his M.D. at the Albert Einstein College of Medicine, did residency and fellowship training at the Hospital of the University of Pennsylvania and at the University of California, Los Angeles (UCLA), where he was also chief medical resident, and is board certified in internal medicine, oncology, and infectious diseases. He trained in the virology laboratory of Jack Stevens at UCLA and has had an active laboratory program in the molecular pathogenesis of infectious diseases. In 1995 his laboratory isolated the etiologic agent of human granulocytic ehrlichiosis (HGE) and subsequently characterized fundamental events involved in infection of leukocytes, including their cellular receptors. He is editor of the book *Tick Borne Diseases of Humans* published by ASM Press in 2005 and is a staff physician and infectious diseases consultant at the NIH Clinical Center and the National Naval Medical Center/Walter Reed Army Medical Center, as well as adjunct professor of medicine at the University of Minnesota. He is active in a wide variety of clinical, public health, and product development issues, including pandemic and emerging infectious disease threats, bioterrorism preparedness and response, and blood, tissue, and vaccine safety and availability. In these activities, he has worked closely with the CDC, NIH, and other HHS components, academia, and the private sector, and he has put into place an interactive team approach to emerging threats. This model was used in the collaborative development and rapid implementation of nationwide donor screening of the U.S. blood supply for West Nile virus. He has been elected to the American Society for Clinical Investigation (ASCI) and to the IOM.

Eduardo Gotuzzo, M.D., is principal professor and director at the Instituto de Medicina Tropical "Alexander von Humbolt," Universidad Peruana Cayetan Heredia in Lima, Peru, as well as chief of the Department of Infectious and Tropical Diseases at the Cayetano Heredia Hospital. He is also an adjunct professor of medicine at the University of Alabama, Birmingham School of Medicine. Dr. Gotuzzo is an active member in numerous international societies and has

been president of the Latin America Society of Tropical Disease (2000-2003), the IDSA Scientific Program (2000-2003), the International Organizing Committee of the International Congress of Infectious Diseases (1994 to present), president-elect of the International Society for Infectious Diseases (1996-1998), and president of the Peruvian Society of Internal Medicine (1991-1992). He has published more than 230 articles and chapters as well as six manuals and one book. Recent honors and awards include being named an honorary member of the American Society of Tropical Medicine and Hygiene in 2002, associate member of the National Academy of Medicine in 2002, honorary member of the Society of Internal Medicine in 2000, and distinguished visitor at the Faculty of Medical Sciences, University of Cordoba, Argentina, in 1999. In 1988 he received the Golden Medal for Outstanding Contribution in the Field of Infectious Diseases awarded by Trnava University, Slovakia.

Jo Handelsman, Ph.D., received her Ph.D. in molecular biology from the University of Wisconsin, Madison (UW-M) in 1984 and joined the faculty of the UW-M Department of Plant Pathology in 1985, where she is currently a Howard Hughes Medical Institute (HHMI) professor. Her research focuses on the genetic and functional diversity of microorganisms in soil and insect gut communities. The Handelsman lab has concentrated on discovery and biological activity of novel antibiotics from cultured and uncultured bacteria and has contributed to the pioneering of a new technique called metagenomics that facilitates the genomic analysis of assemblages of uncultured microorganisms. Handelsman is studying the mid-gut of the gypsy moth to understand the basis for resistance and susceptibility of microbial communities to invasion, developing it as a model for the microbial community in the human gut. In addition to her passion for understanding the secret lives of bacteria, Dr. Handelsman is dedicated to improving science education and the advancement of women in research universities. She is director of the HHMI New Generation Program for Scientific Teaching, which is dedicated to teaching graduate and postdoctoral students the principles and practices of teaching and mentoring. She is co-director of The National Academies Summer Institute for Undergraduate Education in Biology, a collaborative venture between HHMI and The National Academies that aims to train a nationwide network of faculty who are outstanding teachers and mentors. Dr. Handelsman is co-director of the Women in Science and Engineering Leadership Institute at UW-M, whose mission is to understand the impediments to the successful recruitment and advancement of women faculty in the sciences and to develop and study interventions intended to reduce those barriers.

