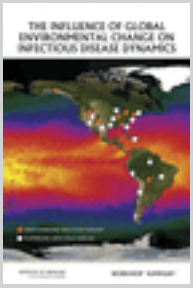

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THE INFLUENCE OF GLOBAL ENVIRONMENTAL CHANGE ON INFECTIOUS DISEASE DYNAMICS

WORKSHOP SUMMARY

Eileen R. Choffnes and Alison Mack, *Rapporteurs*

Forum on Microbial Threats

Board on Global Health

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This workshop summary 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 workshop summary as sound as possible and to ensure that the workshop summary 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 process. We wish to thank the following individuals for their review of this workshop summary:

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop summary before its release. The review of this workshop summary was overseen by **Melvin Worth**. Appointed by the Institute of Medicine, he was responsible for making

certain that an independent examination of this workshop summary was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this workshop summary rests entirely with the rapporteurs and the institution.

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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 regularly meet and examine issues of shared concern regarding research, prevention, detection, and management of emerging, reemerging, and novel infectious diseases in humans, plants, and animals. 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.

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Workshop Overview[1]

THE INFLUENCE OF GLOBAL ENVIRONMENTAL CHANGE ON INFECTIOUS DISEASE DYNAMICS

The twentieth century witnessed an era of unprecedented, large-scale, anthropogenic changes to the natural environment. Many of the planet's natural resources are treated as a "commons," wherein individuals have the right to freely consume its resources and return their wastes to the collective environment. The "logic of the commons" ultimately results in the ruin of the commons as well as the demise of those who depend upon it for survival (Diamond, 2005).

The commons relationship between people and their environment was noted over 40 years ago by ecologist Garrett Hardin in a seminal article published in the journal *Science* (Hardin, 1968). His "tragedy of the commons" has proven to be a useful metaphor for understanding how we have come to be at the brink of numerous environmental catastrophes—whether it be land use, global climate change, or access to uncontaminated and plentiful freshwater resources. Simply stated, we face a serious dilemma—an instance where individual rational behavior, acting without restraint to maximize personal short-term gain—can cause long-range, catastrophic damage to the environment, others, and ultimately to oneself.

The 2003 Institute of Medicine (IOM) report, *Microbial Threats to Health*, identified changing ecosystems; economic development and land use; climate

[1] The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs (with the assistance of Rebekah Hutton, Katherine McClure, and Priyanka Nalamada) as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants and are not necessarily endorsed or verified by the Forum, the Institute of Medicine, or the National Research Council, and they should not be construed as reflecting any group consensus.

and weather; and international travel and commerce as ecological and environmental factors that can influence the emergence and spread of infectious diseases. The last several decades have provided ample evidence of the impact of these factors—individually and synergistically—on the ecology of microbes, vectors, and animal reservoirs; the transmissibility of microbes; and the exposure pathways between microorganisms and new hosts. For example:

- Modern, intensive farming practices in association with trade, travel, and ecological change are implicated in the emergence of diseases including bovine spongiform encephalopathy (mad cow disease), foot-and-mouth disease, and Nipah virus. The livestock disease of greatest contemporary concern for global human health is avian influenza. The size and crowding of flocks found in many poultry farms—an ecosystem that could never exist in nature—creates many opportunities for infectious disease emergence, establishment, and spread.
- The direct movement of people into habitats associated with bushmeat[2] hunting inevitably leads to contact with a wide variety of wild animal species. In Central Africa alone, between 1 and 3.4 million tons of bushmeat are harvested annually. It is likely that bushmeat hunting and the associated trade in wildlife have contributed to the emergence of "novel" infectious diseases such as Ebola and HIV/AIDS.
- Dam building and irrigation projects to "manage" the flow of freshwater resources have been associated with the emergence and spread of infectious diseases including schistosomiasis, malaria, Rift Valley fever, filariasis, leishmaniasis, dracunculiasis, onchocerciasis, and Japanese encephalitis. In the case of schistosomiasis—a parasitic worm disease that causes chronic urinary tract disease and often results in cirrhosis of the liver and bladder cancer—humans become exposed to this parasitic worm as they work or bathe in water infested with schistosoma larvae released by snails. The rise in water levels and change in flow rates that result from dam building may increase the contact between snails and parasites, as well as create fertile soil and sand beds that propagate the development of snails.
- Land use changes such as deforestation and irrigation are often associated with increased incidence of malaria—a disease of global health importance that is responsible for more than 1 million deaths annually. Irrigation projects in India in the 1990s, for example, improved breeding sites for the dominant malaria vector and led to endemic "irrigation" malaria among roughly 200 million people.
- Climate change has been implicated in the emergence of known diseases in new regions. Bluetongue, a midge-borne viral disease of ruminant

[2] Bushmeat is a term commonly applied to meat of terrestrial wild animals, killed for sustenance or commercial purposes throughout the humid tropics of the Americas, Asia, and Africa.

animals, is endemic in tropical and subtropical countries and can cause major morbidity and mortality in sheep. Since 1998, outbreaks of bluetongue in mainland Europe have become common events, moving steadily northward. The disease emerged for the first time in northern Europe in 2006, during the hottest summer on record for that region—following nearly a decade of anomalously warm years. In the summer of 2007, the disease was reported in nine European countries, including the United Kingdom and Denmark, during a massive outbreak that affected tens of thousands of farms.

- International travel and commerce drives the rapid global distribution of microbial pathogens and the organisms that harbor them. These include humans, whose migrations have been implicated in the spread of diseases including, but not limited to, SARS, drug-resistant malaria, and chikungunya (a mosquito-borne viral disease). In 2010, cholera—a disease that had been absent from the island of Haiti for more than 80 years—was brought to Haiti by humanitarian workers from Nepal, who served as United Nations peacekeepers in the aftermath of the island's 2010 earthquake.

Understanding how environmental factors directly and indirectly affect the emergence and spread of infectious disease has assumed global importance for life on this planet. While the causal links between environmental change and disease emergence are complex, progress in understanding these links, as well as how their impacts may vary across space and time, will require transdisciplinary, transnational, collaborative research. This research may draw on the expertise, tools, and approaches from a variety of disciplines. Such research may inform improvements in global readiness and capacity for surveillance, detection, and response to emerging microbial threats to plant, animal, and human health.

Statement of Task

Progress in understanding and addressing the complex causal links between environmental change and disease emergence will require collaborative research that draws on expertise, tools, and approaches from a variety of disciplines. The Forum on Microbial Threats hosted a public workshop on September 24 and 25, 2013, to explore the scientific and policy implications of the impacts of global environmental change on infectious disease emergence, establishment, and spread. Participants examined and discussed the observed and potential influence of environmental factors, acting both individually and in synergy, on infectious disease dynamics, and considered a range of approaches to improve global readiness and capacity for surveillance, detection, and response to emerging microbial threats to plant, animal, and human health in the face of ongoing global environmental change. This meeting served to update two previous Forum workshops, *Infectious Disease Movement in a Borderless World* (IOM, 2010) and *Global Climate*

Change and Extreme Weather Events (IOM, 2008), as well as the aforementioned report *Microbial Threats to Health* (IOM, 2003).

Organization of the Workshop Summary

This workshop summary was prepared by the rapporteurs for the Forum's members and includes a collection of individually authored papers and commentary. The contents of the unattributed sections of this summary report provide a context for the reader to appreciate the presentations and discussions that occurred over the 2 days of this workshop.

The summary is organized into sections as a topic-by-topic description of the presentations and discussions that took place at the workshop. Its purpose is to present information from relevant experience, to delineate a range of pivotal issues and their respective challenges, and to offer differing perspectives on the topic as discussed and described by the workshop participants. Manuscripts and reprinted articles submitted by workshop participants may be found, in alphabetical order by participant, in Appendix A.

Although this workshop summary provides a description of the individual presentations, it also reflects an important aspect of the Forum's philosophy. The workshop functions as a dialogue among representatives from different sectors and allows them to present their views about which areas, in their opinion, merit further study. This report only summarizes the statements of participants over the course of the workshop. This summary is not intended to be an exhaustive exploration of the subject matter, nor does it represent the findings, conclusions, or recommendations of a consensus committee process.

Accelerating Toward Tragedy

> *Although Earth has undergone many periods of significant environmental change, the planet's environment has been unusually stable for the past 10,000 years. This period of stability—known to geologists as the Holocene—has seen human civilizations arise, develop and thrive. Such stability may now be under threat. Since the Industrial Revolution, a new era has arisen, the Anthropocene, in which human actions have become the main driver of global environmental change. This could see human activities push the Earth system outside the stable environmental state of the Holocene, with consequences that are detrimental or even catastrophic for large parts of the world.*
>
> —Rockström et al., 2009a

Mounting scientific evidence supports the proposition that the rise of industrialization in the nineteenth century ushered in a new geological epoch, the Anthropocene (Autin and Holbrook, 2012; Revkin, 2011; Steffen et al., 2011; Zalasiewicz, 2008). First coined by biologist Eugene Stoermer and championed

by atmospheric chemist and Nobel laureate Paul Crutzen, the term *Anthropocene*—which has yet to achieve formal acceptance—marks the advent of humankind as an agent of global change. Researchers studying how humans influence the global environment have noted a sharp increase in anthropogenic, environmental impacts in the post–World War II era, a period they have named the "Great Acceleration" (Steffen et al., 2011). Figure WO-1 illustrates a range of social and economic indicators from the beginning of the Industrial Revolution to the beginning of the new millennium—each of which undergoes a dramatic shift around 1950.

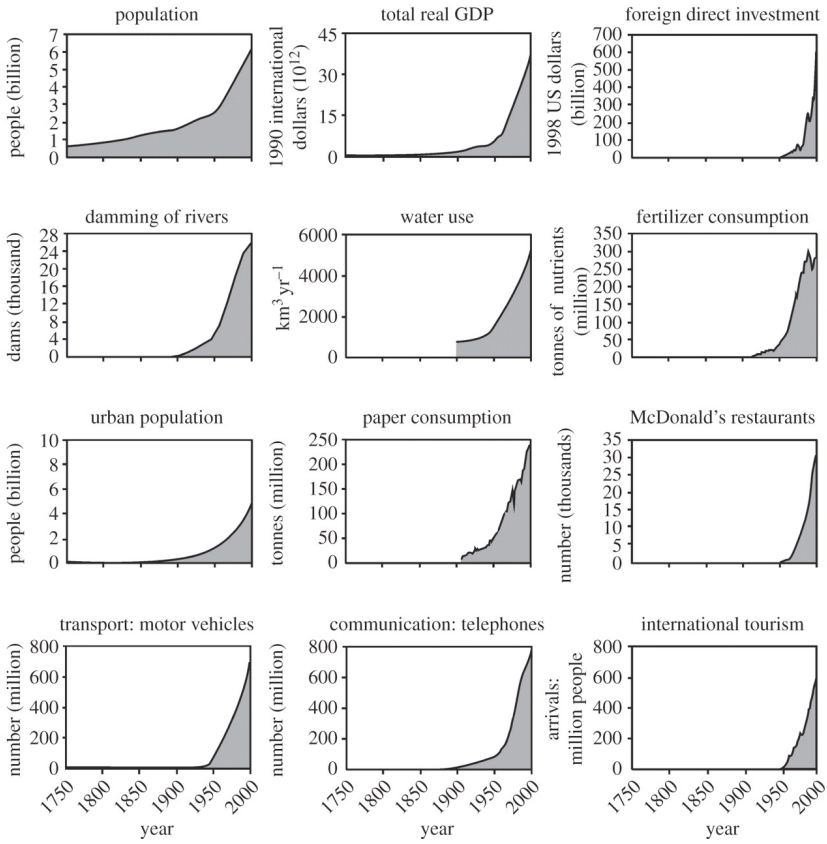

FIGURE WO-1 The increasing rates of change in human activity since the beginning of the Industrial Revolution. Significant increases in rates of change occur around the 1950s in each case and illustrate how the past 50 years have been a period of dramatic and unprecedented change in human history. From Steffen et al. (2004), including references to the individual databases on which the individual figures are based.
SOURCE: Steffen et al., 2011.

According to Steffen and coauthors (2011),

> [o]ne of the most dramatic trends of the past half-century has been the widespread abandonment of the farm and the village for a life in the city. Over half of the human population—over three billion people—now live in urban areas, with the fraction continuing to rise. Migration to cities usually brings with it rising expectations and eventually rising incomes, which in turn brings an increase in consumption, forming yet another driver for the Great Acceleration.

A similar suite of indicators, presented in Figure WO-2, reveals the wide-scale, global effects of human activity during the same time period, including rising atmospheric greenhouse gas concentrations, conversion of natural ecosystems to human-dominated landscapes, increasing reactive nitrogen in the environment (due to the use of fertilizers), and dramatic global loss of species biodiversity. The recent, rapid development of populous countries such as Brazil, China, and India is further spurring the Great Acceleration.

Fueled as it is by Earth's finite resources, the Great Acceleration cannot last forever. How close we are to collapse is a matter of considerable debate. What is clear is that the global environment has been rapidly and drastically altered by human activities at a scope and scale that is unprecedented in geologic time. Rockström and coworkers (2009a) have defined several biophysical thresholds that, if crossed, could be catastrophic for sustaining life as we know it on this planet (see Figure WO-3 and Table WO-1), including climate change, biodiversity loss, and the use of land and water. The authors emphasize those planetary systems underlying key thresholds may respond in nonlinear ways to environmental change, and that these systems are also tightly coupled. "If one boundary is transgressed, then other boundaries are also under serious risk," they warn.

Ecosystems and Disease Dynamics

> *Energy, food, and water crises; climate disruption; declining fisheries; increasing ocean acidification; emerging diseases; and increasing antibiotic resistance are examples of serious, intertwined global-scale challenges spawned by the accelerating scale of human activity.*
>
> —Walker et al., 2009

Changing Ecosystems—Changing Disease Patterns?

Over the last century, large-scale, anthropogenic changes to the natural environment have altered the structure and functioning of the world's ecosystems at an accelerating pace. According to Myers and Patz (2009),

> We now appropriate 1/3 to 1/2 of global ecosystem production for human consumption. We have converted roughly 40 percent of the planet's ice-free land surface to croplands or pasture. We use roughly half of the planet's accessible

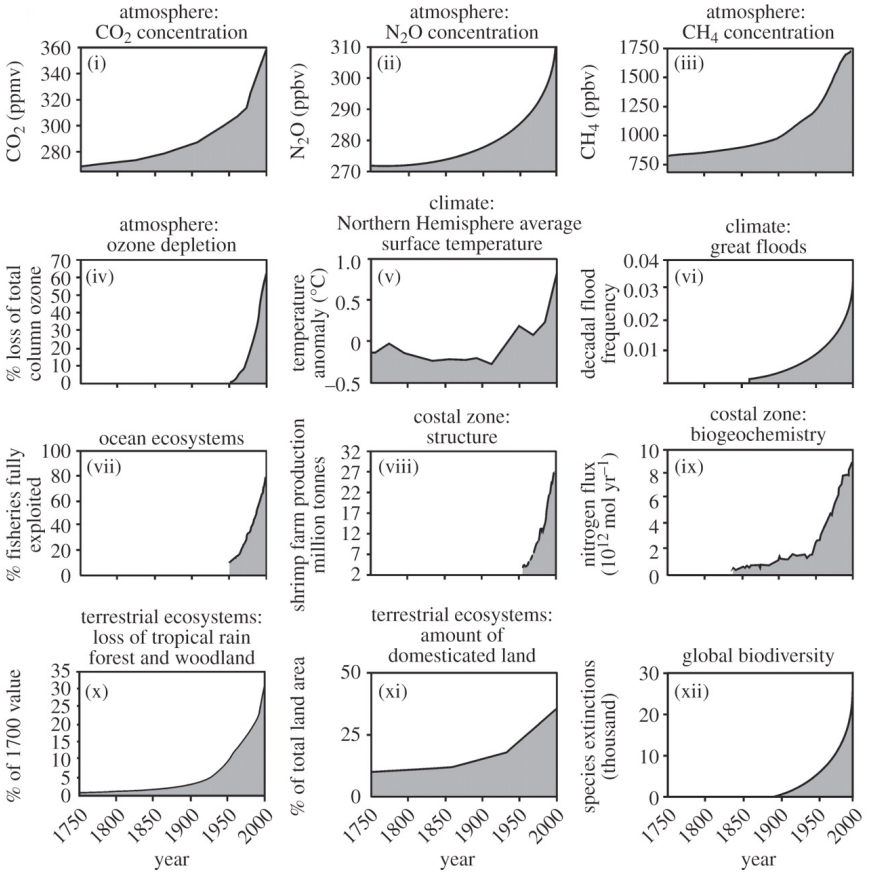

FIGURE WO-2 Global scale changes in the Earth system as a result of the dramatic increase in human activity: (i) atmospheric CO_2 concentration; (ii) atmospheric N_2O concentration; (iii) atmospheric CH_4 concentration; (iv) percentage total column ozone loss over Antarctica, using the average annual total column ozone, 330, as a base; (v) Northern Hemisphere average surface temperature anomalies; (vi) natural disasters after 1900 resulting in more than 10 people killed or more than 100 people affected; (vii) percentage of global fisheries either fully exploited, overfished, or collapsed; (viii) annual shrimp production as a proxy for coastal zone alteration; (ix) model-calculated partitioning of the human-induced nitrogen perturbation fluxes in the global coastal margin for the period since 1850; (x) loss of tropical rainforest and woodland, as estimated for tropical Africa, Latin America, and South and Southeast Asia; (xi) amount of land converted to pasture and cropland; and (xii) mathematically calculated rate of extinction. Adapted from Steffen et al. (2004), including references to the individual databases on which the individual figures are based.
SOURCE: Steffen et al., 2011.

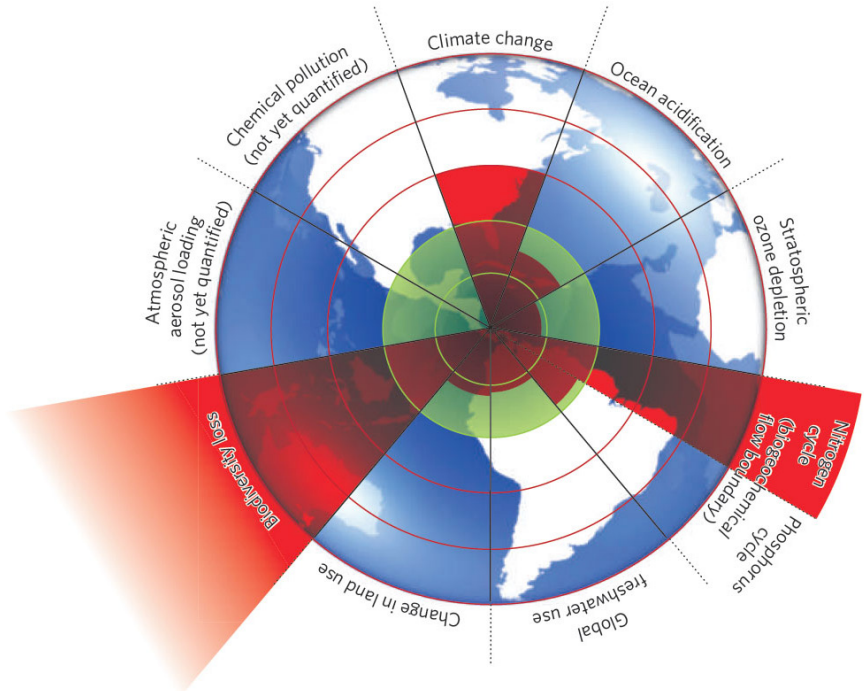

FIGURE WO-3 Beyond the boundary. The inner green shading represents the proposed safe operating space for nine planetary systems. The red wedges represent an estimate of the current position for each variable. The boundaries in three systems (rate of biodiversity loss, climate change and human interference with the nitrogen cycle) have already been exceeded.
SOURCE: Rockström et al., 2009a.

> surface fresh water. . . . To harness electricity, control flooding, and impound fresh water, we have built over 45,000 large dams (the size of a four-story building or larger) and an additional 800,000 smaller dams around the world, changing flows on roughly 60 percent of the world's rivers.

Resource use has also contributed to changes in global nutrient cycles and altered climatic patterns, which in turn may accelerate hydrological cycles and increase the likelihood of extreme weather events, such as droughts, heavy precipitation, heat waves, hurricanes, typhoons, and cyclones. The human population has grown from 1.6 billion in 1900 to more than 7 billion in 2012, and is interacting and gathering at increasingly high rates and densities (urbanization, mass migrations such as the Hajj, sporting and cultural events, cruise ships, etc.).

These changes are bringing people, plants, animals, and microbes together in otherwise improbable combinations and environments. As detailed in the World

TABLE WO-1 Planetary Boundaries

Earth-System Process	Parameters	Proposed Boundary	Current Status	Pre-industrial Value
Climate change	(i) Atmospheric carbon dioxide concentration (parts per million by volume)	350	387	280
	(ii) Change in radiative forcing (watts per metre squared)	1	1.5	0
Rate of biodiversity loss	Extinction rate (number of species per million species per year)	10	100	0.1–1
Nitrogen cycle (part of a boundary with the phosphorus cycle)	Amount of N_2 removed from the atmosphere for human use (millions of tonnes per year)	35	121	0
Phosphorus cycle (part of a boundary with the nitrogen cycle)	Quantity of P flowing into the oceans (millions of tonnes per year)	11	8.5–9.5	–1
Stratospheric ozone depletion	Concentration of ozone (Dobson unit)	276	283	290
Ocean acidification	Global mean saturation state of aragonite in surface sea water	2.75	2.90	3.44
Global freshwater use	Consumption of freshwater by humans (km^3 per year)	4,000	2,600	415
Change in land use	Percentage of global land cover converted to cropland	15	11.7	Low
Atmospheric aerosol loading	Overall particulate concentration in the atmosphere, on a regional basis		To be determined	
Chemical pollution	For example, amount emitted to, or concentration of, persistent organic pollutants, plastics, endocrine disrupters, heavy metals, and nuclear waste in the global environment, or the effects on the ecosystem and functioning of the Earth system		To be determined	

NOTE: Boundaries for climate change, rate of biodiversity loss, and nitrogen cycle have been crossed.
SOURCE: Rockström et al., 2009a,b.

Health Organization's (WHO's) 2005 Millennium Ecosystem Assessment, protection from infectious disease is one of the many ecosystem services provided by the natural environment. Only a tiny fraction of the known microbial species cause disease in their associated human, animal, and plant hosts—in part, because microbes are often constrained geographically or seasonally by complex ecological relationships with their hosts, vectors, and surrounding environments. Human-induced changes to the physical environment can alter these natural constraints on infectious agent range and activity in often unpredictable ways.

Infectious disease dynamics, according to the WHO, are influenced by "destruction of, or encroachment into, wildlife habitat[s through] logging and road construction; changes in the distribution and availability of surface waters [through dam construction, irrigation and stream diversion]; agricultural land use changes, including proliferation of both livestock and crops; uncontrolled urbanization; climate variability and change; migration; and international travel and trade" (WHO, 2005). The reasons for the emergence or reemergence of some diseases in response to environmental change are largely unknown, but may include

- Altered habitat leading to changes in the number of vector breeding sites or reservoir host distribution, or exposure to new host species;
- Niche invasions or transfer of interspecies hosts;
- Biodiversity change, including loss of predator species and changes in host population density;
- Human-induced genetic changes in disease vectors or pathogens—such as mosquito resistance to pesticides or the emergence of antibiotic-resistant bacteria; and
- Environmental contamination by infectious disease agents, such as fecal contamination of source waters.

In this century, disruptions to the natural environment will continue to increase with both population size and intensity of economic activity. Several trends identified in the National Intelligence Council report *Global Trends 2030*, highlighted below, are likely to play a prominent role in shaping the world in the next 15–20 years and may also contribute to conditions that are favorable for the emergence and spread of infectious diseases (National Intelligence Council, 2012). Key trends include

- **Increased urbanization and migration:** The mass relocation of rural populations to urban areas is one of the defining demographic trends of the latter half of the twentieth century. In 2012, close to 50 percent of the world's population lived in urban areas, compared to only 30 percent in 1950. By 2030 60 percent of the world's population will live in urban areas. Growing urbanization will spur economic growth but could put new

strains on food and water resources, and historically such growth has led to reductions in forest covers, adverse shifts in soil quality, alteration to ecosystems (including local extinctions), and changes in the availability and quality of freshwater. Migration and urbanization also provide new pathways for infectious disease exposure. Much of the rapid urbanization occurring today is taking place in urban or peri-urban slums with few services for providing clean water, sewage disposal, solid waste management, or quality housing. Additional health hazards include those posed by open sewers and people living in close association with animals.