Carole A. Heilman, Ph.D., is the director of the Division of Microbiology and Infectious Diseases (DMID), at the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH)/ U.S. Department of Health and Human Services (HHS). As Director of DMID

she has responsibility for scientific direction, oversight, and management of all extramural research programs on infectious diseases (except AIDS) within the NIH. In addition, since 2001 Dr. Heilman has played a critical role in launching and directing NIAID's extramural biodefense research program. Previously, Dr. Heilman served as deputy director of NIAID's Division of AIDS for 3 years. Dr. Heilman has a Ph.D. in microbiology from Rutgers University. She did her post-doctoral work in molecular virology at the National Cancer Institute, and continued at the NCI as a senior staff fellow in molecular oncology. She moved into health science administration in 1986, focusing on respiratory pathogens, particularly vaccine development. She has received numerous awards for scientific management and leadership, including three HHS Secretary's Awards for Distinguished Service for her contributions to developing pertussis, biodefense, and AIDS vaccines.

David L. Heymann, M.D., is currently the executive director of the WHO Communicable Diseases Cluster. From October 1995 to July 1998, he was director of the WHO Programme on Emerging and Other Communicable Diseases Surveillance and Control. Prior to becoming director of this program, he was the chief of research activities in the Global Programme on AIDS. From 1976 to 1989, prior to joining WHO, Dr. Heymann spent 13 years working as a medical epidemiologist in sub-Saharan Africa (Cameroon, Ivory Coast, the former Zaire, and Malawi) on assignment from CDC in CDC-supported activities aimed at strengthening capacity in surveillance of infectious diseases and their control, with special emphasis on childhood immunizable diseases, African hemorrhagic fevers, pox viruses, and malaria. While based in Africa, he participated in the investigation of the first outbreak of Ebola in Yambuku in the former Zaire in 1976, then investigated the second outbreak of Ebola in 1977 in Tandala, and in 1995 directed the international response to the Ebola outbreak in Kikwit. Prior to 1976, Dr. Heymann spent 2 years in India as a medical officer in the WHO Smallpox Eradication Programme. He holds a B.A. from Pennsylvania State University, an M.D. from Wake Forest University, and a Diploma in Tropical Medicine and Hygiene from the London School of Hygiene and Tropical Medicine. He has also completed practical epidemiology training in CDC's Epidemic Intelligence Service training program. He has published 131 scientific articles on infectious diseases in peer-reviewed medical and scientific journals.

Phil Hosbach is vice president of New Products and Immunization Policy at Sanofi Pasteur. The departments under his supervision are new product marketing, state and federal government policy, business intelligence, bids and contracts, medical communications, public health sales, and public health marketing. His current responsibilities include oversight of immunization policy development. He acts as Sanofi Pasteur's principal liaison with CDC. Mr. Hosbach graduated

from Lafayette College in 1984 with a degree in biology. He has 20 years of pharmaceutical industry experience, including the past 17 years focused solely on vaccines. He began his career at American Home Products in Clinical Research in 1984. He joined Aventis Pasteur (then Connaught Labs) in 1987 as clinical research coordinator and has held research and development positions of increasing responsibility, including clinical research manager and director of clinical operations. Mr. Hosbach also served as project manager for the development and licensure of Tripedia, the first diphtheria, tetanus, and acellular pertussis (DTaP) vaccine approved by the FDA for use in U.S. infants. During his clinical research career at Aventis Pasteur, he contributed to the development and licensure of seven vaccines and has authored or co-authored several clinical research articles. From 2000 through 2002, Mr. Hosbach served on the board of directors for Pocono Medical Center in East Stroudsburg, Pennsylvania. Since 2003 he has served on the board of directors of Pocono Health Systems, which includes Pocono Medical Center.

James M. Hughes, M.D., is professor of medicine and public health at Emory University's School of Medicine and Rollins School of Public Health, serving as director of the Emory program in Global Infectious Diseases, associate director of the Southeastern Center for Emerging Biological Threats, and senior advisor to the Emory Center for Global Safe Water. He also serves as senior advisor for Infectious Diseases to the International Association of National Public Health Institutes funded by the Bill and Melinda Gates Foundation. Before joining Emory in April 2005, Dr. Hughes served as Director of the National Center for Infectious Diseases (NCID) at the Centers for Disease Control and Prevention (CDC). Dr. Hughes received his B.A. and M.D. degrees from Stanford University and completed postgraduate training in internal medicine, infectious diseases, and preventive medicine. After joining CDC in 1973, Dr. Hughes worked initially on foodborne and waterborne diseases and subsequently on infection control in healthcare settings. He served as director of CDC's Hospital Infections Program from 1983 to 1988, as deputy director of NCID from 1988 to 1992, and as director of NCID from 1992 to 2005. A major focus of Dr. Hughes' career has been on building partnerships among the clinical, research, public health, and veterinary communities to prevent and respond to global infectious diseases. His research interests include identifying factors contributing to the emergence and reemergence of infectious diseases, with a focus on vectorborne and zoonotic diseases, water-related diseases, and antimicrobial resistance; evaluating policies and practices for preventing, rapidly detecting, and responding to infectious diseases; and assessing approaches to strengthening global capacity to address microbial threats. Dr. Hughes is a member of the Institute of Medicine (IOM) and the Council of the American Society of Tropical Medicine and Hygiene (ASTMH).

Stephen A. Johnston, Ph.D., is currently director of the Center for Innovations in Medicine in the Biodesign Institute at Arizona State University. His center focuses on formulating and implementing disruptive technologies for basic problems in health care. The center has three divisions: Genomes to Vaccines, Cancer Eradication, and DocInBox. The Genomes to Vaccines group has developed high-throughput systems to screen for vaccine candidates and is applying them to predict and produce chemical vaccines. The Cancer Eradication group is working on formulating a universal prophylactic vaccine for cancer. The DocInBox group is developing technologies to facilitate presymptomatic diagnosis. Dr. Johnston founded the Center for Biomedical Inventions (a.k.a., Center for Translation Research) at the University of Texas, Southwestern, the first center of its kind in the medical arena. He and his colleagues have developed numerous inventions and innovations, including the gene gun, genetic immunization, TEV protease system, organelle transformation, digital optical chemistry arrays, expression library immunization, linear expression elements, and others. He also was involved in transcription research for years, first cloning Gal4, then later discovering functional domains in transcription factors and the connection of the proteasome to transcription. He has been professor at the University of Texas Southwestern Medical Center at Dallas and associate and assistant professor at Duke University. He has been involved in several capacities as an advisor on biosecurity since 1996 and is a member of the WRCE SAB and a founding member of BioChem 20/20.

Gerald T. Keusch, M.D., is associate provost and associate dean for global health at Boston University and Boston University School of Public Health. He is a graduate of Columbia College (1958) and Harvard Medical School (1963). After completing a residency in internal medicine, fellowship training in infectious diseases, and 2 years as an NIH research associate at the Southeast Asia Treaty Organization (SEATO) Medical Research Laboratory in Bangkok, Thailand, Dr. Keusch joined the faculty of the Mt. Sinai School of Medicine in 1970, where he established a laboratory to study the pathogenesis of bacillary dysentery and the biology and biochemistry of Shiga toxin. In 1979 he moved to Tufts Medical School and New England Medical Center in Boston to found the Division of Geographic Medicine, which focused on the molecular and cellular biology of tropical infectious disease. In 1986 he integrated the clinical infectious diseases program into the Division of Geographic Medicine and Infectious Diseases, continuing as division chief until 1998. He has worked in the laboratory and in the field in Latin America, Africa, and Asia on basic and clinical infectious diseases and HIV/AIDS research. From 1998 to 2003, he was associate director for international research and director of the Fogarty International Center at NIH. Dr. Keusch is a member of ASCI, the Association of American Physicians, the ASM, and the IDSA. He has received the Squibb (1981), Finland (1997), and Bristol (2002) awards of the IDSA. In 2002 he was elected to the IOM.