- **Increased demand for resources such as food, water, and energy:** As the world's population increases from 7.1 billion in 2012 to an estimated 8.3 billion people in 2030, coupled with an expansion of the middle class by 1 billion people, demand for food, water, and energy will grow by approximately 35, 40, and 50 percent, respectively. Increased use of natural resources will likely be accompanied by severe deterioration of global ecosystems and strain the ecosystem services provided by freshwater resources, including aquatic habitat, fish production, water for households, industry, and agriculture.
- **Climate change:** Climate change will worsen the outlook for the availability of critical resources and is expected to reinforce additional contributors to infectious disease emergence, including global trade and transportation, land use, and human migration. A National Intelligence Council analysis suggests that in the twenty-first century, the severity of existing weather patterns will intensify, with wet areas getting wetter and dry and arid areas becoming more so. Much of the decline in precipitation will occur in the Middle East and northern Africa as well as western Central Asia, southern Europe, southern Africa, and the U.S. Southwest.

An examination of these trends and of how their effects may vary worldwide, across populations and regions, may reveal important implications for targeting and improving infectious disease surveillance, detection, and response efforts.

Human Habitat Expansion and Deforestation

> *Infectious disease is a kind of natural mortar binding one creature to another, one species to another, within the elaborate edifices we call ecosystems.*
>
> —David Quammen, 2007

The advance of human civilization has brought people, plants, animals, and microbes together in otherwise improbable combinations and locations. Such biological introductions were once rare occurrences, but human actions have all but abolished spatial and temporal barriers between species and ecosystems (Carlton,

2004). The profound consequences of human-mediated biological introductions include emerging infectious diseases (EIDs): those caused by pathogens that have increased in incidence, or in geographical or host range; those that have altered capabilities for pathogenesis; those that have newly evolved; or those that have been discovered or newly recognized (Anderson et al., 2004; Daszak et al., 2000; IOM, 1992).

More subtly, but no less importantly, introduced animals, plants, and microbes can disrupt ecosystems in ways that increase the potential for infectious disease outbreaks. Such changes can be difficult to anticipate and even more daunting to prevent. The term *invasive species* is widely used to describe plants and animals that, when introduced to new environments, spread aggressively (Dybas, 2004). Given both the links and similarities between such invasions to those of pathogenic microbes, it should prove fruitful to view the origins of disease emergence through the larger lens of biological invasion, and to consider common strategies to prevent and mitigate threats posed by all kinds of invasive species. Novel associations of pathogens, hosts, vectors, and reservoir organisms are well known to precipitate the emergence of zoonoses,[3] anthropozoonoses,[4] and vector-borne diseases.[5]

Biological introductions have prompted the emergence of vector-borne plant diseases of considerable agricultural importance. An epidemic of Pierce's disease of grapes in California followed the introduction of a highly competent vector for an endemic bacterium, *Xylella fastidiosa*, which had been associated with low levels of disease for over a century (Fletcher and Wayadande, 2002). Until recently, this pathogen was transmitted by the blue-green sharpshooter (*Graphocephala atropuntata*), but with the arrival of the glassy-winged sharpshooter (*Homalodisca coagulata*) in the late 1980s, Pierce's disease emerged as a major threat to the state's viticultural industries. Similarly, the introduction of an efficient Asian aphid vector to the Americas prompted the regional emergence of citrus tristeza virus, which currently threatens California orange crops (Anderson et al., 2004). And, the introduction of a vector-borne bacterial disease—referred to as citrus greening disease—is decimating the citrus industry throughout the state of Florida (Harmon, 2013; USDA/APHIS, 2014).

Given the potential for such circumstances to introduce vector-borne pathogens to immunologically naïve hosts and vectors, it should not be surprising that the initial human occupation of remote ecosystems has resulted in vector-borne disease (VBD) emergence, The clearing and settlement of tropical forests has exposed woodcutters, farmers, and domestic animals to new VBDs (Murphy, 1998). Some species of sandfly that carry leishmaniases—a group of parasitic diseases

[3] Diseases transmitted from animals to humans.

[4] Transmitted from humans to other animals.

[5] Transmitted from one infected host to another through the actions of an intermediate animal such as a biting insect, snail, or rodent; includes many zoonoses, anthropozoonoses, and plant pathogens.

that cause significant death and disability in many countries—and which had long resided in forests and fed on wild animal blood—have adapted to humans as a food source and to their dwellings as a habitat (Walsh et al., 1993). At the same time that VBDs have emerged from formerly isolated locations, vector-borne pathogens have entered new territories along with their human, animal, and plant hosts (Murphy, 1998).

Deforestation also creates new habitats for pathogens and vectors. In South America, for example, epidemic malaria has occurred in recently logged areas where mosquitoes now thrive (Walsh et al., 1993). The modern agricultural practice of planting large acreages with a single monogenic crop is also associated with the emergence of multiple types of fungal diseases and vector-borne plant viruses (Gray and Banerjee, 1999). Conversely, the explosive growth of the white-tailed deer populations and their attendant ectoparasites, coincident with the reforestation of former farmland and the construction of residential properties in semi-rural areas, has been associated with the emergence and spread of Lyme disease (IOM, 2003). As Murphy (1998) has observed, when ecosystems are altered, disease problems follow.

Disruptions to the natural environment are expected to continue unabated throughout this century, accelerating with the size, urbanization, and economic activity of the human population. A recent analysis by the National Intelligence Council—referred to earlier in this chapter—suggests that several key global trends will further encourage the emergence and spread of infectious diseases over the course of the next two decades (National Intelligence Council, 2012). Examining potential impacts of these trends within specific populations and regions may inform the targeting and improvement of infectious disease surveillance, detection, and response efforts.

Health Impacts of Environmental Change

> *(T)he real determinants of disease mortality are the environment and the population, both of which are being "doctored" daily, for better or for worse, by gun and axe, and by fire and plow.*
>
> —Aldo Leopold, 1933

Health and the environment are inextricably linked. This simple truth, which underpins the practice of public health, has been borne out countless times over the history of life on Earth. Before delving into the specific health effects of climate change, land use, and biodiversity loss, keynote speaker Jonathan Patz of the University of Wisconsin noted various ways that the health–environment relationship has been conceptualized—ranging from Aldo Leopold's terse assessment of the consequences of anthropogenic environmental change (above), to the epidemiological triad model of disease, shown in Figure WO-4, to the Health in

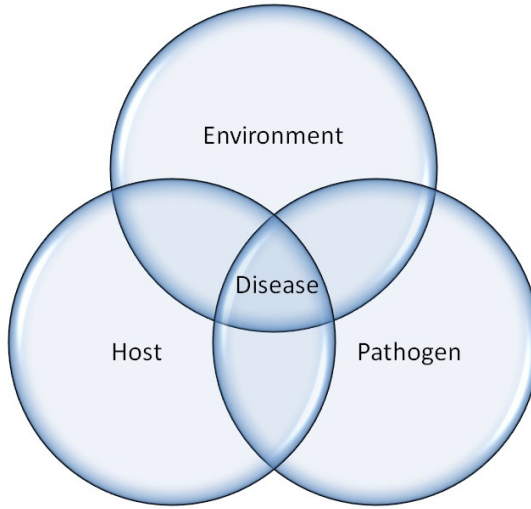

FIGURE WO-4 The epidemiological triad. The familiar epidemiological triad concept (host–pathogen–environment), as illustrated in the famous diagram of Snieszko (1974), neatly illustrates the complex interplay of factors that result in disease at the individual and population levels. The presence of a pathogen is a necessary but not sufficient cause of a particular disease (IOM, 2008).
SOURCE: Snieszko, 1974.

All Policies[6] approach to sustainable development endorsed by the WHO and incorporated into several recent international environmental agreements (Dr. Patz's contribution may be found on pages 328–359 in Appendix A).

Patz then turned to the primary focus of his presentation: health risks associated with climate change. In a recent review article (Patz and Hahn, 2013), he and coauthor Micah Hahn illustrated the state of climate change with the following conclusions from the Intergovernmental Panel on Climate Change (IPCC):

- Average North American temperatures in the mid- to late twentieth century appear to have been warmer than during any similar period in the last five centuries and likely the highest in at least the past 1,300 years.
- From 1906 to 2005, global average temperature rose by 0.74°C.

[6] The Association of State and Territorial Health Officials (ASTHO) defines Health in All Policies as "a collaborative approach that integrates and articulates health considerations into policymaking across sectors, and at all levels, to improve the health of all communities and people." SOURCE: http://www.astho.org/Programs/Prevention/Implementing-the-National-Prevention-Strategy/HiAP-Toolkit (accessed August 6, 2014).

- The rate of change of global temperature is faster now than in any period in the last 1,000 years.
- Since 1961, sea level has risen on average by approximately 2 millimeters per year, and over the next 90 years will rise between 20 and 85 cm.

Patz and Hahn (2013) also noted that higher temperatures evaporate soil moisture, increasing drought risk, and also allow air to hold more moisture, producing heavy rains; the IPCC predicts increased incidence of such "hydrologic extremes" by 2100. At the same time, the melting of the Arctic and Antarctic ice sheets is raising ocean levels and potentially altering their currents. These changes, in turn, are likely to affect weather patterns but in different ways in different locations (Patz and Hahn, 2013).

Patz went on to observe that increases in air temperature and sea level, along with hydrologic extremes, will influence a range of environmental health issues. These include the immediate health consequences of extreme heat, ground-level smog, and ozone pollution, as well as less-direct phenomena such as the recently noted correlation between warm temperatures and extreme rainfall, and rates of interpersonal violence and intergroup conflict (Hsiang et al., 2013). Warmer summers are also associated with the risk of food insecurity (Battisti and Naylor, 2009). "We have almost a billion people at risk of hunger today," Patz reported. "Malnutrition risks could double by mid-century."

Further focusing on infectious diseases, Patz offered the following examples of diseases showing evidence of influence by the suite of environmental shifts collectively known as climate change: temperature and VBDs; hydrologic extremes and disease risk; and climate and land use synergies.

Temperature and Vector-Borne Diseases

Patz noted that diseases transmitted by cold-blooded vectors, such as arthropods,[7] are especially temperature sensitive. Three characteristics of such vectors appear to account for this relationship: their geographic range; their rates of development, survival, and reproduction (as well as those of pathogens that they carry); and biting rates of infected vectors or the prevalence of infection in reservoir or vector populations (which affects the likelihood of transmission resulting from contact with a human) (Patz and Hahn, 2013).

Malaria is a prominent example of a VBD with temperature-dependent transmission dynamics, Patz continued. The malarial parasite's extrinsic incubation period—how long it takes to cross the stomach lining of its mosquito vector, reach the salivary gland, and develop to an infective stage—is strongly temperature dependent. "The warmer the temperature the faster that mosquito becomes infectious," he explained. "You have to have appropriate temperatures or you

[7] Invertebrate animals of the phylum *Arthropoda*, such as insects, spiders, or crustaceans.

cannot have the tropical disease malaria." He described the work by Pascual and colleagues who examined increasing malaria incidence in the relatively cool East African highlands, and its possible—and controversial—link to climate change (Pascual et al., 2006). The authors found evidence for a significant warming trend that was subsequently magnified in terms of mosquito population dynamics by at least one order of magnitude. "Our results emphasize the importance of considering not just the statistical significance of climate trend, but their biological implications with dynamical models," they wrote.

Hydrologic Extremes and Disease Risk

As the Earth warms, droughts and flooding rains are expected to become more frequent, raising the risk for a variety of infectious diseases (IOM, 2008). Heavy precipitation events—rainfall, snowfall, and storms—can inundate agricultural fields, and overwhelm sewers and sewage treatment plants, allowing fecal pathogens to contaminate surface, drinking, and recreational water supplies (Patz and Hahn, 2013). Currently, combined sewer overflows in the United States amount to 1.2 trillion gallons per year—the amount of water that passes over Niagara Falls in 18 days, Patz reported (Whitman, 2000) (this issue was also considered by workshop speaker Joan Rose, of Michigan State University, whose presentation is described in the section "Anthropogenic Factors Driving Disease Emergence" on page 29).

Using a suite of models of precipitation intensity and emissions scenarios, Patz and coworkers determined that sewer overflows into Lake Michigan from southern Wisconsin could increase by 50 to 120 percent by the mid-twenty-first century (Patz et al., 2008). Subsequent work by Sandra McLellan of the University of Wisconsin-Milwaukee revealed high concentrations of *E. coli* in Lake Michigan near Milwaukee following storm-water–induced sewage overflows in that city (McLellan et al., 2007). "When it rains, you have contamination," Patz insisted. "If it is going to be raining harder with climate change that is a public health concern."

By contrast, outbreaks of West Nile virus (WNV)—a mosquito-borne infection that can cause fever and severe neurological complications, and which emerged in the Western Hemisphere in the late 1990s—have been associated with heat waves and drought, Patz observed. Several factors contributed to WNV emergence in the Western Hemisphere, including the ubiquity of international transportation. The role of climate appears to involve the virus' principal vector, *Culex* spp., which is well adapted to "dirty, concentrated urban environments," Patz explained. "This is why drought conditions in the summertime can actually favor that mosquito that doesn't get flushed out of the storm drains." Accordingly, he observed that during the summer of 2012, when more than 1,000 temperature records were broken in the United States, "It was a banner year for West Nile virus."

Reisen and coworkers (2006) experimentally determined that the strain of WNV that emerged in New York City during a record heat wave in July 1999 required warmer temperatures for efficient transmission than its South African counterpart. They further noted that "the greatest WNV transmissions during the epidemic summers of 2002–2004 in the United States were linked to above-average temperatures" (Reisen et al., 2006). In addition to regional outbreaks, "hot spots" for WNV transmission were also found to occur within a relatively the small area of the city of Chicago, and may be correlated with the effectiveness of local water drainage, Patz reported (Loss et al., 2009). Identifying such micro-level environmental differences in arboviral transmission will help in predicting future outbreaks, he concluded.

Climate and Land Use Synergy

As the previously noted study of malaria demonstrates, small changes in ambient temperature can produce significant biological effects, often in combination with additional environmental variables (Pascual et al., 2006). Patz noted that, "when we think about climate change, we really cannot view it in isolation. We need to look at synergistic issues on the ground. Things happen locally." Similarly, he added, local factors may dampen the effects of climate change. To illustrate this point, Patz described another malaria study, in which a temperature differential introduced by deforestation was found to significantly increase reproductive fitness of the mosquito vector (Afrane et al., 2006).

Indeed, the transformation of wild lands through human enterprise is proceeding exponentially around the globe and—as Andrew Dobson, of Princeton University, argued in his keynote address to the workshop (see the section "Understanding Infectious Disease Dynamics" on page 20)—may represent an even more consequential source of environmental upheaval than climate change. As we alter the landscape, Patz queried, "Are we giving up some ecosystem services and intact functioning ecosystems that could be useful for human health?"

To explore this question on a local scale, Patz's group compared the behavior of the primary mosquito vector of malaria, *Anopheles darlingi*, between forested and deforested sites along a road in the Peruvian Amazon (Vittor et al., 2006). "There were lots of mosquitoes in the forest, but just not the main one that carries malaria," Patz explained. "So this is a biodiversity story: the bad actor mosquito was in the disturbed landscape." The researchers also determined that deforestation provoked ecological changes—especially in the aquatic environment where *Anopheles darlingi* breeds—that favored the species' presence (Vittor et al., 2009). The causes of this altered biodiversity remain to be determined, he said, "But you see an altered mosquito biodiversity from this land-use change, and you also have artificial breading sites from road culverts, fish ponds, and a higher abundance of *Anopheles darlingi*, leading to a high risk of malaria."

Patz observed, however, there is little site-specific data linking actual human cases of malaria to deforestation. To address this question, Patz's group analyzed malaria reports obtained from Brazilian health districts together with satellite imagery to determine the relationship between deforestation and malaria incidence in a single county. His group calculated that for every 4 percent loss in forest cover, malaria incidence increased by 48 percent (Olson et al., 2010). Similarly, he reported that graduate student Micah Hahn, in collaboration with speakers Steve Luby, of Stanford University, and Peter Daszak, of the EcoHealth Alliance (whose presentations are summarized in the section, "Approaches to Identify and Address Factors Contributing to Disease Emergence" on page 76), recently examined the relationship between land use and spillover (bat-to-human transmission) of the Nipah virus in Bangladesh. The investigators discovered that viral spillover tends to occur more frequently in forested areas, a local phenomenon limited to certain villages within a general area known as the "Nipah belt" (Hahn et al., 2013).

Addressing the Health Consequences of Environmental Changes

The multifactorial nature of global environmental change means that the health effects of its components are interdependent, and therefore need to be considered together (Rockström et al., 2009a,b). "The good news is that if the risks are all interconnected so too will be the [intervention] opportunities," Patz declared. Both urban and rural settings offer abundant design opportunities to reduce humankind's environmental impact, he continued. Urban adaptations could include the use of porous surfaces, in order to reduce runoff and thereby minimize or mitigate the risks associated with waterborne diseases, he noted. He also described a system to convert potentially infectious human and animal waste to biogas fuel, recently constructed in rural Uganda, which provides both economic and health benefits.

During the discussion that followed Patz's presentation, Forum chair David Relman, of Stanford University, raised the possibility that "natural experiments," in environments where the effects of climate change were found to be minimal, might reveal mitigating factors that could be exploited elsewhere. Patz agreed, and noted two examples of such observations that shade-grown coffee plantations fared far better than open-grown plantings during Hurricane Mitch;[8] and that minimizing asphalt "heat islands" in cities could reduce the impact of heat waves.

Several participants advised framing the discussion of the health effects of environmental change in ways that emphasize the benefits of environmental stewardship, rather than warn against future catastrophe, which they dismissed as (at

[8] Hurricane Mitch was the most powerful hurricane and the most destructive of the 1998 Atlantic hurricane season, with maximum sustained winds of 180 mph (285 km/h). The storm was the thirteenth tropical storm, ninth hurricane, and third major hurricane of the season. SOURCE: http://en.wikipedia.org/wiki/Hurricane_Mitch (accessed April 7, 2014).

best) ineffective. Patz agreed, and observed that many steps that could be taken to improve human health, such as redesigning cities to emphasize human-powered and public transportation, would also address climate change. For example, he said, "We did a study showing that switching short car trips to bicycle trips would save $8 billion in avoiding mortality and health costs every year just for our region" (Grabow et al., 2012).

A convincing business case for addressing the health effects of global environmental change needs to be made, advised Forum member Jeffrey Duchin, of the Seattle and King County Department of Public Health. "There are plenty of examples in the history of medicine and science of problems that were recognized as big issues from the scientific and human health perspectives that did not get addressed until someone realized that it affected the bottom line," he observed. For example, he said, the threat of antimicrobial resistance (another example of a "tragedy of the commons") was largely ignored until the infectious disease community convinced hospitals that they would save money by taking preventive measures against resistance.

Patz suggested that an important tool for making such a case is the health impact assessment (HIA), a systematic process to evaluate the potential health effects of a plan, project, or policy prior to its implementation (CDC, 2013c). HIAs can demonstrate to policy makers the health benefits their communities can expect to gain from specific environmental protections and can expose unintended consequences of environmental development projects that might seem, on balance, beneficial to growing economies, he explained.

"Health needs to be on the table, and there are trade-offs," Patz stated. "That is step one. Step two is that there are better ways to develop" than to pursue Western-style fossil fuel–dependent growth. "You can't tell a country 'Don't cut that tree, and don't burn those fossil fuels,'" he continued. "We can tell them there are ecosystem services. There are alternative transportation options . . . [and] an opportunity to have a better city if you forego the path we took for a newer path."

"Economic growth and technological progress should be partners and friends of the ecology and the environmental movement," added Forum member Lonnie King, of Ohio State University. Although seemingly at odds in the current marketplace of ideas, both objectives could be united by a value proposition that defines investment in the environment as a means to a society's long-term well-being, he asserted.

On the other hand, observed Forum member Jesse Goodman, of the U.S. Food and Drug Administration,[9] even economic trade-offs that we can all agree could be win-win long term, considering the big picture, may not result in needed policy changes if there is a disconnect between who reaps immediate economic rewards (such as in fossil fuels) and who pays for long term broader effects and costs (e.g., to the environment). "Right now, with respect to fossil fuels and

[9] Dr. Goodman is now at Georgetown University.

global warming, the entities that are making money are not then economically accountable for the environmental costs accrued by the world as a whole." Such disconnects will continue unless policies, including incentives, such as a carbon tax—begin to broadly link benefits to costs," he stated. "Unfortunately, we don't have an international governance system that can deal with that challenge," Patz replied. "That is the toughest problem, I think."

Returning to the local level, several participants expressed frustration at the lack of evidence-based recommendations available to help policy makers understand and address the health effects of climate change that they are confronting in their communities. For example, during last summer's severe WNV outbreak in Dallas, Texas, some neighborhoods were affected far worse than others, though all suffered drought and record temperatures, recalled Beth Bell of the Centers for Disease Control and Prevention (CDC). "Policy makers are asking me, why is this, and what do we do about it? My answers from the community perspective are pretty limited," she said. To develop such guidance, Forum member Carole Heilman, of the National Institute of Allergy and Infectious Diseases (NIAID), suggested that such local variations should be studied in detail, perhaps by ecologists working alongside epidemiologists during outbreak investigations.

"Where you have to start building is locally," Heilman insisted. "They are the people who make decisions in terms of what our laws really are," she continued. "There are probably areas that we can change attitudes . . . [including those of] important people that will be involved and invest in changing the world."

Understanding Infectious Disease Dynamics

Identifying and interpreting how multifactorial, interacting environmental forces influence the emergence and spread of infectious diseases is essential to reducing the harm they cause. Keynote speaker Andrew Dobson, of Princeton University, an ecologist studying infectious disease dynamics, offered a provocative view of this effort by attempting to debunk the following six misconceptions about emerging pathogens, as he described them (Dr. Dobson's contribution may be found on pages 193–212 in Appendix A).

Misconception One: Disease Has No Effect on National Economies

"One of the most cited papers in economics . . . explains how everything about economies of different countries is simply a product of governance," Dobson reported, referring to the work of Acemoglu and coauthors (Acemoglu et al., 2001). Posing the question, "What are the fundamental causes of the large differences in income per capita across countries?," these economists assert that disease merely shaped governmental institutions established by nations in their colonies—institutions that persist to this day and that strongly influence each former colony's relative economic success.

This analysis statistically removes the significant contemporary effects of diseases that infected early settlers, such as malaria, schistosomiasis, and hookworm, Dobson declared. Dobson and coworkers conducted their own version of this analysis, in which they estimated the relative effects of vector-borne and parasitic diseases and income on each other, and found a significant inverse association between residual levels of disease and per-capita income (Bonds et al., 2013). "The diseases still causing the biggest economic damage are things like malaria," he observed. "So we have to keep worrying about those if we are worried about the world's economy, and indeed I would say we should be worried about those certainly as much as governments." Their analysis also suggested that the economic effects of vector-borne and parasitic diseases are to some extent buffered by local biodiversity—a strong argument for protecting it, Dobson concluded.

Misconception Two: Climate Will Drive Disease Emergence

Climate change will influence infectious disease dynamics, Dobson said, but its significance may be difficult to discern among the multiple, interacting forces underlying global environmental change. As Patz also noted, changes in land use—prompted by rapid growth in the human population—are dramatically transforming the global environment. According to the Millennium Ecosystem Assessment, a comprehensive scientific appraisal of the state of global ecosystems and ecosystem services released by the United Nations in 2005 (United Nations Environmental Programme, 2005), the influence of land use as a force for environmental change over the next century will at least equal that of climate change in tropical and temperate regions, as illustrated in Figure WO-5.

"Climate change will have a huge effect on the tiny proportion of birds (and all other species) that live up in the Arctic. Land use change will have a huge effect on the huge proportion of birds that live near the equator, and that is going to be true for all biodiversity," Dobson predicted—including pathogens and humans. As a result, he explained, signals of climate change effects on infectious diseases will be difficult to detect in the tropics, as has occurred in the case of malaria (as Patz also noted). This controversy illustrates the importance of recognizing the heterogeneous nature of global environmental change, Dobson concluded.