Rima F. Khabbaz, M.D., is director of the National Center for Preparedness, Detection, and Control of Infectious Diseases at CDC. She became director of the National Center for Infectious Diseases (NCID) at CDC in December 2005 and led its transition to the current centers. She is a graduate of the American University of Beirut, Lebanon, where she obtained both her bachelor's degree in science and her medical doctorate degree. She trained in internal medicine and completed a fellowship in infectious diseases at the University of Maryland in Baltimore. She is also a clinical associate professor of medicine (infectious diseases) at Emory University. She began her CDC career in 1980 as an epidemic intelligence service officer in the Hospital Infections Program. She later served as a medical epidemiologist in CDC's Retrovirus Diseases Branch where she made major contributions to defining the epidemiology of non-HIV retroviruses (human T lymphotropic viruses [HTLV] I and II) in the United States and developing guidance for counseling HTLV-infected persons. Following the hantavirus pulmonary syndrome outbreak in the southwestern United States in 1993, she led CDC's efforts to set up national surveillance for the syndrome. Prior to becoming director of NCID, she was acting deputy director of the Center, and before that associate director for epidemiologic science, NCID. Additional positions held at CDC include associate director for science and deputy director of the Division of Viral and Rickettsial Diseases. She played a leading role in developing CDC's blood safety programs and CDC's food safety programs related to viral diseases. She also had a key role in CDC's responses to outbreaks of new and/or reemerging viral infections including Nipah, Ebola, West Nile, SARS, and monkeypox. She led the CDC's field team to the nation's capital during the public health response to the anthrax attack of 2001. She is a fellow of the Infectious Diseases Society of America (IDSA), a member of the American Epidemiologic Society, the American Society for Microbiology, and the Council of State and Territorial Epidemiologists. She served on the Blood Product Advisory Committee of the Food and Drug Administration (FDA) and on FDA's Transmissible Spongiform Encephalopathy Advisory Committee. She also served on IDSA's Annual Meeting Scientific Program Committee, and serves on the society's National and Global Public Health Committee. She is a graduate of the National Preparedness Leadership Initiative at Harvard University and of the Public Health Leadership Institute at the University of North Carolina.

Lonnie J. King, D.V.M., is currently the director of CDC's new National Center for Zoonotic, Vector-Borne, and Enteric Diseases (NCZVED). Dr. King leads the center's activities for surveillance, diagnostics, disease investigations, epidemiology, research, public education, policy development, and disease prevention and control programs. NCZVED also focuses on waterborne, foodborne, vector-borne, and zoonotic diseases of public health concern, which also includes most of CDC's select and bioterrorism agents, neglected tropical diseases, and emerging zoonoses. Before serving as director, he was the first chief of the

agency's Office of Strategy and Innovation. In 1996 Dr. King was appointed dean of the College of Veterinary Medicine, Michigan State University. He served for 10 years as dean of the college. As dean, he was the chief executive officer for academic programs, research, the teaching hospital, diagnostic center for population and animal health, basic and clinical science departments, and outreach and continuing education programs. As dean and professor of large animal clinical sciences, Dr. King was instrumental in obtaining funds for the construction of the $60 million Diagnostic Center for Population and Animal Health, initiated the Center for Emerging Infectious Diseases in the college, served as the campus leader in food safety, and had oversight for the National Food Safety and Toxicology Center. He brought the Center for Integrative Toxicology to the college and was the university's designated leader for counterbioterrorism activities for his college. Prior to this, Dr. King was administrator for USDA's Animal and Plant Health Inspection Service (APHIS). Dr. King served as the country's chief veterinary officer for 5 years and worked extensively in global trade agreements within the North American Free Trade Agreement and the World Trade Organization. Before beginning his government career in 1977, he was in private veterinary practice for 7 years in Dayton, Ohio, and in Atlanta, Georgia. He received his B.S. and D.V.M. from Ohio State University in 1966 and 1970, respectively. He earned his M.S. in epidemiology from the University of Minnesota while on special assignment with the U.S. Department of Agriculture in 1980. He received his master's in public administration from The American University in Washington, DC in 1991. Dr. King has a broad knowledge of animal agriculture and the veterinary profession through his work with other governmental agencies, universities, major livestock and poultry groups, and private practitioners. Dr. King is a board-certified member of the American College of Veterinary Preventive Medicine and has completed the senior executive fellowship program at Harvard University. He served as president of the Association of American Veterinary Medical Colleges from 1999 to 2000 and was vice chair for the National Commission on Veterinary Economic Issues from 2000 to 2004. Dr. King helped start the National Alliance for Food Safety, served on the Governor's Task Force on Chronic Wasting Disease for the state of Michigan, and was a member of four NAS committees; most recently he chaired The National Academies Committee on Assessing the Nation's Framework for Addressing Animal Diseases. Dr. King is one of the developers of the Science, Politics, and Animal Health Policy Fellowship Program, and he lectures extensively on the future of animal health, emerging zoonoses, and veterinary medicine. He served as a consultant and member of the Board of Scientific Counselors to CDC's National Center for Infectious Diseases, and is a member of the IOM's Forum on Microbial Threats. Dr. King was an editor for the *OIE Scientific Review on Emerging Zoonoses*, is a current member of the FDA's Board of Scientific Advisors, and is president of the American Veterinary Epidemiology Society. Dr. King was elected to the IOM in 2004.

Col. George W. Korch, Ph.D., is commander, U.S. Army Medical Research Institute for Infectious Diseases, Ft. Detrick, Maryland. Dr. Korch attended Boston University and earned a B.S. in biology in 1974, followed by postgraduate study in mammalian ecology at the University of Kansas from 1975 to 1978. He earned his Ph.D. from the Johns Hopkins School of Hygiene and Public Health in Immunology and Infectious Diseases in 1985, followed by postdoctoral experience at Johns Hopkins from 1985 to 1986. His areas of training and specialty are the epidemiology of zoonotic viral pathogens and medical entomology. For the past 15 years, he has also been engaged in research and program management for medical defense against biological pathogens used in terrorism or warfare.

Joshua Lederberg, Ph.D.,* is professor emeritus of molecular genetics and informatics and Sackler Foundation Scholar at the Rockefeller University in New York City. His lifelong research, for which he received the Nobel Prize in 1958, has been in genetic structure and function in microorganisms. He has a keen interest in international health and from 1990 to 1992 was co-chair of a previous IOM Committee on Emerging Microbial Threats to Health. Currently he is co-chair of the Committee on Emerging Microbial Threats to Health in the Twenty-First Century. He has been a member of the NAS since 1957 and is a charter member of the IOM.

Lynn Marks, M.D., is senior vice president of Infectious Diseases Medicine Development Center at GlaxoSmithKline. Dr. Marks received his medical degree from the University of South Alabama College of Medicine and is board certified in internal medicine and infectious diseases. He joined SmithKline Beecham in 1993 as associate director and later director, Anti-Infectives Clinical Research, Development, and Medical Affairs. He then moved to the Consumer Healthcare Division where he held the positions of worldwide medical director, Rx to OTC Switch and then, vice president and director, Worldwide Medical, Regulatory, and Toxicology. Later he returned to Pharma as vice president, Global Commercial Strategy, Infectious Diseases and subsequently became senior vice president, Infectious Diseases, Medicine Development Center. Prior to joining industry, Dr. Marks was with the University of South Alabama College of Medicine, where he held the positions of assistant professor of medicine in the Division of Infectious Diseases and adjunct assistant professor in the Department of Microbiology and immunology as well as the Department of Pharmacology. His NIH-supported research centered on the molecular genetics of *Rickettsia*.

Edward McSweegan, Ph.D., is a program officer at the National Institute of Allergy and Infectious Diseases (NIAID). He graduated from Boston College

*Deceased February 2, 2008.

with a B.S. in biology in 1978. He has an M.S. in microbiology from the University of New Hampshire and a Ph.D. in microbiology from the University of Rhode Island. He was a National Research Council Associate from 1984 to 1986 and did postdoctoral research at the Naval Medical Research Institute in Bethesda, Maryland. Dr. McSweegan served as an American Association for the Advancement of Science (AAAS) Diplomacy Fellow in the U.S. State Department from 1986 to 1988 where he helped to negotiate science and technology agreements with Poland, Hungary, and the former Soviet Union. After moving to National Institutes of Health (NIH), he continued to work on international health and infectious disease projects in Egypt, Israel, India, and Russia. Currently, he manages NIAID's bilateral program with India, the Indo-U.S. Vaccine Action Program, and represents NIAID in the HHS Biotechnology Engagement Program with Russia and related countries. He is a member of the AAAS, the American Society for Microbiology, and the National Association of Science Writers. He is the author of numerous journal and freelance articles.