Misconception Three: Maps Can Predict Pathogen Emergence

Dobson took issue with the landmark publication by Jones et al. (2008), suggesting that it purports to identify global hot spots for infectious disease emergence, but instead maps global disease research centers. "What happens if you take the first half of the data [used to plot these hot spots], and try and predict the second half of the data?," he wondered. "No one has done that." If they did, he predicted, one might find such phenomena as high skill for prediction of sites for

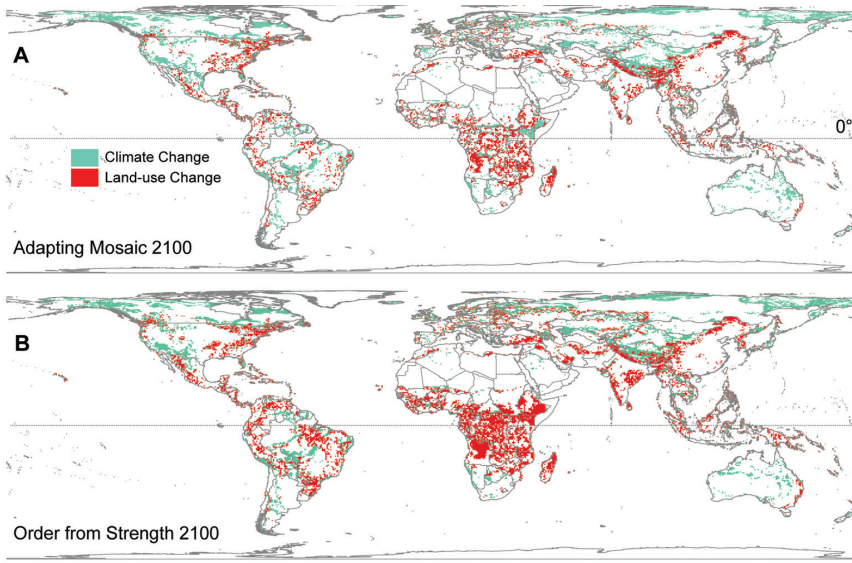

FIGURE WO-5 Patterns of change in land cover due to land use and climate change by 2100. Patterns are given for the environmentally proactive "Adapting Mosaic" scenario as well as the environmentally reactive "Order from Strengh" scenario. (A) Adapting Mosaic, 2100. The "Adapting Mosaic" scenario sees the rise of local ecosystem management strategies, and the strengthening of local institutions. There is also great variation among nations and regions in styles of governance, including management of ecosystem services. Some regions explore actively adaptive management, investigating alternatives through experimentation. Others employ bureaucratically rigid methods to optimize ecosystem performance. Eventually, the focus on local governance leads to failures in managing the global commons. Problems like climate change, marine fisheries, and pollution grow worse and global environmental problems intensify. Using good regional solutions and discarding poor ones eventually improves approaches to a variety of social and environmental problems, ranging from urban poverty to agricultural water pollution. As more knowledge is collected from successes and failures, provision of many services improves. (B) Order from Strength, 2100. This scenario represents a regionalized and fragmented world, emphasizing primarily regional markets, and paying little attention to common goods. The role of government expands. Regionalization exacerbates global inequality. Treaties on global climate change, international fisheries, and the trade in endangered species are only weakly and haphazardly implemented, resulting in degradation of the global commons. Ecosystem services become more vulnerable, fragile, and variable in Order from Strength. For example, parks and reserves exist within fixed boundaries, but climate changes around them, leading to the unintended extirpation of many species. Conditions for crops are often suboptimal. As a result, there are frequent shortages of food and water, particularly in poor regions. Low levels of trade tend to restrict the number of invasions by exotic species; however, ecosystems are less resilient, and invaders are therefore more often successful when they arrive.
SOURCE: Jetz et al., 2007.

emergence of drug-resistant pathogens as these will consistently occur in areas with modern hospitals and high levels of drug use. They will be very limited in their ability to predict hot spots for emergence of novel pathogens. "Maps are only as powerful as the data and analysis that goes into their construction," he warned. "It is essential to clearly state the underlying analysis that creates a map, rather than assume powerful mapping techniques have done this for you."

In reply, Daszak noted that Dobson may have referred to the wrong map in his formal presentation—a map of raw data—rather than the predictive hot spot maps that correct for reporting bias by including a measure of global research effort that "specifically accounts for the location of disease identification centers!" Daszak went on to observe that his research group included a specific measure of reporting bias in their General Linear Models that produced the hot spot maps.[10] Daszak reminded the Forum members that these maps were not intended to invite fine comparisons between specific locations, but rather to reveal broad trends and associations including that the majority of pandemics, such as wildlife zoonoses, have emerged in the tropics. Daszak provided a detailed account of the theory and process of disease mapping in Jones et al. (2008) in his presentation, which is summarized in the section "Approaches to Identify and Address Factors Contributing to Disease Emergence" on page 76.

Misconception Four: Virus Hunting Is an Effective Strategy for Detecting Emerging Diseases

Virus hunters who head for the tropics in search of the next emerging pathogen are, in Dobson's opinion, wasting time and resources for two key reasons related to infectious disease dynamics. First, he observed, "Wherever you go, there is a huge amount of undiscovered bacterial and viral tissue. We do not have to go off to the swamps of Africa to find it." To illustrate his point, Dobson described his group's intensive study of three estuarine ecosystems, which proved to be rife with microbes (Hechinger et al., 2011). "There is much parasitic biomass moving around in those salt marshes—and I would posit, in any other ecosystem—as there is free-living biomass. It is just in tiny little particles, and it turns over really quickly," he said. "Parasites are probably the dark matter that holds the whole ecosystem together."

Their results also suggest that an organism's parasite load scales with its trophic level (its position in the food chain),[11] and that species abundance scales with

[10] "This work involved gathering information on around 15,000 authors of papers from *Journal of Infectious Diseases*, then gridding each author out spatially with a specific latitude and longitude—a huge amount of work that Dr. Dobson may have overlooked in reading the paper."

[11] Primary producers such as photosynthetic plants occupy the first trophic level; herbivores that feed on the plants form the second trophic level; carnivores feeding on herbivores occupy the third trophic level, and so on. SOURCE: http://www.biology-online.org/dictionary/Trophic_Level (accessed August 6, 2014).

body size, Dobson explained (Hechinger et al., 2011). Guided by these scaling laws, the abundance of viruses and bacteria in a given ecosystem can be readily estimated based on an understanding of feeding patterns. As a result, Dobson concluded, "Undiscovered viruses are abundant everywhere . . . [and] we need to think more about the dynamics of emergence than the romance of fishing for viruses with computer chips."

Dobson's second criticism of virus hunting derives from an understanding of two dynamic features of emerging pathogens: basic reproductive number (R_0) is the number of cases one case generates on average over the course of its infectious period in an otherwise uninfected population (Fraser et al., 2009). Because SARS and smallpox have relatively low R_0s and produce symptoms quickly, it was possible to control those diseases by isolating infectious people, he explained. Influenza, with its higher R_0 and lag between infectious and symptomatic stages, and HIV/AIDS, with an extended asymptomatic period, are difficult to impossible to eradicate, he said. "Would virus hunters have detected HIV? I think it would have gone straight past them," Dobson asserted. "Very long incubation period—so you are likely to dismiss it as harmless. Cost of extensive lab trials—you are never going to get money in the current climate for that. And HIV is still the emerging pathogen that has had a bigger impact than all the others put together."

Daszak also took issue with this point and noted that the frequency and impacts of pandemics are growing, so discovering new approaches for proactive infectious disease identification might be a critical strategy that should be taken seriously. "I concede that finding a new virus does not necessarily mean we can stop it." However, Daszak continued, the majority of emerging diseases originate from mammals in the tropics, so that is where efforts should be concentrated. "If we are going to sit here and wait for them to come to our backyard, as you suggest, then are we too late? Shouldn't we get there ahead of the curve, go to places where diseases are likely to emerge, and try and at least characterize the diversity of fauna viruses out there so we can do something about it?"

Relman observed that while the emerging diseases shown on Daszak's maps constitute overt cases of pathogenicity (parasites receiving benefits by damaging their hosts), Dobson's analyses incorporated more subtle and ongoing forms of parasitism, which in some cases are merely assumed to occur based on microbial taxonomy. These two models of parasitism differ not only in terms of the magnitude of damage to the host, but also in the duration of the host–parasite relationship, he added. "How does that play into the way in which you devise a model, the ways in which you try to estimate impact on a network when you think about a wide range of both magnitude of damage and timescale over which it happens?" he asked Dobson.

All parasites cause energetic damage, Dobson responded. "Any form of parasitism, even if it is a tiny microbe or a virus, is causing some energetic change in its host [at] some cost. It may be incredibly small, but aggregated across all the viruses and all the worms it will build up." Moreover, he added, the statistical

distribution of parasites across the host population is such that the few hosts at the top of the food chain receive the bulk of damage caused by parasites, which in turn damages the parasites. Relman agreed, but speculated that, when all selective factors—not just energetics—are taken into account, some parasites may not actually prove harmful to their hosts.

Misconception Five: Emerging Pathogens Will Evolve to Higher Virulence

What happens when an infectious disease spreads rapidly and no one tries to stop it? Does it necessarily gather virulence like a ball rolling down a hill gathers momentum? Dobson described a model system for exploring this question: a bacterial pathogen of birds, *Mycoplasma gallisepticum,* which, in 1993 in the northeastern United States, jumped from domestic poultry into house finches, in which it causes a readily identifiable eye infection. The disease spread rapidly through the regional finch population, causing dramatic population declines but little local extinction, he reported—so the disease's main impact was to reduce the size of the birds' typical social groups. Upon reaching less abundant finch populations in the north and Midwest, the rate of disease spread slowed, but increased again when it reached the more densely populated western United States (Hochachka et al., 2013).

After *Mycoplasma gallisepticum* emerged in house finches on the East coast, it became increasingly virulent, Dobson reported—but as it spread across the country its virulence declined (Hawley et al., 2013). He and coworkers then replicated this natural experiment in the laboratory, demonstrating that high rates of contact between groups favors a relatively stable evolution of virulence; they also developed a predictive mathematical model based on their results.

"We can use this system to actually look at the dynamics of the interaction between the pathogen and the host immune systems," he continued. "We can take samples from the bird's eyes, look at what the bacteria population is doing from day to day, and we can look at what the immune system does in response to that. So we can make models of the immune system that look at the dynamics of the interaction between the pathogen and the host immunity."

Misconception Six: Immunology Is Science and Ecology Is Natural History

As the virulence evolution model demonstrates, an ecological view of the immune system offers both insight and predictive capacity. To provide further evidence of the advantages of this approach, Dobson depicted the vertebrate immune system as a network of predator/prey relationships known as a food web (see Figure WO-6).

Dobson's group develops mathematical models to characterize food webs and identify the dominant interactions among them. To demonstrate how this works, he offered the example of the Serengeti, a complex system they found to

be dominated by a few major interactions, particularly that between wildebeest and rinderpest virus. Based upon mathematical descriptions of these relationships, Dobson and colleagues were able to construct a predictive model of interspecies dynamics (Holdo et al., 2009). Using the same mathematical tools, he said, "You can write the immune system down as two equations for each of the different dominant terms in their interaction." As compared with mainstream, descriptive, immunological studies—which Dobson characterized as "natural history"—the mathematical approach favored by ecologists affords "a much deeper understanding of how the immune system works," he asserted.

"If we really want to understand emerging diseases we need to move beyond high-tech natural history description of novel components to develop mathematical models that capture the essential dynamics of immunity, and then examine how those things vary as we move from the mammals to the birds to the bats," Dobson concluded. This approach could, among other things, reveal why bats are reservoirs of several emergent pathogens, including the SARS, Nipah, and Hendra viruses (Dobson, 2005), he suggested. More generally, he later noted, little is known about the energetics of the immune system; what energetic costs does fever impose on host and parasite, for example? Answering that question would require thinking about the immune system in purely thermodynamic terms, he observed—an example of "risky science" that, in his opinion, was worth doing.

Heilman, of NIAID, noted that while the agency is responsible for funding basic science that can improve human health, such as Dobson's approach to immunology, the National Institutes of Health are also involved in identifying and developing interventions for individual diseases. "Can you explain to me how your ecological network or food network could develop targets for human intervention?" she asked.

Dobson agreed that identifying disease-specific targets is a worthwhile activity beyond the reach of his approach. However, he continued, target-based interventions act within metabolic networks, which are essentially food webs, through which the knock-on effects of the intervention can be anticipated. Mathematical epidemiology has, for example, shown how the average age of first infection for rubella might change as we vaccinate, he observed. "If you just identify targets and try and hit them you are going to get side effects that might be much more damaging than not having intervened in the first place," he concluded. "You cannot predict those until you have some sort of food web model of how those things interact."

"You reduce some very complicated systems, like immune function, to some very simple mathematically defined models," Duchin said to Dobson. "How do we develop models that are better at predicting, or how would you suggest we approach the idea of modeling the determinants of the emergence of disease, rather than just describing it better?"

"The type of models I am interested in are not really designed for prediction, they are designed for understanding," Dobson replied—models like the

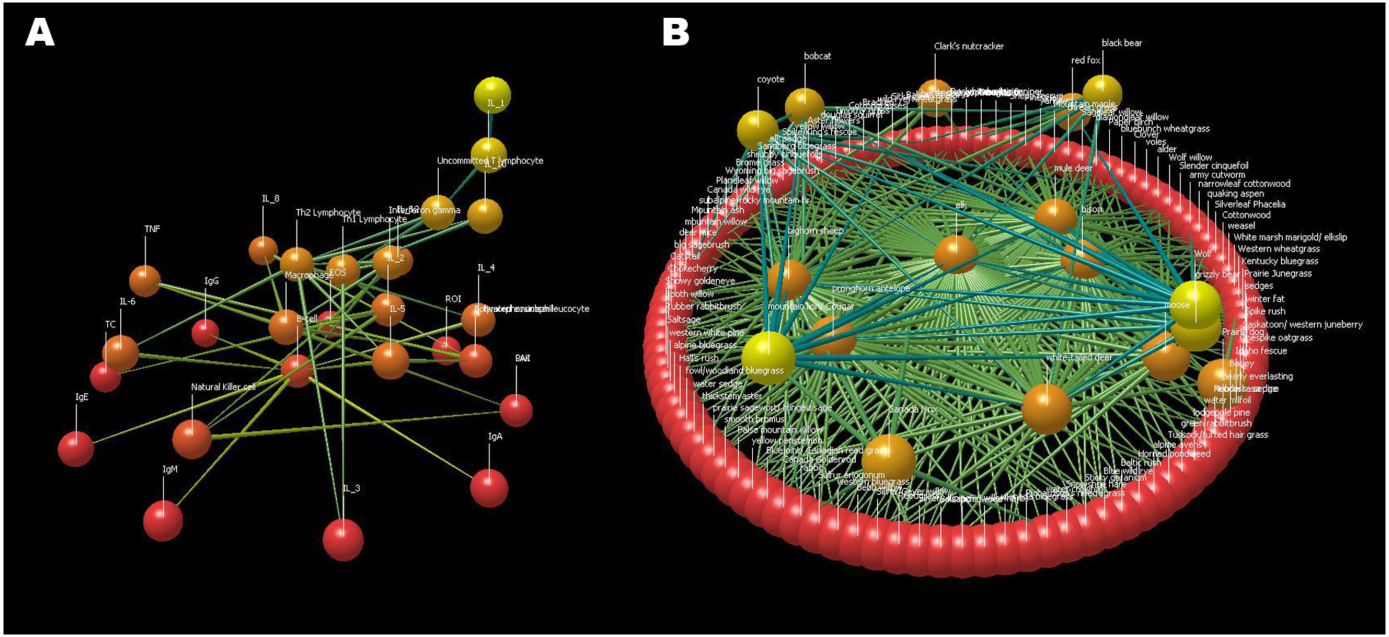

FIGURE WO-6 These two figures illustrate computer realizations of the network structure of (a) the fauna and (vertebrate) fauna of Yellowstone National Park (Barmore, 2003; Frank and McNaughton, 1992) and (b) the vertebrate immune system (based on Cox and Liew, 1992). The central point of this exercise is to illustrate that food webs and the vertebrate immune system have a network structure that can be examined using ecological food web models. The figures were realized using Network 3D Version 1.0.0 Copyright Microsoft Corporation; Microsoft Research and PEaCE Lab, C# OpenGL Framework Copyright © 2006 devDept, Berkeley, California.
SOURCE: Images courtesy of Andrew Dobson.

immunological "food web," developed from the simplest assumptions of how a system works, which reveal its essential dynamics. "If those dynamics are very complicated, even with the simplest possible model, then prediction is going to be hard," he observed—or worse than that, dangerous, because unlike the structural models he favors, they cannot be held up against reality and corrected, except in hindsight. "I would rather understand the processes, understand why the bat's immune system is different from other mammals, why can it have things in it that suddenly become pathologic. That has to be some function of the way the physiology of bats work versus the physiology of the other mammals." Similarly, with regard to emerging diseases, Dobson said, it is important to characterize pathogen diversity, including the various ways pathogens interact immunologically with different host species, and to attempt to develop a predictive framework for those interactions. Where pathogens are going to come from, he said, "is the least interesting of those questions."

Forum member Jacqueline Fletcher, of Oklahoma State University, pursued the notion, raised earlier by Relman, that the category of parasites includes indigenous microbes that are harmless or beneficial to their hosts. How are such interactions factored into models of emerging diseases, she inquired? What might shift such microbes to become pathogens—a new host? Environmental change?

"I think we'll never know what proportion of viruses or bacteria will be epidemic, because to know that we would have to take every virus and test it in every host species that it goes into," Dobson replied. Moreover, he said, a single host is likely to respond differently to a given pathogen under different environmental conditions, such as if the host is malnourished or stressed.

Nipah virus underwent such a transition as a result of changes in land use, which caused it to infect pigs and humans in addition to its longstanding host, bats, noted audience participant Dr. Joe Dudley of SAIC. Viruses do not gain particular advantage in "jumping" host species, he observed; spillover is a product of global environmental change. "In the tropics, you have more people, you have more vectors, you have more viruses, and you have more disruptions, and more people making more people more quickly."

Upon introduction to a host, pathogens are generally surrounded by communities of diverse indigenous microbes, noted Forum member Margaret McFall-Ngai. Can these complex relationships be factored into models, she wondered? They can be captured in essence and corrected through comparison with relevant data, Dobson said. However, he added, "The microbiome is fascinating, but I just see it as something that kicks up [the immune response]."

At the conclusion of his talk, Dobson posed this rhetorical question: should we be worried, about emerging disease? "Yes, particularly if you . . . don't believe in evolution," he remarked. "Yes times six if you believe . . . any of the above misconceptions. No, I don't think you should be worried, because I think the field has produced many bright young people, many of whom would agree completely with [my view of] the above misconceptions. And no, we should not worry if we

change the way we fund things. But if we continue to fund things the way we are, be very worried, and perhaps start praying."

Anthropogenic Factors Driving Disease Emergence

The global environmental impact of human activity results from the collective effects of interacting processes, including travel, trade, migration, urbanization, conflict, land development, water use, and fossil fuel combustion—each of which represents a potential influence on infectious disease dynamics, but none of which is likely to act alone. A series of workshop presentations examined the effects of anthropogenic factors on infectious disease establishment, adaptation, and spread, and through case studies, revealed multiple forces at work in shaping disease patterns at the local scale.

Travel and Trade

Perhaps no aspect of the Great Acceleration is better described by that phrase than the recent, rapid expansion of the human capacity for mobility, a hallmark of our species. Figure WO-7 offers three perspectives on this phenomenon and its intersection with population growth. A central feature of global environmental change, increased human mobility and migration have both caused and resulted from environmental influences (such as deforestation, drought, land use, climate change) and sociopolitical upheaval (urbanization, globalization, and conflict) (IOM, 2010).

"There are millions of people engaged in [an] international journey every day," observed speaker Martin Cetron, of the CDC (Dr. Cetron's contributions may be found on pages 165–170 and 170–181 in Appendix A). He noted that more than 1 billion individual international border crossings take place each year, among them those of an estimated 900 million tourists (Castles and Miller, 2009). The explosive growth of travel and trade over the last century, having all but eliminated previously existing spatial and temporal barriers between the world's species and ecosystems, now drives the global distribution of microbial pathogens and the organisms that harbor them (Carlton, 2004; IOM, 2003, 2010). Of particular interest is the practice of medical tourism, discussed in Box WO-1.

Human migration has long been associated with the spread of disease. The practice of quarantine originated in fourteenth century Venice, and was intended to prevent the spread of the Black Death into the city (and continent) by isolating passengers and products on arriving ships for 40 days before they were permitted to come ashore, Cetron explained. In the United States, cholera outbreaks among immigrants in the nineteenth century led to the stigmatization of immigrants as bearers of disease and the creation of a national quarantine program. As has occurred throughout history, immigrants were thought to be disease vectors, rather than victims of disease, he observed—a notion that ignores complex interactions

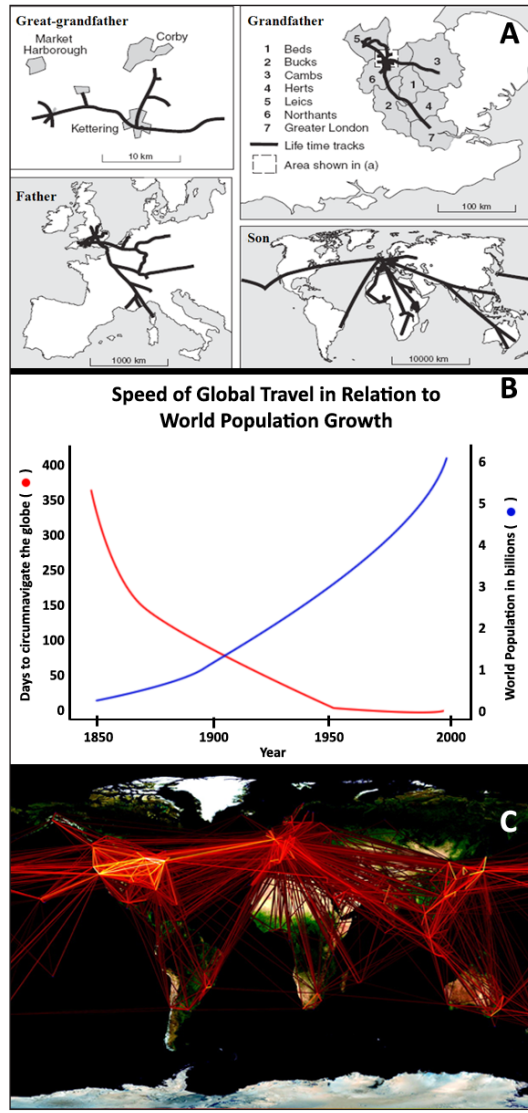

FIGURE WO-7 (A) Travel over four male generations of the same family. Each map shows in a simplified manner the individuals "life-time tracks" in a widening spatial context, with the linear scale increasing by a factor of 10 between each generation. (B) Speed of global travel and population growth. (C) International plane arrivals. Global aviation network. A geographical representation of the civil aviation traffic among the 500 largest international airports in >100 different countries is shown. Each line represents a direct connection between airports.
SOURCES: (A) Cliff and Haggett, 2004; (B) Murphy and Nathanson, 1994; (C) Hufnagel et al., 2004.

BOX WO-1
Medical Tourism and Infectious Disease

International travel for medical treatment has undergone rapid expansion, particularly among residents of developed countries, who receive medical procedures in low- or middle-income countries at often vastly lower cost, and more quickly, than they would in their home countries. Common procedures include dental work, arthroplasty, certain surgeries (cataract, bariatric, cosmetic, and cardiac procedures), reproductive care, and tissue and organ transplants. Popular destinations for medical tourists include the Caribbean, China, Europe, India, Latin America, Mexico, the Middle East, Pakistan, Singapore, and Thailand. Although limited data exist to describe medical tourism on the basis of volume, destinations, services, or procedures received, as many as an estimated 4 million patients have received treatment outside their home countries each year.