Stephen S. Morse, Ph.D., is founding director of the Center for Public Health Preparedness at the Mailman School of Public Health of Columbia University and is an associate professor in the epidemiology department. He recently returned to Columbia after 4 years in government service as program manager at the Defense Advanced Research Projects Agency (DARPA), where he co-directed the Pathogen Countermeasures Program and subsequently directed the Advanced Diagnostics Program. Before coming to Columbia, he was assistant professor of virology at Rockefeller University in New York, where he remains an adjunct faculty member. He is the editor of two books, *Emerging Viruses* (Oxford University Press, 1993; paperback, 1996), which was selected by *American Scientist* for its list of 100 Top Science Books of the 20th Century, and *The Evolutionary Biology of Viruses* (Raven Press, 1994). He currently serves as a section editor of the CDC journal *Emerging Infectious Diseases* and was formerly an editor-in-chief of the Pasteur Institute's journal *Research in Virology*. Dr. Morse was chair and principal organizer of the 1989 NIAID/NIH Conference on Emerging Viruses, for which he originated the term and concept of *emerging viruses/infections*. He has served as a member of the IOM-NAS Committee on Emerging Microbial Threats to Health, chaired its Task Force on Viruses, and was a contributor to the resulting report, *Emerging Infections* (1992). He was a member of the IOM's Committee on Xenograft Transplantation, and he currently serves on the Steering Committee of the IOM's Forum on Emerging Infections (now the Forum on Microbial Threats). Dr. Morse also served as an adviser to WHO, the Pan-American Health Organization, the FDA, the Defense Threat Reduction Agency, and other agencies. He is a fellow of the New York Academy of Sciences and a past chair of its microbiology section, a Fellow of the American Academy of Microbiology of the American College of Epidemiology, and an elected life member of the Council on Foreign Relations. He was the founding chair of ProMED, the nonprofit inter-

national Program to Monitor Emerging Diseases, and was one of the originators of ProMED-mail, an international network inaugurated by ProMED in 1994 for outbreak reporting and disease monitoring using the Internet. Dr. Morse received his Ph.D. from the University of Wisconsin, Madison.

Michael T. Osterholm, Ph.D., M.P.H., is director of the Center for Infectious Disease Research and Policy and director of the NIH-sponsored Minnesota Center for Excellence in Influenza Research and Surveillance at the University of Minnesota. He is also professor at the School of Public Health and adjunct professor at the Medical School. Previously, Dr. Osterholm was the state epidemiologist and chief of the acute disease epidemiology section for the Minnesota Department of Health. He has received numerous research awards from NIAID and CDC. He served as principal investigator for the CDC-sponsored Emerging Infections Program in Minnesota. He has published more than 300 articles and abstracts on various emerging infectious disease problems and is the author of the best-selling book *Living Terrors: What America Needs to Know to Survive the Coming Bioterrorist Catastrophe*. He is past president of the Council of State and Territorial Epidemiologists. He currently serves on the IOM Forum on Microbial Threats. He has also served on the IOM Committee to Ensure Safe Food from Production to Consumption, the IOM Committee on the Department of Defense Persian Gulf Syndrome Comprehensive Clinical Evaluation Program, and as a reviewer for the IOM report on chemical and biological terrorism.

George Poste, Ph.D., D.V.M., is director of the Biodesign Institute and Del E. Webb Distinguished Professor of Biology at Arizona State University. From 1992 to 1999, he was chief science and technology officer and president, Research and Development of SmithKline Beecham (SB). During his tenure at SB, he was associated with the successful registration of 29 drug, vaccine, and diagnostic products. He is chairman of Orchid Cellmark. He serves on the board of directors of Monsanto and Exelixis. He is a distinguished fellow at the Hoover Institution at Stanford University. He is a member of the Defense Science Board of the U.S. Department of Defense and the Institute of Medicine's Forum on Microbial Threats. Dr. Poste is a board-certified pathologist, a fellow of the Royal Society, and a fellow of the Academy of Medical Sciences. He was awarded the rank of Commander of the British Empire by Queen Elizabeth II in 1999 for services to medicine and for the advancement of biotechnology. He has published more than 350 scientific papers; has co-edited 15 books on cancer, biotechnology, and infectious diseases; and serves on the editorial board of several technical journals.