Medical tourists (as well as all travelers who receive medical care away from home) are vulnerable to both procedure- and travel-related infections. They also risk introducing pathogens and resistance determinants to new host populations while abroad, and upon their return home. Malaria, dengue, and other infections are endemic in many countries with high volumes of medical tourism. These countries may also have high background rates of tuberculosis, antibiotic resistance, hepatitis B and C, and HIV. Blood and blood products used in hospitals certified by Joint Commission International (http://www.jointcommissioninternational.org/About-JCI) are screened for common blood-borne pathogens, but not necessarily for region-specific pathogens such as dengue and West Nile viruses.

SOURCE: Chen and Wilson, 2013.

between human migration and infectious disease emergence, as discussed below (Figure WO-8) (see the sections "Migration," "Urbanization," "Conflict and Complex Emergencies," and "Road Development" on pages 38, 39, 43, and 51, respectively).

A more straightforward relationship exists between the global movement of animals and animal products and the emergence of zoonoses, which are estimated to comprise 60 percent of newly identified infectious diseases (Jones et al., 2008). This topic was addressed by speaker Nina Marano, of the CDC's Division of Global Migration and Quarantine, which regulates the importation of live animals and animal products into the United States (Dr. Marano's contribution may be found on pages 282–296 in Appendix A). In the course of defining the scope of the CDC's mandate in this area—summarized in Box WO-2—Marano described specific zoonotic disease risks associated with international trade that the agency attempts to mitigate through regulation.

FIGURE WO-8 They come arm in arm—American seaports must close their gates to all three.
SOURCE: Judge Magazine, September 17, 1892.

Introducing Plant Pathogens

Global pathogen movement—enabled by international travel and trade, as well as by extreme weather—has also had a profound effect on plant health, and thereby on food security. Along with anthropogenic introduction, winds, and weather—including extreme weather events[12]—are associated with the introduction, establishment, and spread of fungal diseases (Anderson et al., 2004). Because many fungal pathogens are soil associated, wind, weather, or soil disturbances by humans and animals can release spore-associated dusts into the air. Once airborne, spores may be dispersed over great distances—often hundreds or thousands of miles—to new geographic areas and potential new host environments (Figure WO-9) (Brown and Hovmøller, 2002).

This topic was addressed by the presentation of Caitilyn Allen of the University of Wisconsin. Interactions among novel plant, pest, and pathogen species are a frequent and influential consequence of human activities. The effects of such

[12] Includes weather phenomena that are at the extremes of the historical distribution, especially severe or unseasonable weather (e.g., extreme heat or cold, tropical cyclones, tornadoes). SOURCE: http://www.ncdc.noaa.gov/climate-information/extreme-events (accessed August 6, 2014).

introductions often interact with, and are magnified by, the effects of climate change, as shown in Figure WO-10.

Pathogen introductions are a key factor in disease emergence in crop plants, which often are grown in monoculture. These circumstances—which fueled the Irish Potato Famine in the mid-nineteenth century and the 1970 epidemic of southern corn leaf blight in the United States—now threaten banana (plantain), a major food crop in East Africa, Allen noted.

Irish Potato Famine

One of the most tragic outcomes of a weather-induced fungal disease outbreak was the Irish Potato Famine during the nineteenth century in which a sustained pattern of cool, rainy weather between 1845 and 1847 facilitated the emergence and spread of potato late blight (*Phytophthora infestans*) (Money, 2006). Resulting yield losses of this staple crop were catastrophic, leading to the starvation and death of over 1 million people and forcing the migration of more than 1 million more (Vurro et al., 2010).

Southern Corn Leaf Blight

When combined with reduced genetic diversity in agronomically important crops, weather can contribute to a "perfect storm" for a devastating agricultural disease epidemic (Rosenzweig et al., 2001). Southern corn leaf blight (SCLB), a spore-dispersed maize disease caused by the fungus *Helminthosporium maydis* (also known as *Cochliobolus heterostrophus*), swept through the United States between 1970 and 1971. Unusually warm, moist weather, coupled with a wholly susceptible host crop, provided the ideal conditions for the outbreak and spread of disease (Rosenzweig et al., 2001). Over the course of the 1970–1971 growing season, the SCLB epidemic spread from the tip of Florida to Alberta province in Canada, destroying a significant proportion of susceptible maize plants in its path (Ullstrup, 1972). Yield reductions were most severe in the Southern states with many farms experiencing total crop loss. Average yield loss in the Corn Belt states was 20 to 30 percent, with some parts of Illinois and Indiana reporting yield losses of 50 to 100 percent (Ullstrup, 1972). In the 1970 season alone, the SCLB epidemic led to the loss of 710 million bushels of corn—valued at more than $1 billion at the time [or about $5.6 billion in 2009 dollars] (Tatum, 1971; Vurro et al., 2010).

Banana Xanthomonas *Wilt (BXW)*

Sub-Saharan Africa grows about one-third of the world's bananas, which are consumed locally and supply between one- and two-thirds of daily calories in Uganda, Rwanda, and Burundi, Allen stated. As such, they not only represent a dietary staple, but a source of cash income and a driver of local economies. In

BOX WO-2
CDC Regulatory Authority for Importation of Animals and Animal Products

In her workshop presentation, Marano noted the following categories of imports regulated by the CDC's Division of Global Migration and Quarantine, and the rationale behind these regulations.

1. Dogs and cats

Due to the risk of importing the canine strain of rabies, which has been eliminated in the United States but is still endemic in many countries, a valid rabies vaccination certificate is required at a U.S. port for admission of a dog unless the owner shows that dogs have been in a rabies-free country for 6 months before arrival.

The CDC publishes a list of countries each year in which no indigenous cases of the disease have been reported. Nevertheless, Marano noted, dogs imported from such "rabies-free" countries may still pose a risk, as demonstrated by the recent reintroduction of terrestrial rabies—via infected bats—in Greece and Taiwan. As a result, she said, the CDC proposes to change the designation of rabies-free countries to include only those that do not have bat viruses.

A general certificate of health is not required for entry of pet cats into the United States, although some airlines or states may require them. However, pet cats are subject to inspection at ports of entry and may be denied entry into the United States if they have symptomatic evidence of an infectious disease that can be transmitted to humans. If a cat appears to be ill, further examination by a licensed veterinarian at the owner's expense might be required at the port of entry.

2. Turtles, tortoises, and terrapins

Due to the risk of salmonellosis for young children who may put small living or nonliving objects—including turtles—in their mouths, importation by one person of more than six turtles with shells less than 4 inches in long, or viable eggs, is not permitted except for scientific, educational, or exhibition purposes.

The Food and Drug Administration (FDA) imposed restrictions on domestic turtle sales, but producers found ways to skirt these laws (e.g., by giving away turtles with the purchase of habitats). As a result, nearly 400 children contracted salmonellosis in eight multistate outbreaks, of whom about one-third were hospitalized.

3. Nonhuman primates

Importers must register with the CDC and certify that the animals will be used for scientific or educational purposes, or for exhibition. The animals are isolated and quarantined for at least 31 days; disease control measures are implemented as appropriate; and any suspected zoonoses reported.

These regulations were established after an outbreak of Marburg and Ebola viruses in a nonhuman primate facility in Reston, Virginia (chronicled in Richard Preston's bestseller, *The Hot Zone*). Nonhuman primates share several infectious diseases and disease agents with humans, including tuberculosis, viral hemorrhagic fever, herpes B virus, hepatitis A and B viruses, monkeypox, simian immunodeficiency virus (SIV), simian foamy virus (SFV), yellow fever, and meliodosis (*Burkholderia pseudomallei*).

Improved detection and control of disease outbreaks among nonhuman pri-

mates under the CDC's regulations resulted in a reduction in animal mortality from an average of 15 percent to 1 percent, thereby improving the quality of medical research studies.

4. Infectious biological agents, infectious substances, and vectors

A permit is required to import infectious biological agents, infectious substances, or vectors, and only for scientific, educational, or exhibition purposes. The definition of *vector* is constantly being updated, as occurred when SARS emerged, and the difficult search for its reservoir host ultimately revealed it to be bats. The recently emerged Middle East respiratory syndrome (MERS)[a] has been linked with bats, as well as with camels, Marano noted.

5. African rodents and other animals that may carry the monkeypox virus

Neither live nor dead rodents obtained directly or indirectly from Africa may be imported, nor may any products derived from such rodents. These restrictions followed a 2003 outbreak of monkeypox linked to the importation of infected African Gambian pouched rats, which subsequently infected prairie dogs, which in turn infected humans. At the same time, the FDA banned the sale and interstate distribution of both African rodents and prairie dogs; the interstate ban was lifted in 2008.

While the CDC ban stemmed the flow of African rodents into the United States, since its imposition, imports of rodents from Europe, Canada, and South America have skyrocketed, Marano reported. "You can put your finger in the dike, but with the dynamic and fluid pet trade . . . we have to struggle to keep up with the changes," she observed.

6. Persons, carriers, things

If any arriving carrier or article or thing on board the carrier is believed to be infected or contaminated with a communicable disease, it may be subject to detention, disinfection, disinfestation, fumigation, or other related measures.

This regulation covers a range of potentially risky imports, including civets (which, though not the reservoir for SARS, carry a high viral load and therefore pose some risk for human infection), goat hair products from Haiti (associated with cutaneous anthrax), and bushmeat (the likely origin of the first human HIV infection, and a known source of Ebola virus, SIV, and SFV, among other infectious diseases). A pilot project under way in collaboration with the EcoHealth Alliance, the Wildlife Conservation Society, and Columbia University to screen confiscated bushmeat for zoonotic pathogens with PCR detected SFV, herpesvirus, polyomavirus, and coronavirus samples from seized bushmeat shipments (Smith et al., 2012).

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[a] The Middle East respiratory syndrome coronavirus (MERS-CoV) was first reported to cause human infection in September 2012, and by September 20, 2013, was reported to have caused a total of 130 cases, of which 58 (45 percent) were fatal. All cases have been directly or indirectly linked through travel to or residence in four countries: Saudi Arabia, Qatar, Jordan, and the United Arab Emirates (UAE). SOURCE: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6238a4.htm (accessed August 6, 2014).

SOURCES: Marano presentation, 2013; http://www.cdc.gov/animalimportation/cats.html; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6238a4.htm (accessed August 6, 2014).

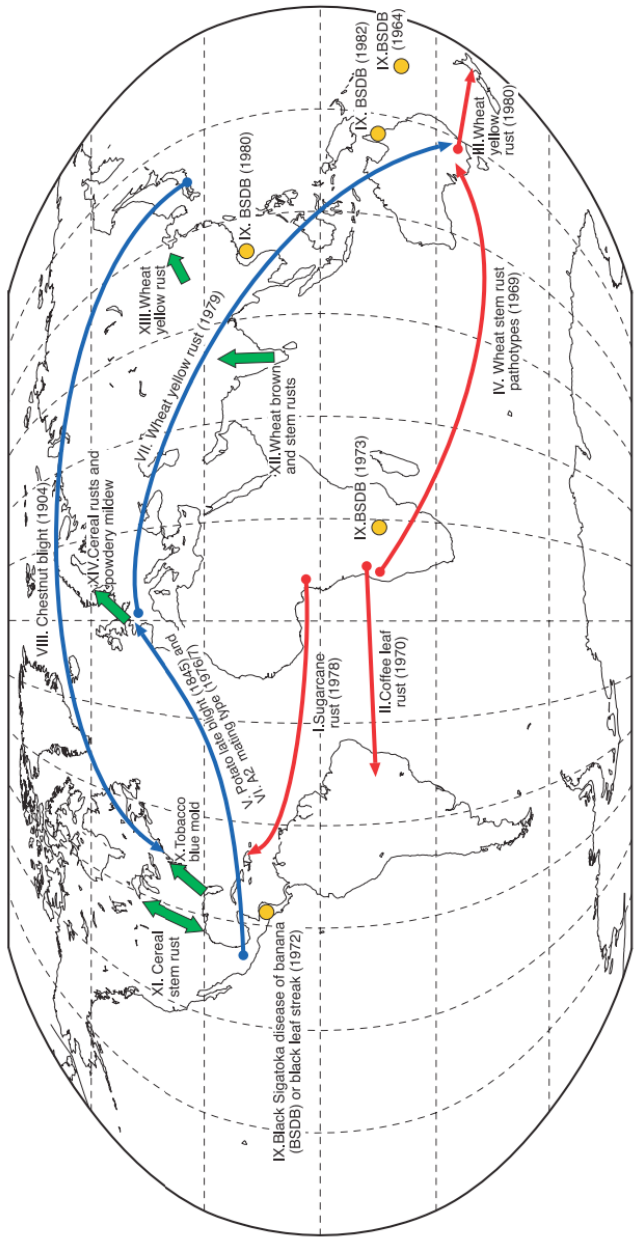


FIGURE WO-9 Selected dispersal events of fungal pathogens. Red and blue arrows indicate invasions of new territories (first year recorded in parentheses). Red arrows indicate dispersal that probably occurred by direct movements of airborne spores (I, II, II, and IV). Blue arrows indicate pathogens that were probably transported to the new territory in infected plant material or by people and spread thereafter as airborne spores (V, VI, VII, and VIII). Orange circles indicate the worldwide spread of black Sigatoka disease of banana; the first outbreak on each continent is marked (X). Green arrows indicate periodic migrations of airborne spores in extinction–recolonization cycles (X, XI, XII, XIII, XIV). SOURCE: Brown and Hovmøller (2002); Background world map © C. Lukinbeal, Southern Connecticut State University, New Haven Connecticut.

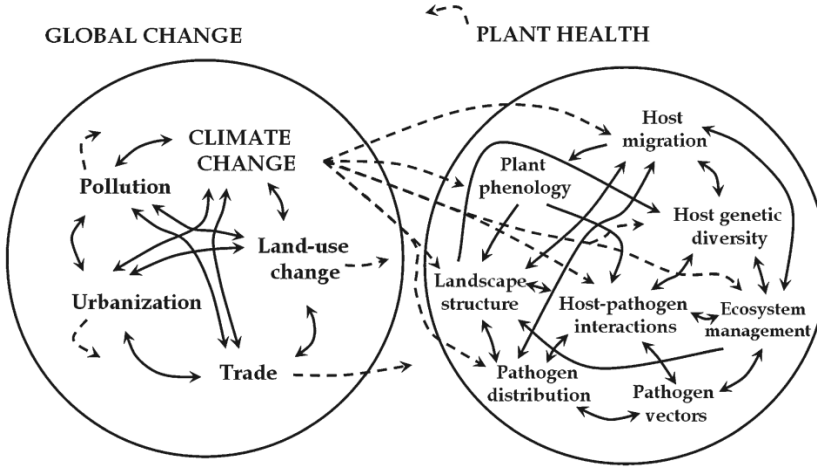


FIGURE WO-10 Global change impacts on plant health. Global change is composed of the interactions of various drivers (climate change, increased trade, land use change, pollution, urbanization). All these factors will have an impact on plant health, through direct effects on host–pathogen interactions, and via indirect effects on host migration, genetic diversity, and phenology, as well as on disease distribution, insect pests, vectors, and landscape structure. There is a feedback from plant health to global change. To be successful in the face of global change, ecosystem management will have to consider the complexity of interactions depicted in this diagram.
SOURCE: Pautasso et al., 2012.

2001, banana trees in east Africa began showing signs of the emerging disease now called banana *Xanthomonas* wilt (BXW): yellowed dying leaves, early fruit ripening, wilted male flowers, and discolored, inedible fruits.

Transmitted by pollinating insects, BXW is caused by the bacterium *Xanthomonas campestris pv. museacearum*, a member of the bacterial family that produces xanthan gum, a common food additive, cosmetic stabilizer, and industrial lubricant. Researchers have since learned that this pathogen jumped from ensete, a native African plant, to banana, which is native to Southeast Asia (Studholme et al., 2010).

Epidemic BXW has caused the loss of more than half of all banana production capacity in the Great Lakes region of Africa, and with them, the livelihoods and food security of many residents, who must now pay approximately 40 percent more for this important foodstuff.

Migration

Human migration in this age of mobility differs significantly from the historical unidirectional flow of people from a place of origin to a single, final destination, Cetron observed (Castles and Miller, 2009). Today, he said, migration tends to be a circulatory process: a complex journey that may be composed of many stops of varied length (and thereby, many opportunities for interchange), some of which return the migrant to his or her place of origin. Internal migration—movement within national borders—accounts for the majority of such journeys, of which an estimated 744 million take place each year, in addition to tourism. International migration is also significant, involving approximately 3 percent of the global population, who together would comprise the world's fifth largest country, he reported.

Using the United Nations' strict definition of "migrant" as a person living outside their country of birth for at least 12 months, Cetron noted that the majority of migrants are leaving the Middle East, Eastern Europe, South Asia, East Asia, and Japan for destinations in North America, Western Europe, and the Middle East. These movements are largely driven by economic and demographic disparities, he observed—which are projected to shift somewhat in the coming decades (Munz, 2013). Population growth in sub-Saharan Africa and India is projected to exceed 200 percent in the twenty-first century and create a workforce that will dominate the structure of the international migrant populations, he reported. At the same time, the populations of Latin America, North America, the United States, and Canada—and even China—will be relatively aged, and therefore in need of the labor that African and Indian immigrants could provide.

Human migration can influence infectious disease dynamics through a variety of mechanisms, according to speaker Chris Beyrer, of Johns Hopkins University (Dr. Beyrer's contribution may be found on pages 146–154 in Appendix A). People seeking transient employment, moving from rural to urban settings, or those fleeing political strife or natural disaster, may be exposed to pathogens as a result of populations mixing or gathering *en masse*, often while ingesting contaminated food or water, he noted. Mobile populations also frequently lack preventive measures against infectious diseases (e.g., water filters, bed nets to prevent malaria, or condoms to prevent sexually transmitted diseases) and have limited access to care facilities or health care workers, resulting in delayed or denied treatment.

Beyrer offered some examples to illustrate these conditions. In South Africa, migrating miners—of which there are many, and for whom extramarital relationships are common—are nearly twice as likely to acquire HIV as nonminers (Beyrer et al., 2008). In China, where the largest human migration in history has already shifted at least 120 million people from rural to urban settings, a recent ecological analysis revealed that as the proportion of immigrants rises in urban

populations, so does the rate of sexually transmitted diseases (Tucker et al., 2005). Recent forced migrations in Zimbabwe caused thousands of people to flee to neighboring countries, where many were considered illegal immigrants; as such, they were unlikely to receive treatment for infectious diseases, or to be recognized in disease surveillance efforts, he observed. See the section "Conflict and Complex Emergencies" on page 43 for further discussion of the role of political conflict in disease emergence.

Urbanization

As Beyrer noted in the case of China, increasing capacity for mobility underlies the urbanization of human populations. Albert Ko, of Yale University, introduced his workshop presentation with an overview of this global demographic transition, illustrated in Figure WO-11. As of 2007, and for the first time in history, more people live in cities than in rural regions, and by 2037, he stated, "More than 50 percent of the world's population will be living in the urban centers of less developed countries, most of which are situated in tropical environments."

This shift has been especially dramatic in Brazil, where nearly 90 percent of people currently reside in cities, Ko reported. There, as in much of the developing world, the transition from a rural agrarian society to an urban one was accompanied by increasing social inequity, which now divides the population into widely separated groups of "haves" and "have nots." Most of the latter groups live in slums, defined by the United Nations as housing with insecure tenure, poor structural quality, overcrowding, and inadequate access to safe water, sanitation, and infrastructure (United Nations Human Settlements Programme, 2003). The United Nations estimates that 1 billion people—nearly half the world's urban population—live in slums.

Ko observed that changing disease patterns affect residents of slums and shantytowns worldwide. Table WO-2 lists several characteristics of urbanization and urban poverty he associated with specific infectious disease risks. Leptospirosis, long recognized as a rural disease of particular concern for subsistence farmers and their livestock, has begun to emerge in both affluent and impoverished urban settings under a variety of circumstances associated with globalization, he reported. In the slums of Salvador, Brazil, a city of more than 2.5 million people on the country's northeast coast, Ko and colleagues tracked annual epidemics of leptospirosis for more than 15 years, beginning in 1996 (Ko et al., 1999).

Case study: Leptospirosis in the slums of Brazil Leptospirosis, an infectious disease caused by bacteria of the genus *Leptospira*, occurs worldwide, but it is most prevalent in the tropics and subtropics. The pathogen, which comprises

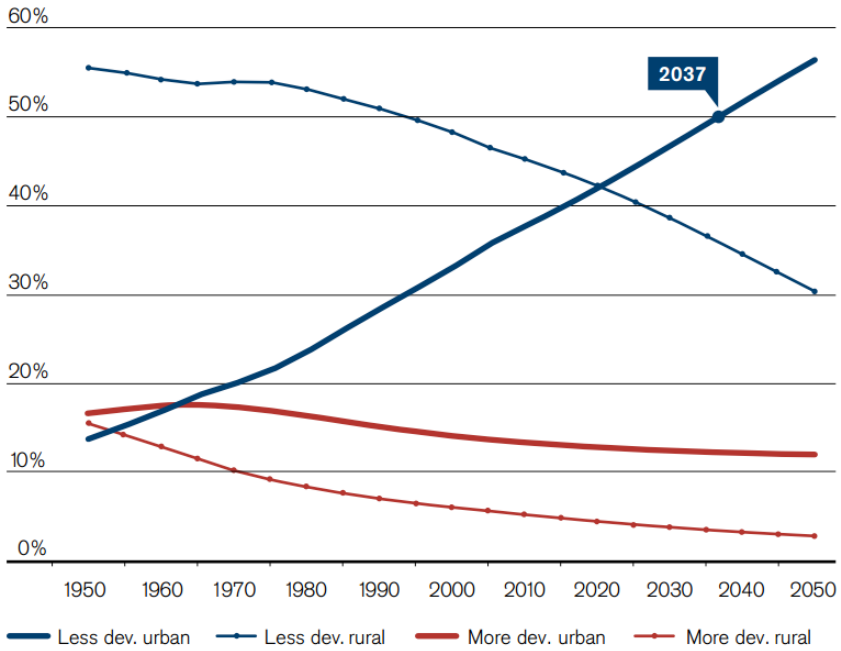


FIGURE WO-11 World urban and rural poplation for developed and developing regions (percent of total). In 2007 the percentage of the planet's population living in urban areas crossed the 50 percent threshold. Initially a developed market phenomenon, the focus of urbanization has switched to developing nations as they rapidly industrialize. After 2020 more people will also live in cities than rural areas in developing nations, and by 2037 those cities will contain half the world's total population.
SOURCE: Figure: Credit Suisse, 2012; Data: Population Division of Department of Economic and Social Affairs of the United Nations Secretariat, Credit Suisse.

9 species and >200 serovars,[13] is present in water contaminated by urine from infected animals—often rats—and can be transmitted to humans through skin lesions or through mucous membranes. Leptospirosis typically is a self-limiting and often unnoticed illness, but a percentage (15 to 19 percent) of untreated cases progress to develop severe life-threatening manifestations such as pulmonary hemorrhagic syndrome and acute renal failure. In developing country settings, case fatality from leptospirosis is often greater than 10 to 15 percent.

[13] *Serotype* or *serovar* refers to distinct variations within a species of bacteria or viruses or among immune cells of different individuals. These microorganisms, viruses, or cells are classified together based on their cell surface antigens, allowing the epidemiologic classification of organisms to the subspecies level. A group of serovars with common antigens is called a serogroup. SOURCE: http://en.wikipedia.org/wiki/Serotype (accessed April 8, 2014).

TABLE WO-2 Infectious Diseases Influenced by Urbanization and Urban Poverty

In Poor Urban Settings…	…Increases Risk For:
…changing ecosystem, breakdown of control programs…	dengue in Latin America.
…expansion of peri-urban slums and deforestation…	visceral leishmaniasis.
…overcrowding and human movement…	meningococcal B and C outbreaks; tuberculosis among commuters from shantytowns.
…migration; increased access to diagnosis and screening…	pseudo-epidemics of leprosy in Brazil.
…increased yet inadequate access to health services…	drug-resistant tuberculosis.

SOURCE: Ko presentation, 2013.