David A. Relman, M.D., is an associate professor of medicine (infectious diseases and geographic medicine) and of microbiology and immunology at Stanford University School of Medicine, and chief of the infectious disease section at the Veterans Affairs (VA) Palo Alto Health Care System. Dr. Relman received

his B.S. in biology from the Massachusetts Institute of Technology and his M.D. from Harvard Medical School. He completed his residency in internal medicine and a clinical fellowship in infectious diseases at Massachusetts General Hospital, Boston, after which he moved to Stanford for a postdoctoral fellowship in 1986 and joined the faculty there in 1994. His research focus is on understanding the structure and role of the human indigenous microbial communities in health and disease. This work brings together approaches from ecology, population biology, environmental microbiology, genomics, and clinical medicine. A second area of investigation explores the classification structure of humans and nonhuman primates with systemic infectious diseases, based on patterns of genome-wide gene transcript abundance in blood and other tissues. The goals of this work are to understand mechanisms of host-pathogen interaction, as well as predict clinical outcome at early time points in the disease process. His scientific achievements include the description of a novel approach for identifying previously unknown pathogens, the characterization of a number of new human microbial pathogens, including the agent of Whipple's disease, and some of the most in-depth analyses to date of human indigenous microbial communities. Among his other activities, Dr. Relman currently serves as chair of the Board of Scientific Counselors of the National Institute of Dental and Craniofacial Research (NIH), is a member of the National Science Advisory Board for Biosecurity, and advises a number of U.S. government departments and agencies on matters related to pathogen diversity, the future life sciences landscape, and the nature of present and future biological threats. He was co-chair of the Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats for the NAS. He received the Squibb Award from IDSA in 2001, the Senior Scholar Award in Global Infectious Diseases from the Ellison Medical Foundation in 2002, an NIH Director's Pioneer Award in 2006, and a Doris Duke Distinguished Clinical Scientist Award in 2006. He is also a fellow of the American Academy of Microbiology.

Gary A. Roselle, M.D., received his medical degree from the Ohio State University School of Medicine in 1973. He served his residency at the Northwestern University School of Medicine and his infectious diseases fellowship at the University of Cincinnati School of Medicine. He is the program director for infectious diseases for the Department of Veterans Affairs (VA) Central Office in Washington, DC, as well as the chief of the medical service at the Cincinnati VA Medical Center. He is a professor of medicine in the Department of Internal Medicine, Division of Infectious Diseases, at the University of Cincinnati College of Medicine. Dr. Roselle serves on several national advisory committees. In addition, he is currently heading the Emerging Pathogens Initiative for the VA. He has received commendations from the Under Secretary for Health for the VA, and the Secretary of Veterans Affairs for his work in the Infectious Diseases Program

for the VA. He has been an invited speaker at several national and international meetings and has published more than 90 papers and several book chapters.

Janet Shoemaker is director of the ASM's Public Affairs Office, a position she has held since 1989. She is responsible for managing the legislative and regulatory affairs of this 42,000-member organization, the largest single biological science society in the world. She has served as principal investigator for a project funded by the National Science Foundation (NSF) to collect and disseminate data on the job market for recent doctorates in microbiology and has played a key role in ASM projects, including the production of the ASM *Employment Outlook in the Microbiological Sciences* and *The Impact of Managed Care and Health System Change on Clinical Microbiology*. Previously, she held positions as assistant director of public affairs for the ASM, as ASM coordinator of the U.S./U.S.S.R. Exchange Program in Microbiology, a program sponsored and coordinated by the NSF and the U.S. Department of State, and as a freelance editor and writer. She received her baccalaureate, cum laude, from the University of Massachusetts and is a graduate of the George Washington University programs in public policy and in editing and publications. She has served as commissioner to the Commission on Professionals in Science and Technology and as the ASM representative to the ad hoc Group for Medical Research Funding, and she is a member of Women in Government Relations, the American Society of Association Executives, and the AAAS. She has co-authored published articles on research funding, biotechnology, biological weapons control, and public policy issues related to microbiology.

Brian Staskawicz, Ph.D., is professor and chair, Department of Plant and Microbial Biology, University of California, Berkeley. Dr. Staskawicz received his B.A. in biology from Bates College in 1974 and his Ph.D. from the University of California, Berkeley in 1980. Dr. Staskawicz's work has contributed greatly to understanding the molecular interactions between plants and their pathogens. He was elected to the NAS in 1998 for elucidating the mechanisms of disease resistance, as his lab was the first to clone a bacterial effector gene from a pathogen and among the first to clone and characterize plant disease-resistance genes. Dr. Staskawicz's research focuses on the interaction of the bacteria, *Pseudomonas* and *Xanthomonas*, with *Arabidopsis*, tomato, and pepper. He has published extensively in this area and is one of the leading scientists in the world working on elucidating the molecular basis of plant innate immunity.

Terence Taylor is director of the Global Health and Security Initiative and president and director of the International Council for the Life Sciences (ICLS). He is responsible for the overall direction of the ICLS and its programs, which have the goal of enhancing global biosafety and biosecurity. From 1995 to 2005, he

was assistant director of the International Institute for Strategic Studies (IISS), a leading independent international institute, and president and executive director of its U.S. office (2001-2005). He studies international security policy, risk analysis, and scientific and technological developments and their impact on political and economic stability worldwide. At IISS he was one of the Institute's leading experts on issues associated with nuclear, biological, and chemical weapons and their means of delivery. In his previous appointments, he has had particular responsibilities for issues affecting public safety and security in relation to biological risks and advances in the life sciences. He was one of the commissioners to the United Nations Special Commission on Iraq, for which he also conducted missions as a chief inspector. He was a science fellow at the Center for International Security and Cooperation at Stanford University, where he carried out, among other subjects, studies of the implications for government and industry of the weapons of mass destruction treaties and agreements. He has also carried out consultancy work for the International Committee of the Red Cross (ICRC) on the implementation and development of the laws of armed conflict and serves as a member of the editorial board of the *ICRC Review*. He has served as chairman of the World Federation of Scientists' Permanent Monitoring Panel on Risk Analysis. He was a career officer in the British Army on operations in many parts of the world, including counterterrorist operations and UN peacekeeping. His publications include monographs, book chapters, and articles for, among others, Stanford University, the World Economic Forum, Stockholm International Peace Research Institute (SIPRI), the Crimes of War Project, *International Herald Tribune*, *Wall Street Journal*, the *International Defence Review*, the *Independent* (London), *Tiempo* (Madrid), the *International and Comparative Law Quarterly*, the *Washington Quarterly*, and other scholarly journals, including unsigned contributions to IISS publications.

Murray Trostle, Dr.P.H., is a foreign service officer with the United States Agency for International Development (USAID) presently serving as the deputy director of the Avian and Pandemic Influenza Preparedness and Response Unit. Dr. Trostle attended Yale University where he received a master's in public health in 1978 focusing on health services administration. In 1990 he received his doctorate in public health from UCLA. His research involved household survival strategies during famine in Kenya. Dr. Trostle has worked in international health and development for approximately 38 years. He first worked overseas in the Malaysian national malaria eradication program in 1968 and has since focused on health development efforts in the former Soviet Union, Africa, and Southeast Asia. He began his career with USAID in 1992 as a postdoctoral fellow with the AAAS. In his career he has worked with a number of development organizations such as the American Red Cross, Project Concern International, and the Center for Development and Population Activities. With USAID, Dr. Trostle has served

as the director of the child immunization cluster where he was the chairman of the European Immunization Interagency Coordinating Committee and the USAID representative to the Global Alliance on Vaccines and Immunization. Currently Dr. Trostle leads the USAID Infectious Disease Surveillance Initiative as well as his position with the Avian Influenza Unit.