In Salvador, a city in Northeast Brazil, as well as in the large urban centers throughout the country, outbreaks of leptospirosis occur annually within the same slum communities and involve a single serovar of the pathogen, for which domestic rats serve as a reservoir (Ko et al., 1999). Rainfall is an important driver of leptospirosis in urban slums, with large outbreaks occurring during seasonal periods of heavy rainfall. Epidemics of leptospirosis are well recognized to occur after large disaster events, such as hurricanes, monsoons, and typhoons. However, Ko and colleagues found that in slum communities there was a direct association such that "for every 1 centimeter of weekly rain fall, a week or two weeks later there would be a 5 percent increase in case counts," he explained. "So, small amounts of rainfall, and not only extreme events, contribute to risk. And there is also a 7 to 14 day lag in the effect of rainfall in cases, indicating that exposures to the pathogen among slum residents occur during or shortly after these rainfall events," he added.

Decade-long cohort studies in the crowded peri-urban slum community of Pau da Lima—where 14,000 people occupy 0.5 square kilometers—allowed Ko's group to examine environmental determinants and outcomes of leptospirosis in a slum environment (Reis et al., 2008). They found that men—especially young men—had the highest attack rates for the disease, but Ko's group has yet to determine why young men have a significantly increased (>10-fold) risk for acquiring severe life-threatening manifestations of leptospirosis acquisition than adult women and children. These investigators also observed that households at the lowest elevations in this hilly area were at greatest risk for disease, for a number of possible reasons: these were the most destitute of the slum's residents, and their poorly drained homes tended to accumulate pathogen-laced mud when

flooded. Clearly, he observed, there is a significant social gradient of risk even within this highly impoverished community.

Ko's group is working with the Brazilian Ministry of Health to prevent disease among slum dwellers through a range of interventions, including early warning and response; health and education; and targeted rodent control. He noted, however, that "the majority of rodent control campaigns were actually targeting the richest neighborhoods where all the politicians were calling to get rid of the rats." In response, he and coworkers developed maps that clearly identified the peri-urban regions at highest risk for disease. They also convinced community leaders to extend closed sewage projects beyond wealthy neighborhoods. Ko reported that after these interventions were implemented slum dwellers experienced a four-fold decrease in leptospirosis. Ko and colleagues are now conducting observational studies to determine the significance of sewer improvements in lessening disease risk.

Lessons learned With an estimated 1 billion additional people expected to join slum populations within the next two decades, we must anticipate disease risks such as those identified in the Pau da Lima community and prepare for them, Ko insisted. The "sanitation revolution" that occurred in Victorian London, as in much of the developed world in the 1800s, led to important health improvements for the population. Although imperative, much of the developing world does not have plans in place, has not made investments or does not have the capacity to mount such a revolution to address the needs of their urban slum populations. Furthermore, the paradigm of the sanitation revolution in the 1980s may not adequately address the complexities of contemporary slum communities, he observed. Ko asserted that new paradigms need to be constructed which incorporate interdisciplinary approaches to these inherently complex health problems, based on an understanding and linkage of ecological and social drivers for all infectious diseases—something we have yet to achieve for marginalized urban slum populations, he said (Riley et al., 2007).

Ko noted the great strides that have been made in the past century toward advancing human rights and social cohesion through both policy and research. He concluded that addressing the health risks faced by the urban poor is more than just a matter of generating political will; it will require, in addition, a recognition of and response to the specific role that social justice influences human health (Dye, 2008).

Urbanization of animals A less discussed, but ecologically important aspect of urbanization concerns wildlife species—such as raccoons, coyotes, and white-tailed deer—that have acclimated well to urban environments and are found there in large numbers. In making the transition from diverse ecosystems in which humans play a relatively small role, to less-diverse, human-controlled environments, these species undergo a "huge shift in ecology," noted speaker Sonia Altizer, of

the University of Georgia (see also the sections "Climate Shifts, Animal Migrations, and Infectious Disease Dynamics" on page 57 and "Ecophysiology of Host–Pathogen Interactions" on page 67) (Dr. Altizer's contributions may be found on pages 111–129 and 129–146 in Appendix A).

Altizer works with colleagues at the University of Georgia who study one such animal—the white ibis—that naturally forages on aquatic animals and vertebrates in the Florida Everglades, but is now "starting to hang out in urban parks following people around, eating Cheetos and popcorn as handouts," she said. This change in diet, combined with more sedentary behavior that tends to go with it, could have important effects on the ibis' gut microbiome, she observed, and thereby, its susceptibility to infectious diseases. At the same time, these birds are exposed to *Salmonella* and influenza viruses through their frequent contact with peri-domestic species (S. Hernandez, unpublished). How these circumstances influence the dynamics of these diseases in wild ibis remains to be determined, she said.

Conflict and Complex Emergencies

Following his more general introduction to the ways in which human mobility and migration may directly or indirectly influence infectious disease dynamics, Beyrer focused on two multifaceted phenomena in which human migration and mobility play a central role: conflict and complex humanitarian emergencies, which he defined as a humanitarian challenge, such as a natural disaster, combined with social conflict or political upheaval. Both circumstances are unfortunately common, especially in the context of environmental change, he observed.

To present a typical picture of the health consequences of civil conflict, Beyrer described the 2002 political crisis in Côte d'Ivoire, which resulted in the displacement of 25 to 55 percent of that country's adult population and 68 to 95 percent of its health care workers. Thereafter, the incidence of sexually transmitted infections increased dramatically—even by what were doubtless incomplete measures, given the few health care workers left to compile this assessment (Betsi et al., 2006). More recently, similar devastation has plagued Syria, where more than 6 million people had been displaced by civil war at the time of the workshop, Cetron noted. More than 2 million of these migrants had fled the country—the largest such exodus since the 1994 Rwandan genocide, according to the United Nations (BBC, 2013). The destruction of the Syrian health care system had led to increased numbers of infectious disease outbreaks in the region, he added. These are discussed in greater depth in the section, "Approaches to Identify and Address Factors Contributing to Disease Emergence" on page 76.

Natural disasters[14] often represent tipping points in political crises, and frequently lead to complex humanitarian emergencies, Beyrer observed. Human rights are often at risk when natural disasters strike, he noted. A 2008 report from the Brookings Institution warned that disaster victims often face unequal access to assistance, discrimination in aid provision, enforced relocation, sexual and gender-based violence, loss of documentation, and child recruitment into fighting forces, among other challenges (Brookings-Bern Project on Internal Displacement, 2008). "The longer displacement lasts, the greater the risk of human rights violations," Beyrer added. "Discrimination and violations of economic, social, and cultural rights tend to become more systematic over time."

Case study: Cyclone Nargis and its aftermath in Burma Most, if not all, of the human rights challenges outlined above occurred in Burma after the largest storm in the country's history, which—in 2008—killed an estimated 146,000 people, displaced 2.4 million more, and destroyed about 700,000 homes in Burma, Beyrer said. Cyclone Nargis washed over about 5,000 square kilometers, altering the geography of the Ayeyarwady Delta, and destroying 60 percent of the country's rice crop, he continued.

This devastation occurred as the country's corrupt leader, General Than Shwe, was fighting for political survival in the face of an increasingly popular opposition. "What was happening in the lead up to this storm was not preparations for the storm, but preparations for a referendum on a military-backed constitution," Beyrer recalled. The ill-prepared dictatorship was, uncharacteristically, all but absent in the storm's aftermath—and far worse, blocked access to the country to a host of western nations ready to offer assistance. "The Burmese government was asking for direct donations, and they got some of them from their allies, but they insisted that everything go through them," he said. Beyrer recounted his own attempts to gain admittance to the country to assist with recovery, only to be denied because he was deemed "a humanitarian doctor," and therefore, a threat to the dictatorship.

Amazingly, no major infectious disease outbreaks occurred in Burma following Cyclone Nargis, Beyrer reported; nevertheless, the population suffered epidemic posttraumatic stress disorder, widespread depression, and impoverishment. The causal loop diagram depicted in Figure WO-12 illustrates how climate change, international and national governance, and conflict intersected to produce this crisis—from which Burma has yet to recover, Beyrer concluded.

Stability bias In addition to the immediate repercussions of migration, conflict, and civil disruption for human health in general and infectious disease in particular, these circumstances often compromise our ability to understand, track,

[14] Such as the death, devastation, social, and economic disruptions caused by Typhoon Hainan in the Philippines in November 2013.

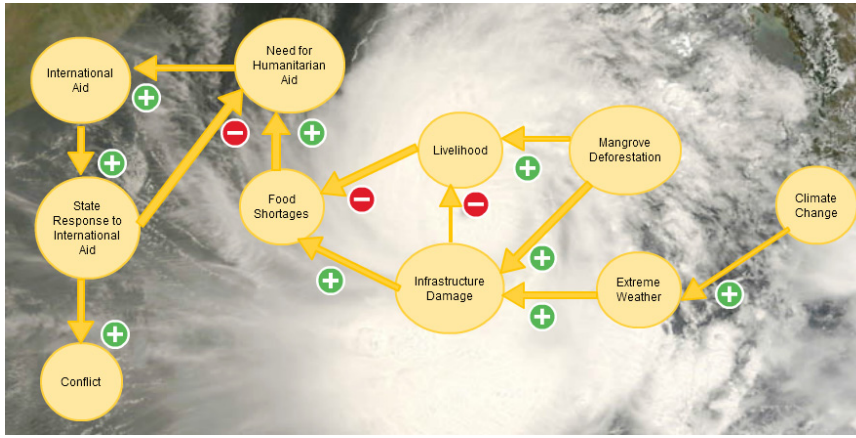


FIGURE WO-12 Causal loop diagram illustrating the relationship between climate change, international and national governance, and conflict in Myanmar in the aftermath of Cyclone Nargis in 2008.
SOURCE: American University, 2011.

respond, and mitigate infectious disease threats, Beyrer observed. He has coined a term for this dilemma: "stability bias," which he defines as "the systematic undersampling of populations and health threats in context of conflict and instability in favor of more stable settings where health research can more easily be conducted" (Beyrer et al., 2007).

To illustrate this concept, Beyrer described the fate of HIV/AIDS and malaria research in the Democratic Republic of Congo (DRC), once a key location for studies of the emergence of HIV (Beyrer et al., 2007). The number of new HIV/AIDS studies conducted in the DRC peaked between 1986 and 1988, he said, then declined rapidly and were halted by the government of Mbuto Sese Seko in 1994; much the same was true for studies of malaria. "Political conflict can really turn off our ability to understand what is happening in these contexts," Beyrer concluded. "That is really an important thing to be mindful of when we think about these interactions."

Water Contamination

Changes in temperature, humidity, precipitation, and water salinity have been shown to influence the quality of water used for drinking, recreation, and commercial uses. Temperature increases of just a few degrees can produce rapid growth in several types of bacteria that cause diarrheal diseases, including *Salmonella* and *Vibrio* species. In addition, an increase in water temperature coupled with eutrophication has been known to promote dormant strains of cholera,

sheltered by marine phytoplankton and zooplankton, to become infectious. Outbreaks of cholera, *Cryptosporidium,* and *Giardia* have also been associated with periods of heavy rainfall and flooding. Storm water runoff from heavy precipitation events may also increase fecal bacterial counts in coastal waters and nutrient loading. This may, in turn, lead to increases in the range and frequency of harmful algal blooms (red tides), which pose a threat of food poisoning to humans when consumed by fish and shellfish, and when coupled with increased sea-surface temperatures, the production of potent toxins by marine microorganisms (IOM, 2009).

Waterborne diseases have emerged throughout world history as a result of complex interactions between human and animal pathogens that are influenced by land and water use, and by climate, according to speaker Joan Rose, of Michigan State University (Dr. Rose's contribution may be found on pages 375–389 in Appendix A). "Water quantity is well described worldwide, but water quality, which we equate to health, is not," she observed. The importance of safe water has been expressed in the United Nations Millennium Development Goals (United Nations Millennium Development Goal 7).[15] However, new Sustainable Development Goals are focusing on water quality and sustainable water security. To achieve universal access to clean water and basic sanitation, and ensure efficient allocation through integrated water-resource management, various goals have been suggested:

- Restrict global runoff.
- Limit withdrawals from river basins.
- Contribute to health targets (access, drinking water free of *E. coli*).

As Rose noted, however, the infrastructure necessary for ensuring access to safe drinking water is lacking in much of the world. Home water treatment is in theory a viable alternative, she added, but "it's not about whether we can get the technology into the hands of the people, it's whether they're going to use it." It has recently been demonstrated that, unless compliance rates for home water treatment in a community are near 100 percent, high rates of diarrhea will persist due to the extreme contagiousness of many waterborne pathogens (Enger et al., 2013). Clearly, meeting the goal of sustainable water security will require both innovation and insight into human behavior, Rose observed.

[15] The eight Millennium Development Goals (MDGs)—which range from halving extreme poverty rates to halting the spread of HIV/AIDS and providing universal primary education, all by the target date of 2015—form a blueprint agreed to by all the world's countries and leading development institutions. They have galvanized unprecedented efforts to meet the needs of the world's poorest. The United Nations is also working with governments, civil society, and other partners to build on the momentum generated by the MDGs and carry on with an ambitious post-2015 development agenda. SOURCE: http://www.un.org/millenniumgoals/environ.shtml (accessed August 6, 2014).

Threats to water quality in the United States Rose remarked that before using water or developing water resources, people ask the simple yet difficult question, "How safe is the water?" While the effect of global environmental change on waterborne disease risks at all geographic levels remain largely to be determined, it is known that human fecal contamination and zoonotic pathogens present major threats to the biological safety of water globally, and that failing wastewater facilities, combined sewer overflows,[16] and agricultural runoff contribute to water contamination in both economically developing and developed countries, she stated. In the United States—the focus of Rose's presentation—an estimated 30 to 40 percent of the millions of existing septic systems are failing, she noted.

Following the introduction of water filtration, chlorination, and sewage treatment in the first decade of the twentieth century, death rates for typhoid fever, an important waterborne disease, dropped rapidly in the United States, Rose reported. In the succeeding decades, fewer community waterborne disease outbreaks occurred. Yet, she added, as typhoid declined, other waterborne diseases emerged—such as giardiasis, which was first reported in the 1960s. Today, an estimated 12 to 19 million cases of waterborne illness occur each year among customers of community water systems in the United States, she said. They are caused by a wide variety of pathogens, many of which are generally excreted from hosts in large numbers; resist treatment; and may persist in the environment. As a result, Rose observed, "We cannot just throw chlorine in there, we have to know how we can kill some of these more resistant pathogens."

These treatment-resistant pathogens include microbes that are highly infectious at low doses, and those that can be transmitted by inhalation such as the amoeba *Naegleria fowleri*, recently discovered in two Louisiana water systems, which causes fatal meningoencephalitis, she explained. Organisms such as tiny single-stranded cycloviruses—animal viruses found in significant numbers in sewage, and recently associated with acute central nervous system infections—may escape standard disinfection and filtration, she added (Tan et al., 2013).

The emergence of these and other waterborne diseases raises an important set of intersecting questions, Rose observed, including

[16] Combined sewer systems are sewers that are designed to collect rainwater runoff, domestic sewage, and industrial wastewater in the same pipe. Most of the time, combined sewer systems transport all of their wastewater to a sewage treatment plant, where it is treated and then discharged to a water body. During periods of heavy rainfall or snowmelt, however, the wastewater volume in a combined sewer system can exceed the capacity of the sewer system or treatment plant. For this reason, combined sewer systems are designed to overflow occasionally and discharge excess wastewater directly to nearby streams, rivers, or other water bodies. These overflows, called combined sewer overflows, contain not only storm water, but also untreated human and industrial waste, toxic materials, and debris. They are a major water pollution concern for the approximately 772 cities in the United States that have combined sewer systems. SOURCE: http://cfpub.epa.gov/npdes/home.cfm?program_id=5 (accessed August 6, 2014).

- How and why is water quality changing?
- What are the sources of emerging waterborne pathogens, and how does their emergence relate to ecosystem health?
- What measures must be taken to restore and protect water systems over the long term?

To examine these issues, Rose and coworkers use two model frameworks: pathogen-specific quantitative microbial risk assessments (QMRAs), to evaluate water management strategies (Coulliette et al., 2012; Enger et al., 2013), and an integrated systems model (see Figure WO-13) to inform more general decision making.

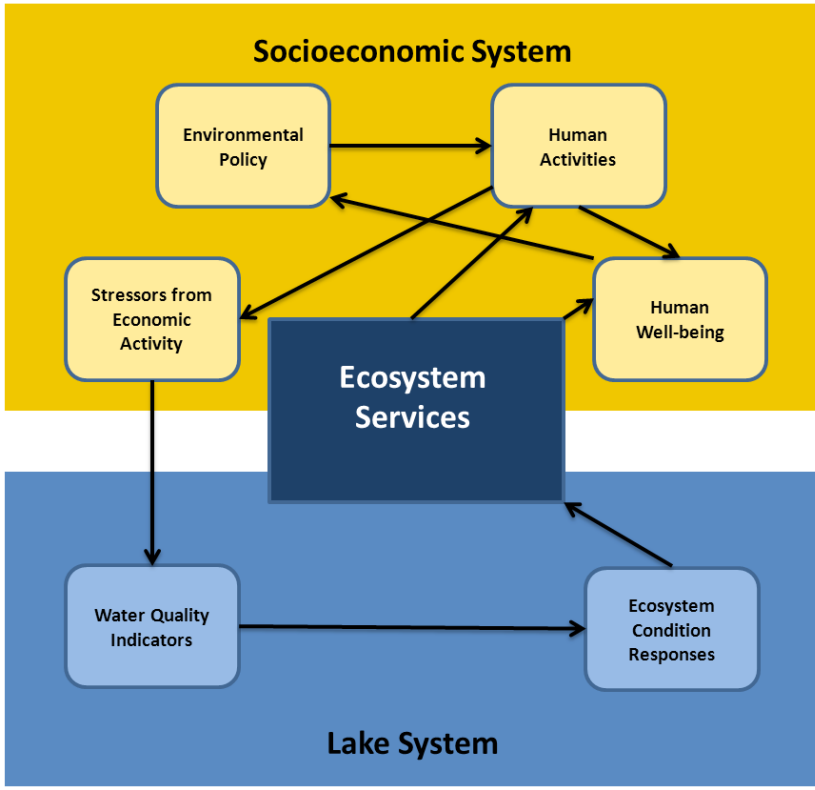


FIGURE WO-13 Coupled human and natural systems (CHANS) framework. The socioeconomic system is composed of four interrelated subsystems: human activities, stressors from socioeconomic activities, human well-being, and environmental policies. The lake system is described through two subsystems: water quality indicators and the ecosystem responses.
SOURCE: Adapted from Mavrommati et al., 2013.

Linking water quality to health Using historical data, Rose and coworkers are attempting to examine interactions between ecological and socioeconomic systems as they affect water quality—and thereby, human health and well-being—in the Great Lakes region. The earliest source was a 1913 bacteriological study of samples taken from 1,000 locations that identified sewage discharges as a significant source of pollution, and which recommended both wastewater and drinking water treatment for the region.

Focusing on the small but important watershed of Lake St. Clair, which connects the upper and lower Great Lakes and provides drinking water for 4.5 million people, these investigators compared changes in precipitation, lake levels, land use, human population, and household income with trends in water quality over the past century. Wastewater treatment did not significantly eliminate waterborne disease in the watershed until after 1940, Rose stated, and water quality remained inconsistent until reforms mandated by the Clean Water Act were implemented in the 1980s. The resulting improvement in water quality soon reversed, and has since deteriorated to pre-1950s levels, she reported.

To extend their historical study, the researchers obtained cores of lake sediments in two locations—Anchor Bay, which is relatively undeveloped, and the heavily urbanized Clinton River—and are examining them for fecal pollution indicators, antibiotic-resistant microbes, and several markers of eutrophication.[17] Fecal pollution indicators for Anchor Bay increased steeply between 1875 and 1900, when there was heavy logging activity in that area, but remained stable thereafter; by contrast, Clinton River did not reach similar levels of pollution until after 1950, but a steep rise since the 1980s nearly doubled that level. Rose suspects that combined sewer overflows—from sewers installed in increasing numbers between the 1950s and 1980s—played a key role in raising fecal pollution rates in Clinton River.

With the data they have gathered so far, Rose and coworkers developed a complex causal loop diagram—a more detailed and specific version of the integrated systems model shown in Figure WO-14—to illustrate the interacting forces contributing to fecal pollution in Lake St. Clair.

It can be reduced to two main pathways, she explained: one derived from human water use and waste production; the other, from nonpoint sources (e.g., agricultural runoff) related to land use. The model also incorporates socioeconomic variables such as human well-being and income in order to inform decisions on land use and infrastructure. For example, she said, "What if climate gets wetter? We may show that the intensity of the storms is playing a major role . . . as opposed to the water infrastructure. Where are we going to put our dollars?"

[17] Eutrophication is an excessive richness of nutrients in a lake or other body of water, frequently due to runoff from the land, which causes a dense growth of plant life and death of animal life from lack of oxygen. SOURCE: http://www.oxforddictionaries.com/us/definition/american_english/eutrophication (accessed August 6, 2014).

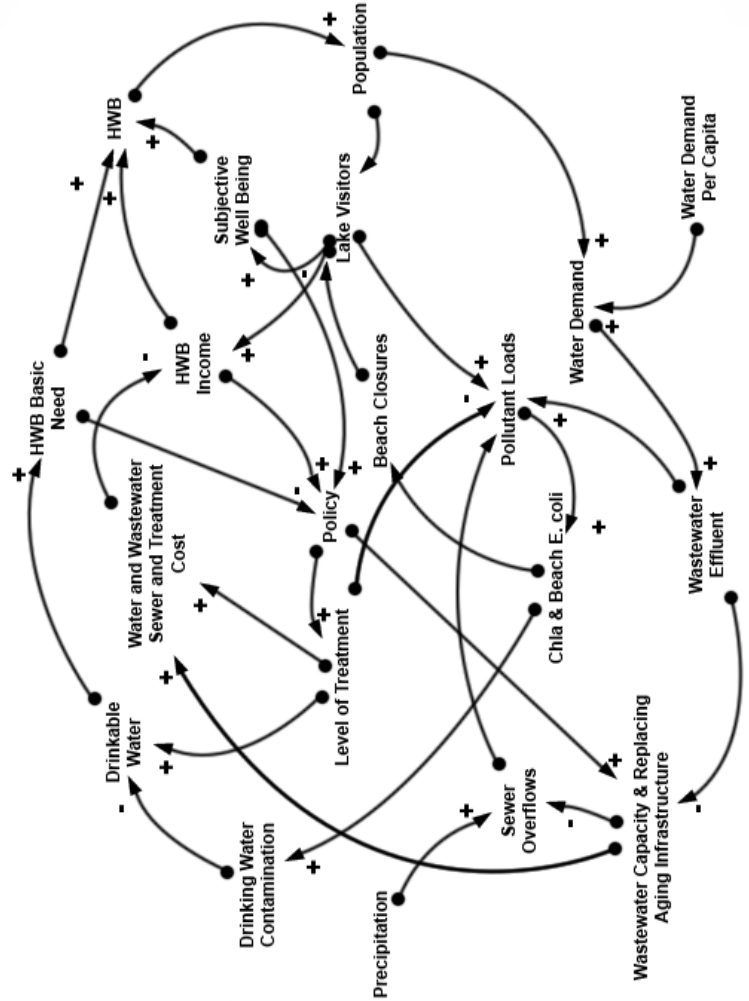


FIGURE WO-14 Causal loop diagram representing two pathways. Pathway 1 is human use of water (residential water demand) and, consequently, the production of pollutant loads; Pathway 2 is nonpoint source pollution related to land use (tourism).
SOURCE: Mavrommati et al., 2013.

Road Development

Both ecological and social drivers of infectious disease transmission are influenced by road development, observed speaker Joseph Eisenberg, of the University of Michigan (Dr. Eisenberg's contributions may be found on pages 213–229, 230–250, and 251–266 in Appendix A). The introduction of primary roads into remote areas inevitably alters both human interactions and ecosystems and, by facilitating movement, changes population structure, he said (see Figure WO-15). These effects are magnified by the subsequent construction of secondary roads in a process that tends to unfold over the course of decades, as increasing numbers of villages within the region gain access and exposure to roadways, he added. To learn how road development interacts with the dynamics of diarrheal disease and with the transmission of antibiotic-resistant enteric pathogens, Eisenberg and coworkers conducted epidemiological studies in an area of coastal Ecuador at the time that its first roads were being constructed (Eisenberg et al., 2006, 2011).

Roads as catalysts for diarrheal disease dispersal While past studies have focused on the influence of road construction on the emergence and spread of sexually transmitted diseases, which are largely shaped by social processes, and VBDs, which are driven by ecological factors, Eisenberg's research has focused on the complex transmission patterns of enteric pathogens, which are affected by both social and ecological forces. An estimated 1 billion people lack access to safe water and adequate sanitation, placing them at high risk for diarrheal diseases, Eisenberg observed. While mortality from these diseases has been declining worldwide, he said, the risk for disease remains—and threatens to increase with the spread of antibiotic-resistant pathogens. This is the case in their study region in northern Ecuador, where roads have led to the rapid development of new settlements with substandard water and sanitation.

"Enteric pathogens can survive in the environment in water, food, and different media, and also have the propensity to transmit person to person," Eisenberg

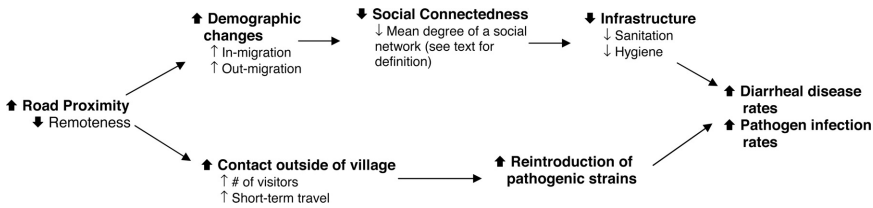


FIGURE WO-15 Causal diagram linking proximity of the road to increases in infection and diarrheal disease.
SOURCE: Eisenberg et al., 2006.

pointed out. A wide range of organisms can cause diarrheal diseases, and a given enteric pathogen may exploit a variety of transmission pathways. Consequently, as he and coauthors have noted, diarrheal diseases are influenced by many interacting and interdependent risk factors (Eisenberg et al., 2012).

To explore how social and environmental changes associated with road construction influence the epidemiology of diarrheal diseases, Eisenberg and coworkers compared enteric pathogen infection rates from case-control studies conducted in 21 villages across their study region in northern Ecuador with infection rates in the regions' major population center, Borbón, as well as between those communities that reside close to the road and those that reside far from the road (Eisenberg et al., 2006). "Prior to the road, these people had lived quite independently, surviving on different kinds of industry that the river transport system supported," he noted. This changed, however, when interest arose in extracting hardwood and other resources from the area, and a road was constructed connecting Borbón to the coast and also up in to the Andes. In the ensuing 10–15 years, he said, secondary roads began to link formerly remote villages to Borbón.

The researchers selected the villages they surveyed to provide a cross-section of remoteness from Borbón, their closest access to the primary road (Eisenberg et al., 2006). They visited each village three times over the course of 2 years, during which they tested each person who reported diarrhea for pathogenic *E. coli*, rotavirus, and *Giardia*, and collected information about his or her social network. Using two different definitions of remoteness (distance and cost/time), they found that diarrheal disease in general, as well as for infection by all three pathogens, was more prevalent in villages closer to Borbón. This trend was weakest for *Giardia* and strongest for *E. coli*, which one might expect based on the contrasting transmission dynamics of the two pathogens, Eisenberg noted; *Giardia* is shed over a longer period by its hosts, persists longer in the environment, and has a lower infectious dose than *E. coli*. As a result, he explained, "*E. coli* is going to be cut out, the transmission potential is going to be cut off much more easily in a village that has better sanitation and hygiene than *Giardia*." *Giardia* is therefore better able than pathogenic *E. coli* to maintain transmission within the more sanitary environment of remote villages, the researchers concluded (Eisenberg et al., 2006).

Pathways to antibiotic resistance The evolution and spread of antibiotic resistance occurs over multiple scales, Eisenberg noted. These range from individual usage, to community-level and regional spread of antibiotics and resistant pathogens through water systems and the soil, as well as through host migration. To examine how each of these processes may be influenced by road construction, he and coworkers analyzed data on antibiotic use and the prevalence of antibiotic-resistant *E. coli* collected as part of the previously described surveys of diarrheal disease in northern Ecuador (Eisenberg et al., 2006, 2011). As with the risk for diarrheal disease in general, they found villages that were close to the road were

more likely to have a significantly higher prevalence of antibiotic resistance as compared with more remote villages.

Interestingly, the researchers were then able to determine that this pattern could not have been caused by differences in antibiotic use between the close and remote villages (e.g., an individual-level influence on antibiotic resistance). Rather, a more complex explanation emerged: under conditions of low antibiotic usage, differences in transmission rates across villages have very little effect on relative risk for antibiotic resistance, Eisenberg stated. Instead, he said, antibiotic resistance is driven by the higher rate of introduction of resistant bacteria in the close communities than in the far communities as a result of increased migration and movement into close villages; conversely, when antibiotic use is high, resistance is driven by transmission rates. The varying levels of antibiotic resistance across their study area appeared to conform to this model of community-level influence (Eisenberg et al., 2011).

Eisenberg and coworkers then considered how the various effects of road proximity on disease could explain community-level influences on disease prevalence. This same approach might be applied as a model system to predict the transmission dynamics of antibiotic resistance. First, increased contact with the outside world in villages close to the road could increase the rate of introduction of antibiotic-resistant pathogens, Eisenberg noted. Second, their research suggested that close villages were less socially cohesive—that is, they had less dense social networks—than those far from the road; they further associated decreased social cohesion in the close villages with reduced sanitation and hygiene. Thus despite the fact that physical closeness among remote village residents (as measured by distance between households) raised the risk of disease, this effect appeared to be overcome by the concomitant advantages of social closeness, as illustrated in Figure WO-16.

These studies taken together suggest that road construction leads to social and ecological changes that influence disease dynamics across a region. These direct and indirect effects of disease dynamics are mediated through local social structures. Eisenberg noted that his team has also determined that climate and hydrological processes related to primary and secondary road construction influence the spread of antibiotic resistance in their study region and influence the patterns of diarrheal disease in their study region, as illustrated in Figure WO-17.)

Climate Change

As Patz previously observed (see the section "Health Impacts of Environmental Change" on page 13), the major features of climate change—warming and hydrologic extremes—can profoundly influence infectious disease dynamics. Yet, it is difficult to identify specific effects of climate change on infectious disease risk among human, animal, and plant communities, and to define how climate change interacts with other drivers of global environmental change (e.g., land

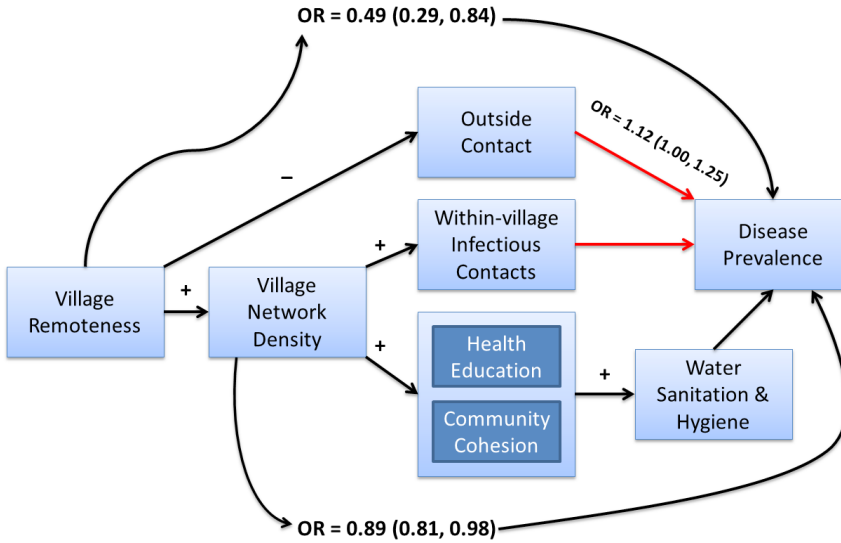


FIGURE WO-16 Postulated conceptual model: Effects of social relationships on disease outcomes, Esmeraldas, Ecuador, 2007. Risks and protective effects are mediated through a number of social processes.
NOTE: OR = odds ratio.
SOURCE: Adapted from Zelner et al., 2012.

use) to alter the spread and transmission of infectious diseases. Several speakers described their efforts to undertake this challenge through their studies of a variety of species and ecosystems.

Changing disease patterns in the Arctic "The Arctic is unique in many respects," observed speaker Alan Parkinson, of the CDC (Dr. Parkinson's contribution may be found on pages 310–327 in Appendix A). While definitions of "the Arctic" vary, Parkinson noted, he includes all of Alaska and northern Canada to about 60 degrees north in this region, together with parts of northern Quebec, Labrador, Greenland, the Faroe Islands, Iceland, Norway, Finland, Sweden, and the northern regions of the Russian Federation. This area covers approximately one-eighth of the Earth's surface, but its residents number only about 4 million, of whom about half live in the Russian Federation, and 10 percent are of indigenous ancestry, he stated.

Investigations in the Arctic provide an opportunity to study climate-sensitive infectious diseases in isolated human and wildlife populations, according to Parkinson. The warming trend that has occurred worldwide over the twentieth century has been amplified in the Arctic by more than three-fold over the past half century, he said. As a result, the average extent of sea ice has diminished by as much as 20 percent—a decline that has quickened as the growing area of open

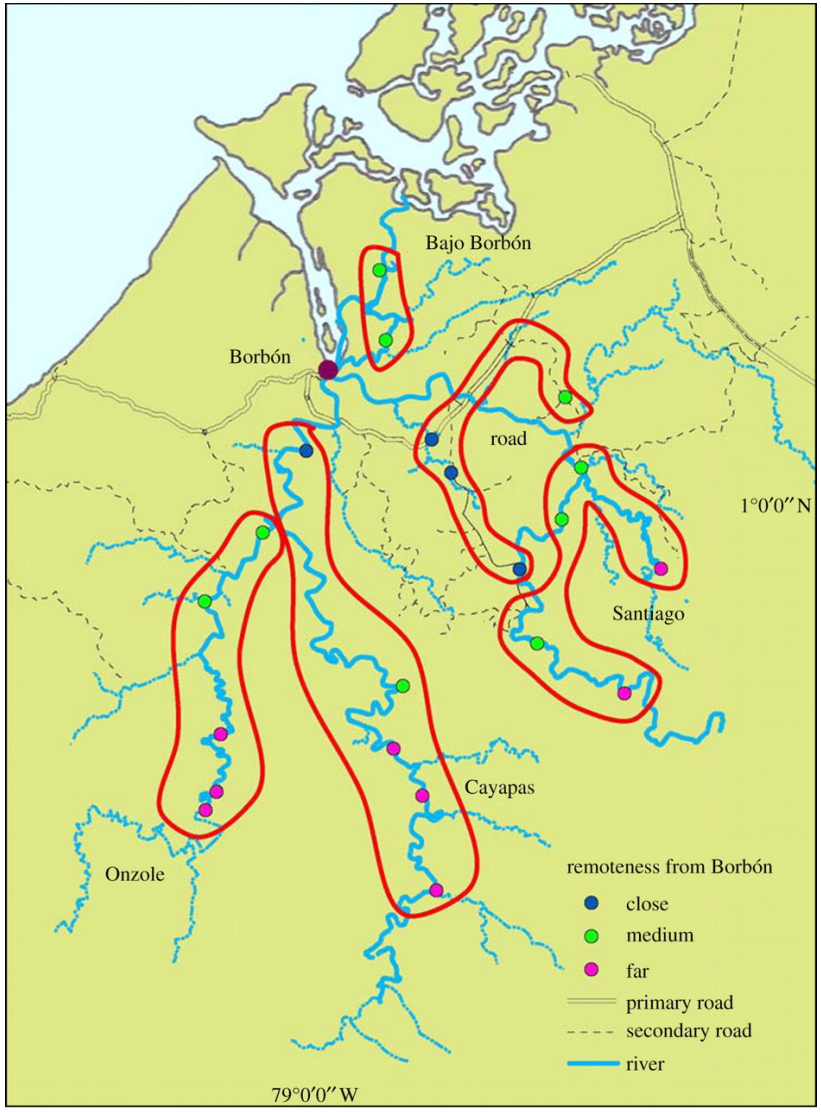


FIGURE WO-17 An ecological perspective. Map of study region. The 21 villages are categorized by river basin (Santiago, Cayapas, Onzole, Bajo Borbón, and road), and by remoteness (close, medium, and far). The presence of a road or roads causes environmental changes (social and ecological). These changes occur differentially across the landscape of villages, affecting social structure (spread of microorganisms differentially through water sanitation and hygiene pathways); movement and migration patterns at multiple scales; and climate and hydrological processes. Regional patterns of environmental change will vary over time.
SOURCE: Eisenberg et al., 2011.

ocean surface warms. "This will accelerate further and will probably result in a total loss of sea ice in the summer projected for later this century," he reported. Warming is also extending vegetation zones and animal ranges northward, increasing the number of species—including those of their associated parasites—in the Arctic, he observed (Revich et al., 2012). At the same time, marine species that are dependent on sea ice are declining in numbers, threatening the already vulnerable indigenous populations that depend on marine animals for food.

Indigenous peoples of the Arctic have significant health disparities compared with nonindigenous populations, Parkinson stated. Many of their communities lack adequate water and sanitation infrastructure. In Alaska, 22 percent of rural homes lack in-home water and sewage service, limiting residential use of water for hygiene to as little as 1.6 gallons per person per day, raising the risk of "water-washed" diseases such as skin and eye infections, he reported. A study conducted in rural Alaskan villages found that higher respiratory and skin infection rates were associated with a lack of in-home water service (Hennessy et al., 2008). In villages like these, sewage is often disposed of in a pit lagoon that is vulnerable to flooding—that is occurring with increasing frequency in recent years, he added. "With the thawing of the permafrost we have flooding, shoreline erosion, storm surges, [and] loss of protective sea ice," he said. "Many communities are facing relocation because village housing, water, sanitation, food storage, [and] structures are being undermined."

Parkinson also noted that many residents of the Arctic depend on hunting for their food supply—preserving meat by drying, smoking, fermentation, and freezing (where permafrost exists)—all processes that are vulnerable to the effects of climate change and are associated with the risk for zoonotic diseases such as trichinellosis, toxoplasmosis, and brucellosis (Hueffer et al., 2013). He observed that large and increasingly frequent (and formerly rare) walrus die-offs have occurred in northwest Alaska coincident with sea ice loss, and warned that animals that scavenge the carcasses could transmit *Trichinella*.

Climate change may also influence the density and distribution of animal hosts of arthropod vectors, resulting in an increase in human illness or a shift in geographical range of disease, Parkinson stated. Milder winters and earlier spring onset have been associated with a shift in the range of tick-borne encephalitis in northwestern Russia (Tokarevich et al., 2011). After a period of unusually high temperatures in 2006, Northern Sweden experienced an outbreak of hemorrhagic fever caused by Puumala virus when large numbers of voles, which carry the virus, sheltered in homes due to a lack of snow cover (Pettersson et al., 2008).

"I think we can learn a lot from outbreaks about climate change and infectious disease emergence," Parkinson concluded. He urged improvements in both surveillance and disease diagnostics (for animals as well as humans) to advance this goal, which is especially important to pursue given the recent openings of the Northwest and Northeast Passages to commercial shipping. Regional public health institutes and laboratories collaborating in a program called International

Circumpolar Surveillance (Parkinson et al., 2008) have begun to meet this challenge by monitoring certain infectious diseases and their relationship to climate change, and are bringing the One Health paradigm to the Arctic, he reported.

Climate shifts, animal migrations, and infectious disease dynamics While the influence of climate change on pathogen dynamics is readily apparent in Arctic wildlife and in some marine ecosystems, detecting such effects in human populations inhabiting temperate regions has proven difficult, noted Altizer. "The wealth of nations; the better infrastructure; and the better health care, surveillance, and control aimed at human pathogens in developed countries, might actually be masking the climate signals," she explained.

Accordingly, the effects of climate change on disease dynamics are more apparent among animals in the wild, Altizer observed (Altizer et al., 2013). For example, she said, in the Arctic, the parasitic worms of musk oxen are developing faster in the tundra due to warmer summers and longer growing seasons (Kutz et al., 2013). More prevalent lungworm infections are reducing musk ox populations, and thereby, food security for residents who rely on this animal for food. At the same time, coral reefs in the Caribbean have become more disease susceptible due to outbreaks associated with warmer water temperatures (Harvell et al., 2009).

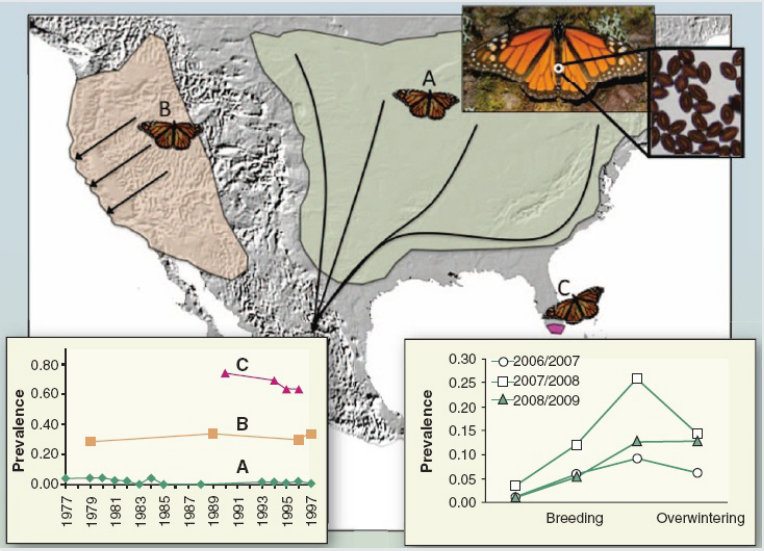
In addition to affecting pathogens and vector behavior, climate change indirectly influences disease dynamics by altering animal migration patterns, Altizer stated (Altizer et al., 2011, 2013). Migration can lower disease risk in some animal populations, she explained, through several mechanisms:

- by allowing animals to periodically escape habitats where parasitic infectious stages have accumulated (thereby starving parasites left behind before the migrants return);
- by imposing stress during strenuous journeys that serves to cull infected—and therefore weakened—animals from the populations; and, in some cases
- by physically separating more vulnerable juveniles from infected adults (Altizer et al., 2011).

However, she noted, animal migrations have been altered, and in some cases have disappeared altogether, as a result of human activities including habitat destruction and climate change (Wilcove and Wikelski, 2008).

Using the monarch butterfly and its protozoan parasite, *Ophryocystis elektroscirrha*, as a model system, Altizer and coworkers have explored the connections between animal migration and infectious disease risk (see figure in Box WO-3). They determined that monarchs in eastern and western North America, which migrate long distances to wintering grounds in Mexico, suffer lower rates of infection than nonmigratory monarch populations that breed year-round in southern

BOX WO-3
Lessons from a Model System: Monarch Migration Drives Large-Scale Variation in Parasite Prevalence



During the past 10 years, Altizer and colleagues studied monarch butterflies (*Danaus plexippus*) and a protozoan parasite (*Ophryocystis elektroscirrha*) (top-right images) for the effects of seasonal migration on host–pathogen dynamics. Monarchs in eastern North America (A) migrate up to 2,500 km each fall from as far north as Canada to wintering sites in Central Mexico (Brower and Malcolm, 1991). Monarchs in western North America (B) migrate shorter distances to winter along the coast of California (Nagano et al., 1993). Monarchs also form nonmigratory populations that breed year-round in southern Florida (C), Hawai'i, the Caribbean Islands, and Central and South America (Ackery and Vane-Wright,

Florida and other locations. Importantly, year-round breeding in monarchs is enabled by mild winters, as well as by the availability of exotic food sources. Sedentary (nonmigratory, winter breeding) monarchs have recently become more common in North America along the south Atlantic and Gulf coasts, and Altizer noted that monarchs at these locations face greater infection risk than their migratory counterparts.

In addition to these effects on disease dynamics, migration can also affect the evolution of pathogen virulence and host resistance in this system, Altizer noted,

1984). Because monarchs are abundant and widespread and can be studied easily both in the wild and in captivity, field and experimental studies can explore effects of annual migrations on host–pathogen ecology and evolution. A recent continent-scale analysis showed that parasite prevalence increased throughout the monarchs' breeding season, with highest prevalence among adults associated with more intense habitat use and longer residency in eastern North America, consistent with the idea of migratory escape (bottom-right graph) (Bartel et al., 2010). Experiments demonstrated that monarchs infected with *O. elektroscirrha* flew shorter distances and with reduced flight speeds, and field studies showed parasite prevalence decreased as monarchs moved southward during their fall migrations (Bartel et al., 2010; Bradley and Altizer, 2005), consistent with the idea of migratory culling. Parasite prevalence was also highest among butterflies sampled at the end of the breeding season than for those that reached their overwintering sites in Mexico (bottom-right graph). Collectively, these processes have likely generated the striking differences in parasite prevalence reported among wild monarch populations with different migratory behaviors (bottom-left graph) (Altizer et al., 2000).

Laboratory studies also showed that parasite isolates from the longest-distance migratory population in eastern North America (A) were less virulent than isolates from short-distance (B) and nonmigratory (C) populations (Altizer, 2001; de Roode and Altizer, 2010), suggesting that longer migration distances cull monarchs carrying virulent parasite genotypes. Work on this model system illustrates how multiple mechanisms can operate at different points along a migratory cycle and highlights the role that migration plays in keeping populations healthy. Monarch migrations are now considered an endangered phenomenon (Brower and Malcolm, 1991) due to deforestation of overwintering grounds, loss of critical breeding habitats, and climate-related shifts in migration phenology. If climate warming extends monarch breeding seasons into fall and winter months, migrations may eventually cease altogether. Evidence to date indicates that the loss of migration in response to mild winters and year-round resources could prolong exposure to parasites, elevate infection prevalence, and favor more virulent parasite genotypes.

SOURCES: Images reproduced from Altizer et al., 2000, 2011; Bartel et al., 2010. Text reproduced from Altizer, 2011.

because the most virulent strains of *O. elektroscirrha* are found among nonmigrating monarch populations, and not among those that migrate long distances (de Roode and Altizer, 2009). "Migration is essentially a sieve that's removing infected animals, especially those that harbor the most virulent pathogen strains, from the population," Altizer concluded. Because many animal migrations are likely to be compromised by climate change and other human activities, she urged greater effort to understand the effects of these losses on infectious disease dynamics.

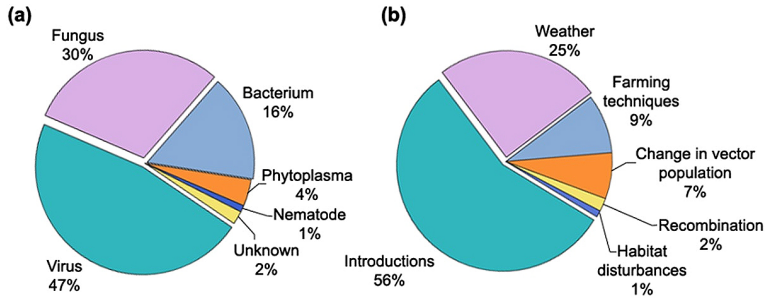


FIGURE WO-18 Major taxonomic groups of pathogens causing plant emerging infectious diseases: (a) viruses, fungi, and bacteria cause the most emerging infectious diseases in plants; (b) introduction of pathogens cause the most plant emerging infectious diseases. SOURCE: Anderson et al., 2004.

Climate effects on plant pathogens As the ultimate source of all food, plants determine the health of all living things; thus the knock-on effects of anthropogenic changes that increase risk for plant diseases are potentially widespread and profound (Flood, 2010; Strange and Scott, 2005; Wheeler and von Braun, 2013). An estimated 16 percent of all crops are lost to disease each year, according to speaker Caitilyn Allen, of the University of Wisconsin; however, if a particular pathogen encounters optimal weather conditions (typically higher temperatures and rainfall), or naïve or abundant host plants, the result may be devastating (Oerke, 2006). A "disease triangle," composed of favorable environment, susceptible host plant, and virulent pathogen, underlies such epidemics, she explained. Human activities influence all of these factors, she added. In particular, anthropogenic factors have contributed to the global warming of the Earth that, in turn, has increased the frequency of flooding rains. Allen went on to observe that humans also move pathogens around the world through trade and travel, and, vast areas of crops are grown as monocultures.[18]

As Figure WO-18 illustrates, infectious disease emergence in plants is strongly influenced by weather, climate change, and pathogen introductions to new host plants, as discussed in Figure WO-19. Concerning the effects of climate change on plant pathogens, speaker Marco Pautasso, from the Centre d'Ecologie Fonctionnelle et Evolutive of France's Centre National de la Recherche Scientifique,[19] has written that plant health is predicted to suffer under climate change due to mechanisms that range from climate- and weather-induced stress to increased pathogen virulence and transmission rates (Dr. Pautasso's contribution may be found on pages 359–374 in Appendix A) (Pautasso et al.,

[18] The cultivation or growth of a single crop or organism especially on agricultural or forest land.
[19] Dr. Pautasso is now with the European Food Safety Authority.

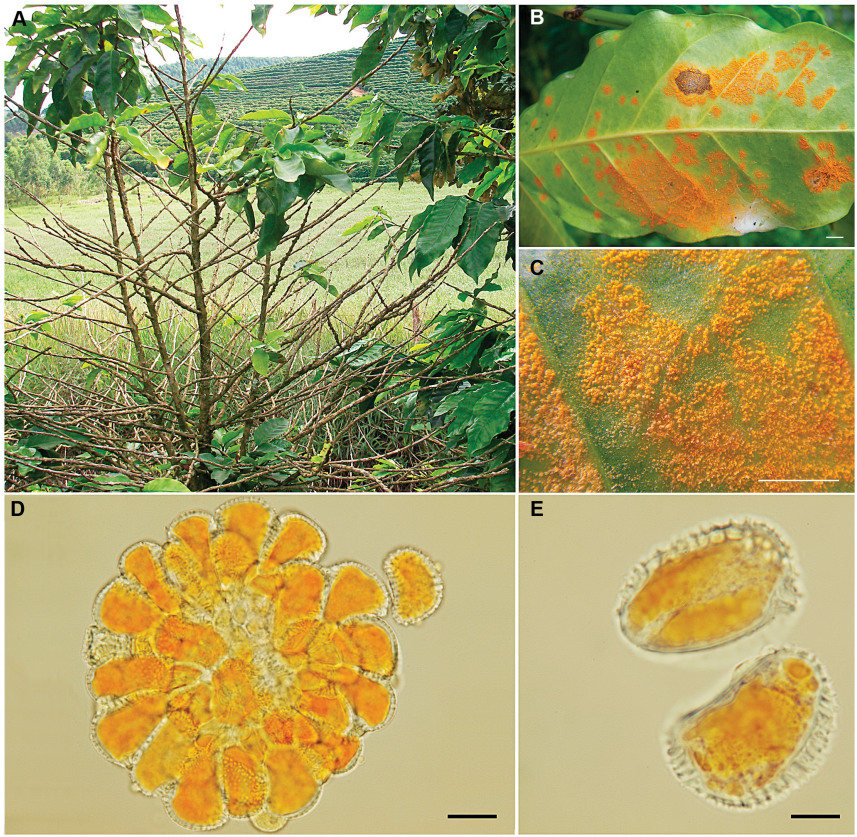


FIGURE WO-19 Coffee rust and climate change. (A) Defoliation in a coffee plantation, Coimbra, Minas Gerais, Brazil; (B) Leaf symptoms on abaxial surface (bar = 0.5 cm); (C) Detail of suprastomatal uredinial pustules coalescing over lower leaf surface (bar = 0.5 cm); (D) Uredinium showing arrangement of spores (bar = 20 µm); (E) Urediniospores—showing the thickened, heavily-ornamented or verrucose upper wall containing carotenoid lipid guttules imparting the yellow-orange color (bar = 10 µm).
SOURCE: Carvalho et al., 2011.

2012). As Allen pointed out, however, climate change has yet to be identified as the sole cause of any plant disease outbreak (Bebber et al., 2013). Allen noted that the emergence of coffee rust in Latin America—described in Figure WO-19—offers an opportunity to characterize the influence of climate change on a plant disease epidemic.

Next to oil, coffee—with an annual crop worth some $80 billion—is the most valuable commodity traded by developing countries. Coffee is grown in more than 50 tropical countries, mainly in large plantations. An understory tree, coffee thrives in shade, but lower-quality sun-tolerant varieties predominate the market,

because they are more profitable. Coffee is native to Ethiopia, but for centuries has been planted and consumed throughout the world; coffee rust (*Hemileia vastatrix*), a wind-blown fungal infection, has followed every move. Coffee rust (Figure WO-19) is an obligate parasite that causes rapid defoliation and eventually kills its host. Its spores are short-lived, but given access to the large-scale monocultures typical of most coffee plantations, can readily produce an epidemic.

Quarantines kept coffee rust out of Latin America until 1970. The use of fungicides kept this fungal pathogen in check until a major outbreak occurred in Colombia in 2008. This epidemic was preceded, and possibly triggered, by 2 years of atypically warm, wet weather. In the intervening years more outbreaks have followed in Latin America, some of them in locations where coffee rust had never been detected before. Now, according to Allen, "We are in the middle of a major rust epidemic on coffee [plantations] in all of Latin America," with declines in yield of approximately 20 percent resulting in losses of over half a billion dollars to date. Unfortunately, she added, because the pathogen overwinters in dead leaves, even larger losses are expected next year.

This disaster begs the question: if coffee rust emerged in Latin America in 1970, and the pathogen is no more virulent (as researchers have determined), why did it take decades to spark epidemic disease? Weather seems to have been the culprit, Allen asserted, and it drove the disease to higher elevations than it had previously reached. As one researcher observed, "Rust was the explosive, but climate change was the detonator" of this epidemic. It will be years before we can say whether this is the case, Allen remarked. She added, however, that "this is a place where it is worth looking if we are trying to find climate change footprints in plant disease development."

Models also provide a way to examine the consequences of climate change for plant disease (see the section "Characterizing the Effects of Environmental Change on Infectious Disease Dynamics" on page 63 for further discussion of ecological models of infectious diseases). Pautasso offered several examples of such models, pointing out their strengths and weaknesses. Most climate change models fail to incorporate the role of plants in carbon release, and thereby, a crucial feedback cascade that could be triggered by warming temperatures or extreme weather events, he observed. Uncertainty regarding the effects of climate change on precipitation levels in specific locations diminishes the predictive capacity of some models, he added. "When we develop scenarios for plant diseases with climate change, it is important to know whether we will just have increasing temperature and decreasing precipitation, or whether both temperature and precipitation will increase," he said, because most plant species and many pathogens will respond differently to these contrasting regimes. Models predicting future plant diseases also should take into account efforts to reduce carbon emissions—and thereby, the ongoing effects of climate change—through the use of plant-based fuels produced in large-scale monocultures.

Another potential unintended consequence of attempts to mitigate the effects of climate change could result from so-called assisted migration: human-mediated movement of plant species threatened by warming temperatures poleward, or to higher elevations, in order to protect them from extinction (McLachlan et al., 2007; Mueller and Hellmann, 2008; Vitt et al., 2010). These efforts seldom take into account the concomitant risk for pathogen introductions to novel environments, Pautasso noted. Such risks need to be examined through both empirical approaches and modeling studies—both of which are relatively scarce in comparison to the numerous review articles on plant disease and climate change, he observed (Pautasso et al., 2012).

Characterizing the Effects of Environmental Change on Infectious Disease Dynamics

The previously described case studies illustrate the daunting challenges involved in measuring the effect of individual anthropogenic factors on disease dynamics, host–microbe interactions, and in understanding the interplay of multiple factors that influence these relationships. These direct and indirect forces are not only challenging to disentangle, but they are highly localized in their individual and collective effects. These conditions must be taken into account in efforts to explain—let alone predict—the overall impact of environmental change on disease transmission patterns, Relman observed.

Conceptual frameworks, models, and maps provide ways to organize the wealth of information required to characterize the complex ecological relationships that shape the dynamics of infectious diseases across a range of spatial and temporal scales. Several speakers described the design, refinement, and application of such approaches to analyze existing information, to identify knowledge gaps and research goals, and as a foundation for prediction.

Frameworks and Models: Epidemics as Networks

As illustrated in work presented by Dobson on food webs, and by Eisenberg on social relationships within villages, networks provide a means to portray interconnections between components of a system. Epidemiologists use networks to illustrate the spread of human and animal pathogens, but according to Pautasso (2013), plant pathologists have made limited use of this tool. In his presentation, however, Pautasso described the application of network epidemiology to address emergent tree pathogens (see next section). He also noted that in addition to analyzing the spread of disease through large populations, networks could be used to examine heterogeneity in contacts among members of subgroups (e.g., within social or ecological communities such as schools, workplaces, farms, or plant nurseries), which has been demonstrated to shape the course of epidemics, and could therefore inform their control (Jeger et al., 2007; Pautasso and Jeger, 2014).

Exotic Tree Pathogens: Assessing Impact and Options for Response

Tree diseases, along with other plant diseases caused by exotic pathogens, have increased in number and severity over the course of the Great Acceleration, and in particular, with the expansion of global trade (Pautasso et al., 2012; Santini et al., 2013). Spatial models depicting the presence and absence of emerging diseases among susceptible host species can inform strategic responses to these threats, Pautasso observed; he described two such efforts, directed against *Phytophthora ramorum* (the cause of Sudden Oak Death in North America, and Sudden Larch Death in the United Kingdom), and *Hymenoscyphus pseudoalbidus* (the cause of ash dieback in Europe; Queloz et al., 2011).

Since it was first described in 2001 (Werres et al., 2001), *P. ramorum*, a generalist oomycete, has infected and killed a wide range of both wild and ornamental host plants in North America and Europe, including oak, camellia, and rhododendron (Pautasso, 2013). Molecular evidence suggests that this pathogen was spread efficiently through global plant trade networks. Before 2009, the disease affected relatively few trees in Britain; since then, its spread to Japanese larch, which is widely planted, has affected thousands of hectares of tree plantations, Pautasso said.

To assess the potential impact of this pathogen in the United Kingdom, researchers built a spacially explicit simulation model of epidemic development that incorporates data on the distribution of susceptible host plants as well as plant trade networks (see Figure WO-20).

Investigating pathogen invasion routes and identifying environmental variables associated with disease severity can help set priorities for monitoring and predict the likely further development of the epidemic (Pautasso, 2013). A further development of this model has accurately predicted increased risk for disease in southern and western Scotland, Pautasso reported.

As Pautasso observed, Ash dieback likely spread, via the plant trade, to Poland from East Asia in the early 1990s, and thence throughout Europe; it was first reported in the United Kingdom in 2012 (Gross et al., 2014). The highly lethal fungal disease threatens the existence of the common ash (*Fraxinus excelsior*), a keystone tree species throughout temperate Europe, and its associated biodiversity; it could potentially affect several *Fraxinus* species in North America as well (Pautasso et al., 2013).[20] Determining the origin of the pathogen is important in order to prevent further introduction of the pathogen to new environments and

[20] Asian *Fraxinus* spp. appear to be resistant to the pathogen, as they are likely to have coevolved with it.

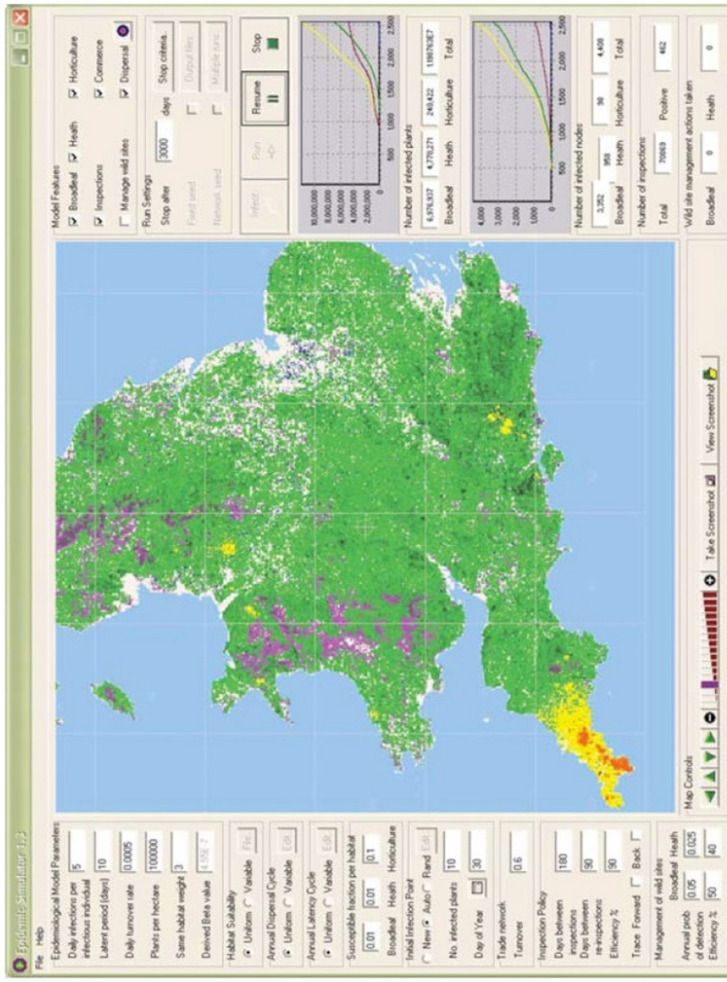


FIGURE WO-20 Example of the spatially explicit simulation model of *P. ramorum* dispersal in England and Wales developed by Tom Harwood (Harwood et al., 2009). The model integrates data on the distribution of main susceptible hosts and a realistic reconstruction of the plant trade involving ornamental plants susceptible to *P. ramorum*.
SOURCE: Image courtesy of Tom Harwood, CSIRO, Australia.

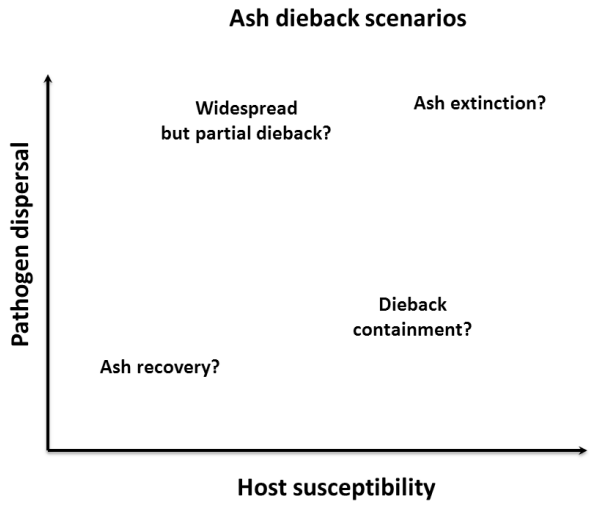


FIGURE WO-21 Four basic scenarios for the further development of ash dieback in Europe, based on levels of pathogen dispersal and host susceptibility. If both are consistently high, host disappearance may take place.
SOURCE: Pautasso et al., 2013.

of new strains of the pathogen worldwide, as well as to inform the search for biological controls and candidate species and cultivars for resistance breeding.[21]

Because of its recent emergence—and in contrast to *P. ramorum*—relatively little is known about environmental factors that might influence ash dieback severity following infection. What is known is that the pathogen is dispersed through wind-blown spores and also on infected ash saplings, which can be asymptomatic. Pautasso and coauthors (2013) propose four basic scenarios for the further development of ash dieback in Europe, based on future levels of pathogen dispersal and host susceptibility, as shown in Figure WO-21.

Luckily, some resistant ash trees have been observed in Denmark, Lithuania, and Sweden (McKinney et al., 2014). If pathogen dispersal is limited, high host susceptibility may matter less, but this scenario is made less realistic by long-distance dispersal due to trade in infected ash saplings, such as to the

[21] As Allen noted in discussion, breeding for disease tolerance or resistance has long been considered the best way to manage plant disease threats. "If you have good disease resistance in your crops—not an option available to human doctors—then you don't have to worry about the disease," she observed. "You don't have to spray. You can grow with impunity the crop of interest—until the pathogen evolves . . . the ability to overcome that resistance, which happens all the time, unfortunately." This approach has been used with mixed success to save disease-threatened tree species such as the American chestnut (*Castanea dentata*) against chestnut blight and elm trees (*Ulmus* spp.) against Dutch elm disease (Pautasso et al., 2013).

United Kingdom and Ireland. Should common ash susceptibility be limited in some regions (e.g., those with hot and dry summers typical of the Mediterranean climate), the impact of the dieback would be less devastating. Each scenario can be considered for various regions and countries, as well as for the whole distribution of common ash. Further dimensions to be considered are the conduciveness of the environment to disease, other pests such as emerald ash borer (which has been reported to be spreading westward from the Moscow region of Russia), as well as human actions to prevent further worsening of the dieback.

Ecophysiology of host–pathogen interactions In a recent review article, Altizer and coauthors (2013) pointed out that integrating knowledge from ecophysiological responses of organisms to temperature variation with modeling approaches is needed to better predict how different host–pathogen relationships will respond to climate warming. This approach combines established relations between metabolism, ambient temperature, and body size, with epidemiological modeling to predict how general classes of pathogens (e.g., directly transmitted or vector-borne) and hosts (ectotherms or endotherms) will change with increasing temperatures (see Figure WO-22).

"Building from this foundation, the next step is to extend such general models to specific pathogens of concern for human health, food supply, or wildlife conservation, which will require empirical parameterization, with attention to the on-the-ground conditions," the authors wrote. "Modeling efforts should be integrated with experiments to test model predictions under realistic conditions, and with retrospective studies to detect the 'fingerprint' of climate-induced changes in infection." Because detecting signals of climate change in many human diseases remains problematic, the authors emphasize the importance of long-term ecological studies to examine past distributions of pathogens, important hosts, and disease severity.

Case study: Weather-based risk for coccidioidomycosis (valley fever) Coccidioidomycosis, also known as valley fever, is a lung infection of humans or animals by the fungal pathogens *Coccidioides immitis* and *C. posadasii* (Nguyen et al., 2013). These fungi occur in desert soils in the Western Hemisphere. In the United States, two-thirds of all cases occur in the "valley fever corridor," that includes Phoenix and Tucson, Arizona, and areas along the 150-mile stretch of highway that connects the two cities, according to speaker John Galgiani, of the University of Arizona (Dr. Galgiani's contribution may be found on pages 266–282 in Appendix A). While most people who inhale these fungal spores suffer a mild illness and develop resistance to reinfection, a few—perhaps 500 per year in Arizona—manifest life-threatening pneumonia or serious, potentially chronic, infections outside the lungs, resulting in about 160 deaths per year. Among diagnosed and reported cases of coccidioidomycosis in Arizona, an estimated 75 percent of people lost at least 2 weeks of work and 40 percent were hospitalized,

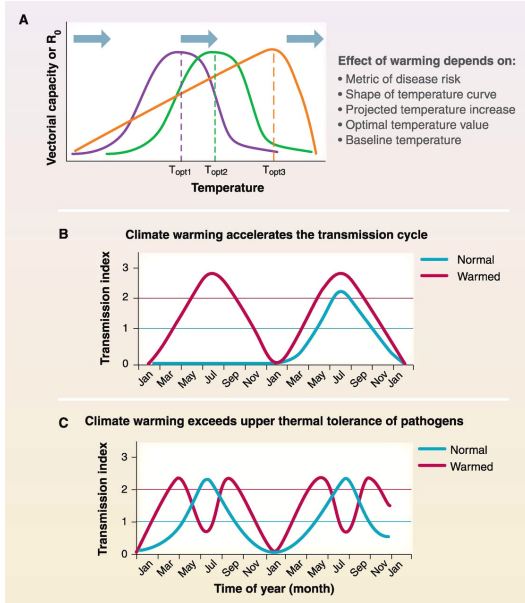


FIGURE WO-22 Pathogen responses to climate change depend on thermal tolerance relative to current and projected conditions across an annual cycle. (A) Gaussian curves relating temperature to a metric of disease risk suggest symmetrical temperature zones over which warming will increase and decrease transmission, whereas left skewing [a common response for many terrestrial ectotherms, including arthropod vectors (Deutsch et al., 2008)] indicates greater potential for pathogen transmission to increase with warming. Bold arrows represent geographic gradients that span cool, warm, and hot mean temperatures, which indicate that the net effect of warming (at point of arrows) depends on whether temperatures grow to exceed the optimum temperature (T_{opt}) for disease transmission. Projected changes in disease will further depend on the starting temperature relative to T_{opt}, the magnitude of warming, measurement error, adaptation, and acclimation. (B) Pathogens at their northern or altitudinal limits might show range expansion and nonlinear shifts in their life cycle in response to warmer temperatures (red) relative to baseline (blue). For example, a shift from 2- to 1-year cycles of transmission has occurred for the muskox lungworm (Kutz et al., 2009). This outcome could generate sporadic disease emergence in a naïve population (if extremes in temperature allow only occasional invasion and/or establishment), or could gradually increase prevalence and establishment. (C) At the low-latitude or low-altitude extent of a pathogen's range, where temperature increases could exceed the pathogen's thermal optimum, transmission might be reduced, or we might see the emergence of a bimodal pattern whereby R_0 peaks both early and late in the season, but decreases during the midsummer [as in the case of the arctic *O. gruehneri*–reindeer example (Molnár et al., 2013)]. In (B) and (C), the lower blue line represents $R_0 = 1$, above which the pathogen can increase; values above the pink line represent severe disease problems owing to a higher peak of R_0 and a greater duration of time during which $R_0 > 1$.
SOURCE: Altizer et al., 2013.

he reported. "If you add in economic impact from lost work, all of the outpatient management of this disease, it is easily probably a couple of hundred million dollars a year for Arizona," he said.

Colleagues of Dr. Galgiani were prompted to create models to describe the relationship between seasonal precipitation and the incidence of coccidioidomycosis after hypothesizing that an annual increase in cases after an intense dust storm struck Phoenix in 2011 was not a consequence of the storm itself, but of weather patterns that raised the risk for both dust storms and disease, he said. Tamerius and Comrie (2011) had created a time series of predicted exposure to *Coccidioides* spores based on laboratory-confirmed cases in two Arizona counties over a 12-year period. Their analysis suggested that spores released during the late summer and fall persist in the environment and remain infectious for several months, and that the size of the spore "bloom" influences human exposure in the winter and spring. They also determined that exposures end abruptly in mid-summer, coincident with the local rainy season, which may suppress aerosolization of the spores. Their model-predicted cycle of "grow and blow," in which precipitation first raises spore levels, then restricts spore distribution—conformed to local observations, as shown in Figure WO-23.

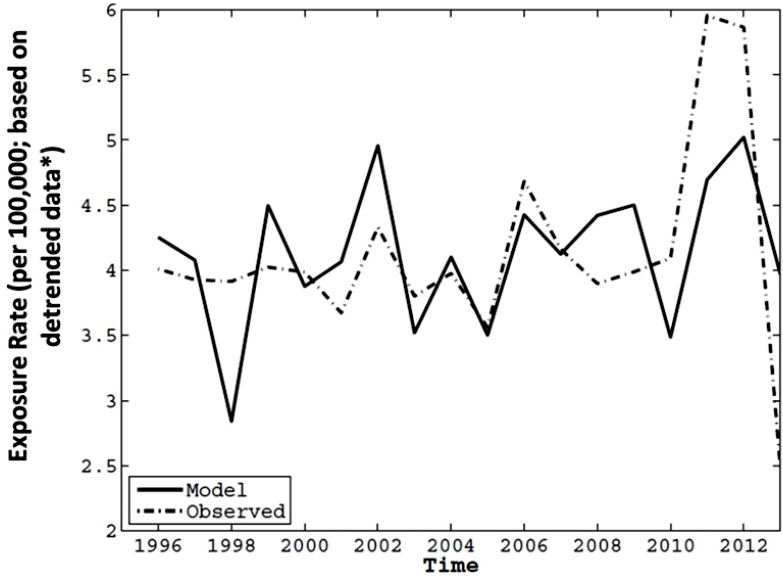


FIGURE WO-23 Modeled versus observed August–March (1995–2013) cocci exposure in Maricopa County, Arizona.

* From Tamerius and Comrie, 2011.

SOURCE: Galgiani presentation, 2013.

To refine this model, Galgiani's colleagues hope to sample spore levels in the air and soil and link those measurements to precipitation and exposure levels. Because spore distribution is suspected to be patchy, locating soils with high spore levels and protecting them from disturbance could reduce the risk of exposure, he noted. Environmental mechanism(s) linking precipitation and spore exposure levels remain to be determined, but they hint at the possibility that rodents serve as a reservoir for this disease—and therefore merit exploration, he stated. "Similar to the trophic cascade hypothesis associated with variable outbreaks of plague and hantavirus, high precipitation during the preceding winter may result in an increase in rodent populations," Tamerius and Comrie (2011) suggest. "This mechanism potentially increases the density of rodent carcasses the following fall, which have been hypothesized to be suitable environments for fungal growth due to their high nutrient content."

Ko observed that environmental methods to predict risk for infectious diseases, such as those proposed by Galgiani's colleagues, must employ both a robust detection method and a rational sampling scheme, and must be proven to be epidemiologically valid. While admitting that detection of *Coccidioides* spores remained problematic, Galgiani proposed strain typing as a means to link spore levels in the environment to infection rates. He also noted a World War II remediation effort that confirmed one of the model's underlying assumptions: precipitation during the "blow" period reduces exposure to aerosolized spores. During wartime, he said, wetting and oiling airfields and other exposed soil in California (another hot spot for coccidioidomycosis) was found to reduce infections (as measured by skin tests) by more than half among troops training at those locations.

Mapping Disease Occurrence and Risk

Maps that portray the extent and magnitude of infectious diseases can support public health decision making, efforts to monitor the success or failure of interventions, and evaluations of specific disease-driving factors in space and time (Hay et al., 2013a,b). Global maps of infectious diseases are of potential use to several audiences, including international funding agencies, public health officials responsible for vaccine distribution, ministries of health with inadequate reporting capacity, and travelers in general, according to speaker Jane Messina, of the University of Oxford, England (Dr. Messina's contribution may be found on pages 297–310 in Appendix A). In her workshop presentation, she described how she and coworkers in the Spatial Ecology and Epidemiology Group create such maps, and discussed ways to improve existing disease maps and to map more infectious diseases. She then used the example of dengue to illustrate the process and utility of global infectious disease mapping.

Global mapping of diseases Of 355 diseases identified in the Global Infectious Disease and Epidemiology Network (GIDEON), 174 have been deemed

"mappable" by Hay and coauthors (Hay et al., 2013b), who report that only seven diseases—all vector-borne—have been mapped comprehensively: coltiviruses (Old World), dengue, Lassa fever, Mayaro, monkeypox, and two forms of malaria (*P. falciparum and P. vivax*) (Hay et al., 2013a). Among mappable diseases, 80 (~46 percent) are caused by vector-borne pathogens, Messina stated.

The mapping process follows the decision pathway illustrated in Figure WO-24, which assigns diseases to one of five categories based on its distribution (because it would be pointless to map ubiquitous diseases) and the availability of information on its ecology, reservoirs and vectors, and prevalence, Messina explained. If only occurrence data are available, as is the case for most VBDs, maps are limited to displaying the possible niches where the disease could exist, she noted; a statistical method known as boosted regression trees (BRTs) is used to construct such maps. If prevalence data are available, more advanced methods, such as model-based geostatistics (MBGs), can be used to map disease endemicity (Hay et al., 2013a).

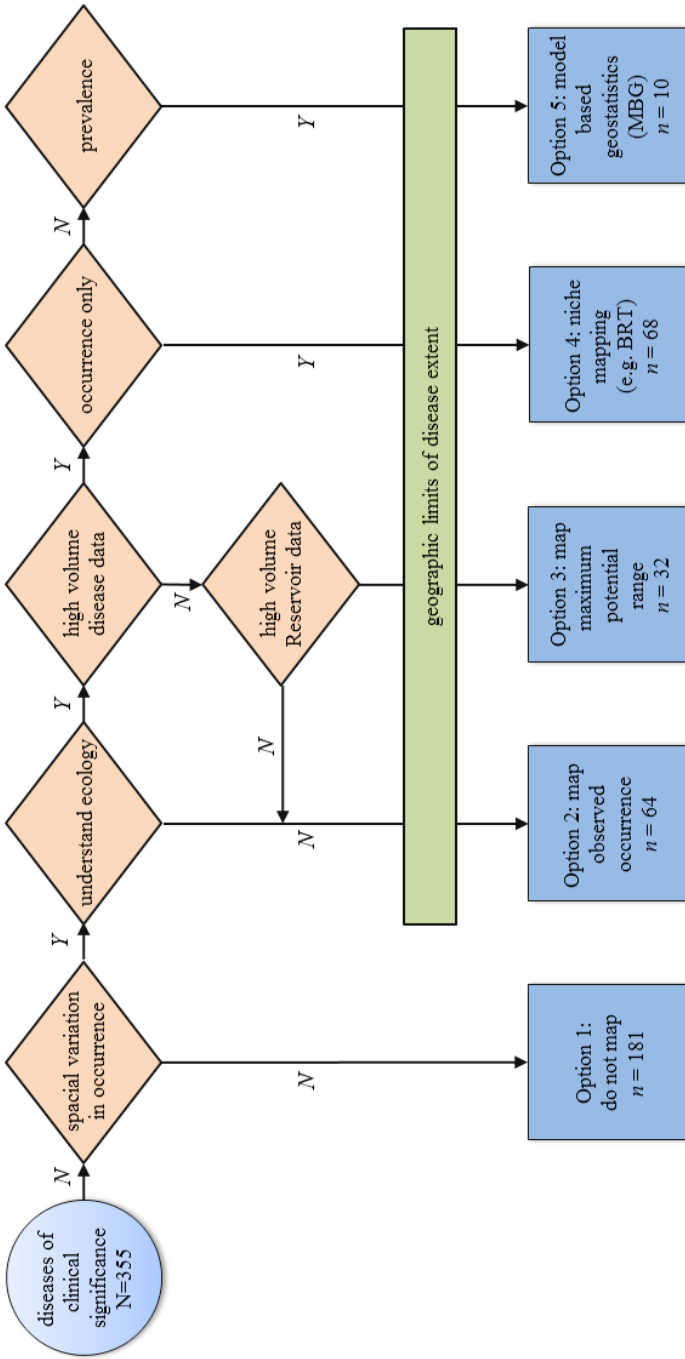
Understanding the current distribution of a disease is the first step toward predicting its response to global environmental change, Messina noted. Descriptions of disease distribution necessarily include uncertainty, which should be incorporated into calculations and made apparent in maps through such devices as confidence intervals associated with probabilities of occurrence, she noted. This is particularly the case for many VBDs, she added, which means constructing maps based on the assumption that disease observations fully represent the range of environments—the ecological niche—in which the pathogen can exist. This approach is known as "niche modeling." However, she continued, even in the best case, "We don't necessarily know all of the places in the world where the disease is absent—all we have is where it has been reported."

While agreeing with Dobson's earlier observation that a map is only as good as the data upon which it is based, Messina described two methods to optimize the statistical processing of this data:

- Cross-validation, which compares a subset of observations with a model generated with the remaining data; and
- Ensembling, which involves iterative modeling to generate mean predictions and confidence intervals based on hundreds of simulations.

Maps are not static, she said; they can always be improved with better data, with information shaped by evidence consensus and expert opinion, and with more discerning analytical and statistical methods.

Case study: Global mapping of dengue More than one-third of the world's population lives in areas at risk for dengue, a mosquito-borne viral disease that is a leading cause of illness and death in the tropics and subtropics. As many as 100 million people are infected yearly; most experience high fever and severe



IGURE WO-24 A schematic of the disease classification process. The classification system results in diseases being categorized into one of five options: (1) do not map; (2) map observed occurrence; (3) map maximum potential range of reservoir or vectors; (4) niche/occurrence mapping with BRT; and (5) MGB-based endemicity maps.
NOTE: BRT = boosted regression tree; MBG = model-based geostatistics.
SOURCE: Hay et al., 2013a.

headache, among other discomforts. An estimated 500,000 people are hospitalized annually with a severe form of the disease, dengue hemorrhagic fever, which can be lethal. There are no specific protections from dengue, as an effective vaccine has yet to be developed, nor are there specific treatments for its symptoms (CDC, 2013b; WHO, 2013a).

Due to its wide distribution and rapidly growing global incidence, dengue has been called a "disease of the future," according to Messina. Figure WO-25A illustrates the group's map of the endemic status of dengue, based on information from multiple sources. Endemicity is depicted using a 200-point scale from certain absence (green) to certain endemicity (red). To create the occurrence map shown in Figure WO-25B, Messina and coworkers conducted a systematic search and treatment of evidence of transmission from nearly 9,000 unique reports in the formal literature and from ProMED and HealthMap. Construction of both maps was hampered by a lack of data from Africa; estimating the level of underreporting of dengue on that continent is a focus of future research, she said.

Using their map of dengue's endemic status (Figure WO-25A–C), which Messina described as "the first step in our niche modeling process," she and

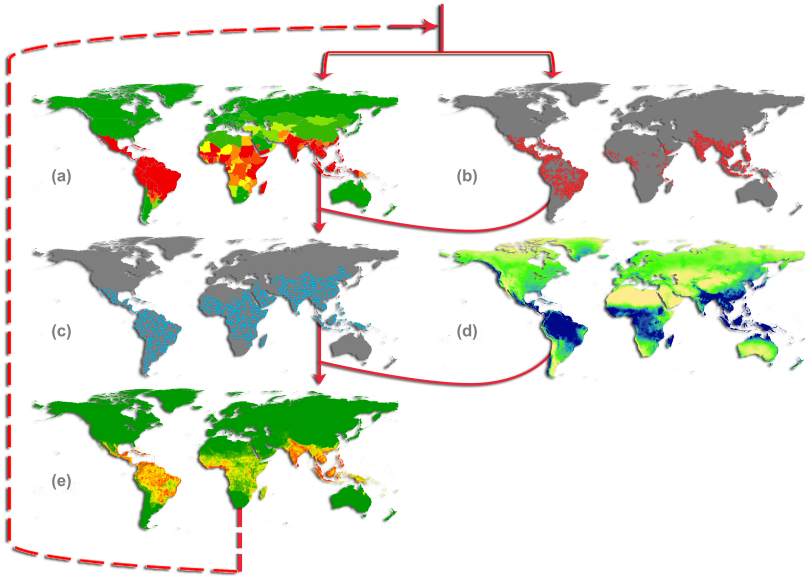


FIGURE WO-25 Infectious disease global risk modeling framework: (a) evidence consensus; (b) disease occurrence locations; (c) pseudo-data; (d) spatial covariates; (e) average risk map produced by BRT ensemble. The dashed arrow represents the iterative nature of the procedure, whereby the new information provided by (e) informs future surveillance efforts, which then enables updating and improvement of both (a) and (b).
SOURCE: Figure courtesy of Jane Messina.

coworkers added geospecific information on several key environmental variables known to influence risk for dengue, including precipitation, temperature, socioeconomic status of local populations, and urbanization. The resulting risk map, shown in Figure WO-25, can be paired with cohort studies to infer unapparent and apparent infections per pixel, and also paired with population surveys to estimate total numbers of infections on a national and global basis, she said. Uncertainty, she noted, "was propagated throughout the entire process," and is reflected in their map's depictions of national-level risk, as well as in confidence ranges for their estimates of infections per year at both national and global levels, she explained.

To modify the current map to reflect global risk for dengue in 2020, 2050, and 2080—as the group has been charged to do by the European Commission—Messina and coworkers will incorporate information on several environmental trends, she said. These include the growth of urbanization in the tropics, warming temperatures, and increased travel and trade originating from endemic areas, all of which could facilitate dengue transmission. On the other hand, socioeconomic development in the tropics may mitigate the risk for disease, Messina noted. As for determining whether climate change has influenced global risk for dengue, she observed that advancements in dengue detection and reporting over the course of the Great Acceleration make such comparisons difficult, and that the apparent growth in disease incidence may not accurately reflect actual trends in its transmission.

Modeling Anthropogenic Effects on Disease Transmission

To consider the effects of global environmental change on the dynamics of VBDs is to address the following unanswered questions, posed by speaker Uriel Kitron, of Emory University (whose talk was a collaborative effort with Charles King from Case Western Reserve University and Dan Colley from the University of Georgia):

- What are the impacts of environmental changes and variation on vector and reservoir populations, and on exposure? Are these relationships universal, and if not, how do they vary locally?
- How can we address heterogeneity of scale—in both time and space—of these impacts?
- Can environmental changes be used to forecast changes in vector and host populations and the risk of outbreaks or spread of disease?
- How do we apply environmental/climate data and models to the study of transmission and disease management?

While it is possible to identify hot spots for disease transmission based on current knowledge of disease dynamics (e.g., as demonstrated by Messina's

mapping of current risk for dengue), it is difficult to predict how transmission may be affected by interventions or by other future anthropogenic activities, Kitron insisted. Moreover, he added, "We cannot assume that what happens globally is relevant to the local conditions and vice versa. We have to do both, and we have to work on many scales." To begin to approach this challenge, he and coworkers have examined VBDs that persist under changing environmental conditions and/or intensive intervention: malaria and schistosomiasis, which have resisted eradication in known, often rural, hot spots, where they frequently infect the same person.

Schistosomiasis is caused by trematode flatworms of the genus *Schistosoma*. Larval forms of the parasites, released by freshwater snails, penetrate the skin of people in the water. The larvae develop into adult schistosomes, which live in the blood vessels. The females release eggs, some of which are passed out of the body in the urine or feces; others remain in body tissues, where they cause an immune reaction. Urogenital schistosomiasis progressively damages the bladder, ureters, kidneys, and reproductive organs. Intestinal schistosomiasis causes progressive enlargement of the liver and spleen, intestinal damage, and hypertension of the abdominal blood vessels. Nearly 800 million people are at risk of schistosomiasis, which ranks second only to malaria among the parasitic diseases with regard to the number of people infected and those at risk (Steinmann et al., 2006; WHO, 2013b).

In the area Kitron's group conducts their research, on the south coast of Kenya, 10.7 percent of the population had malaria, 26.0 percent had schistosomiasis, 21.4 percent had hookworm, and 9.3 percent had filariasis in 2009–2011, he reported. The rates for malaria in this area were higher than originally believed, and appear to be on the rise, he noted. Despite the availability of a treatment intervention for these diseases, it was apparent that asymptomatic cases were going untreated, and the transmission cycle was maintained.

In the case of malaria, in addition to treatment, a transmission-interrupting intervention—the introduction and wide adoption of insecticide-treated bed nets—was so effective as to be "transformative," Kitron observed. A precipitous decline in malaria cases followed their introduction (Mutuku et al., 2011, and many other studies throughout sub-Saharan Africa). However, he continued, malaria rates increased as the bed nets wore out (Mutuku et al., 2013)—but this was not the only reason. The pathogen also adapted to transmission by a more versatile mosquito vector: a species that feeds earlier in the evening and later in the morning, and had also developed resistance to insecticides and adapted to urban habitats such as swimming pools (Impoinvil et al., 2008). Even so, he concluded, urbanization largely disrupts malaria transmission—in contrast to that of dengue—so the disease is on the decline. "Malaria will stay with us for a long time, but dengue will eclipse it both in numbers and distribution," he predicted.

It is difficult to make similar predictions about schistosomiasis, Kitron observed, deeming it "a very hard disease to model" due to its focal distribution

pattern and the age structure and mobility of the infected population. Among the villages they study, there are obvious hot spots for schistosomiasis and obvious superspreaders: young infected boys who swim in multiple water holes, provide a reservoir for the parasite, thereby spreading infection among themselves and others (Clennon et al., 2006). "We do have good treatment against schistosomiasis, one that works very well in reducing infection intensity." However, he added, "It's only partially curative, since there is no residual effect, you treat but do not interrupt transmission, leading to people become[ing] re-infected." Moreover, he added, targeting hot spots for treatment has proven to have limited effectiveness, because they are ephemeral—shifting locations when, for example, drought dries up known, infected, ponds (Clennon et al., 2007).

"After 5 years of not finding snails and finding very little transmission in the known places, we still have about the same prevalence of infection," Kitron said. "Intensity is down somewhat, but not as much as we expected. Even with our very intensive study of an area where transmission is relatively straightforward, we still are missing something big . . . we can't really explain why it hasn't gone down much more than it did." Epidemiological models of transmission indicated that without drastic reductions in transmission, infection prevalence remains at low levels from which it can bounce back. "None of our models really have shown us even the potential strategy to get rid of the disease completely," he admitted; only by eliminating the parasite in snails and people simultaneously is the disease likely to be controlled. Given the mobility of super-spreading boys—who often migrate to distant villages for months at a time—coupled with the difficulties in reducing snail populations, schistosomiasis control in this setting will require intense surveillance and detection of new hot spots as they emerge. "The time frame is long," he concluded. "There is no quick fix."

The problem of shifting hot spots is not limited to schistosomiasis, Kitron observed—similar dynamics have been observed with dengue in Iquitos, Peru (LaCon et al., 2014), WNV in Dallas and Chicago, and Lyme disease in the United States and Europe, for example. Nevertheless, when asked about the overall prospects for managing VBDs, Kitron claimed to be optimistic. While researchers cannot model the long-term impact of current interventions, they are getting better at making connections between interventions and disease dynamics, he said—and are getting better in making short-term predictions, and even more long-term forecasts, albeit more limited ones, in some situations.

Approaches to Identify and Address Factors Contributing to Disease Emergence

Presentations in the final session of the workshop offered diverse examples of efforts to address risk factors for infectious disease emergence—as characterized in earlier sessions—through strategic prevention, surveillance, intervention, and response. While predicting and heading off a potential pandemic is the ultimate

goal of such efforts, several workshop participants emphasized the value of prediction as a means of generating hypotheses that in turn spark the invention of novel diagnostic tools and interventions to reduce the burden of infectious diseases.

Strategies to Predict and Anticipate the Emergence of Novel Pathogens

Predicting where and when the next pandemic will strike, and what pathogen will cause it, is a primary goal of the EcoHealth Alliance, directed by Forum member Peter Daszak (Dr. Daszak's contribution may be found on pages 182–193 in Appendix A). In his workshop presentation, he addressed the following "big questions for pandemic prevention," and in so doing, extended his earlier response to the critique of pandemic prediction presented by Dobson in his keynote address (see the section "Understanding Infectious Disease Dynamics" on page 20):

- Are EIDs really on the rise?
- Can we allocate resources more strategically to combat them?
- Are there predictable patterns to disease emergence?
- Where will the next pandemic originate?
- How likely will a new EID be to spread out of a region?
- Which wildlife do pandemics originate in?
- Can we identify potential pandemic pathogens before they emerge?
- Can we stop them emerging?

Infectious disease emergence is frequently described as occurring in stages (Lloyd-Smith et al., 2009; Morse et al., 2012; Wolfe et al., 2007). Figure WO-26 illustrates pandemic development as a three-stage process:

1. An early stage characterized by environmental disruptions that allow wildlife to make contact with livestock or people, resulting in spillover and small outbreaks;
2. A subsequent increase in number and size of disease outbreaks featuring short, "stuttering" chains of human-to-human transmission; and finally,
3. Pandemic disease, as has occurred with HIV, WNV, and SARS.

"I believe that predicting the last stage is actually fairly straightforward," Daszak stated, noting that several models can successfully predict disease spread based on epidemiological information obtained in the early stages of an outbreak. It is harder to make such predictions based on the dynamics of stuttering chains of transmission, but it can be done with very complex mathematical models, he continued; however, predicting a pandemic's progress from the very early stages of emergence, the first spillover of a new pathogen, remains a significant challenge.

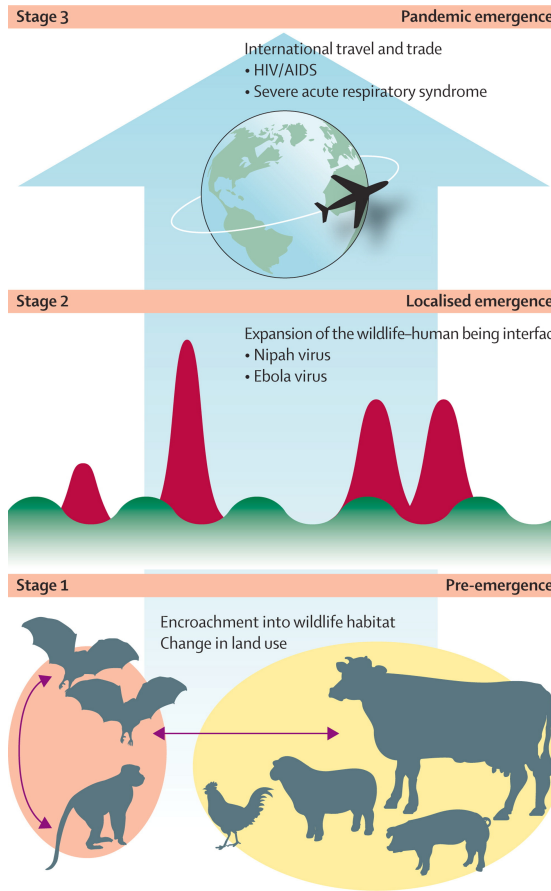


FIGURE WO-26 Emergence of pandemic zoonotic disease. Stage 1 is a preemergence state, in which naturally occurring microbes are transmitted between their animal reservoirs. Disturbances to the ecology of these populations (e.g., due to changes in land use) change the dynamics of microbial transmission and can lead to a heightened risk of pathogen spillover to other nonhuman wildlife or livestock hosts (but not people). Stage 2 is localized emergence, either through self-limiting spillover events (green peaks and troughs, representing the rise and fall in numbers of infected people with time) or large-scale spillover (red peaks, representing spikes in the number of infected people with time), that leads to person-to-person transmission for a few pathogen generations. In stage 3, some spillover events might lead to indefinitely sustained person-to-person outbreaks, international or global spread, and the emergence of a true pandemic. The size, spread, and potential effect of events increase from stage 1 to stage 3, but the frequency falls so that full stage 3 pandemics are quite rare. By dissecting this process and analyzing the interactions of the underlying drivers with the risk of spillover and spread, development of a more structured approach to pandemic prevention is possible. The ultimate goal of successful pandemic prevention is to move the control point to stage 1.
SOURCE: Morse et al., 2012.

As a first step toward improving early detection of potential pandemics, Daszak and coworkers set out to map emergence "hot spots"—places across the globe where infectious diseases are likeliest to emerge (Jones et al., 2008). Their map, based on a comprehensive review of all infectious diseases reported between 1960 and 2008, was critiqued by Dobson in his presentation and briefly discussed afterward by Daszak. In his presentation, Daszak summarized the efforts his group made to correct various biases in their initial map, most importantly geographic (favoring wealthy countries) and chronological (increasing effort over time) biases in emerging disease research. After these corrections were made, their calculations demonstrated that, on average, five new zoonoses emerge each year, and that zoonoses are also increasing as a proportion of emerging disease events.

What factors are driving these changes? Further analysis of their data revealed human activity as a major driving force for disease emergence, and allowed the researchers to produce a predictive map (see Figure WO-27) that, according to Daszak, "tells us right now where the next pandemic is most likely to come from," and therefore could serve as a general guide to allocating global efforts for pandemic prevention.

Can we then predict how likely it is that an outbreak will spread across the globe? Reasonably well, Daszak demonstrated, by using the hot-spot map combined with the number of passengers on planes flying into and out of the outbreak area, and by taking into account that outbreaks tend to be more accurately reported in wealthier countries. Using the recent (2009) H1N1 influenza pandemic as an example, he and coworkers were able to use this method to "reverse predict" the strain's spread out of Mexico, where it emerged, throughout the world (Hosseini et al., 2010). These refinements also enabled global mapping of vulnerability to zoonotic EIDs in general, and also to vector-borne EIDs (Figure WO-28).

If pandemic prevention efforts focus on wildlife in hot spots, which species should they target? "Most zoonoses are mammalian in origin," Daszak stated. Because detailed data on the diversity and number of viruses found on mammals is available, as well as information on the number of viruses animals share with humans, he and coworkers were able to identify those mammals likeliest to share viruses with humans: primates, rodents, and bats (Olival et al., in preparation).

Major challenges While Daszak and coworkers have made significant progress toward answering the aforementioned "big questions," he identified three major obstacles to predicting emergence that remain to be overcome:

- We do not know the number of unknown viruses;
- We do not know how human contact with wildlife varies across a landscape, nation, or planet; and,
- We do not know how likely a new virus will be to infect people.

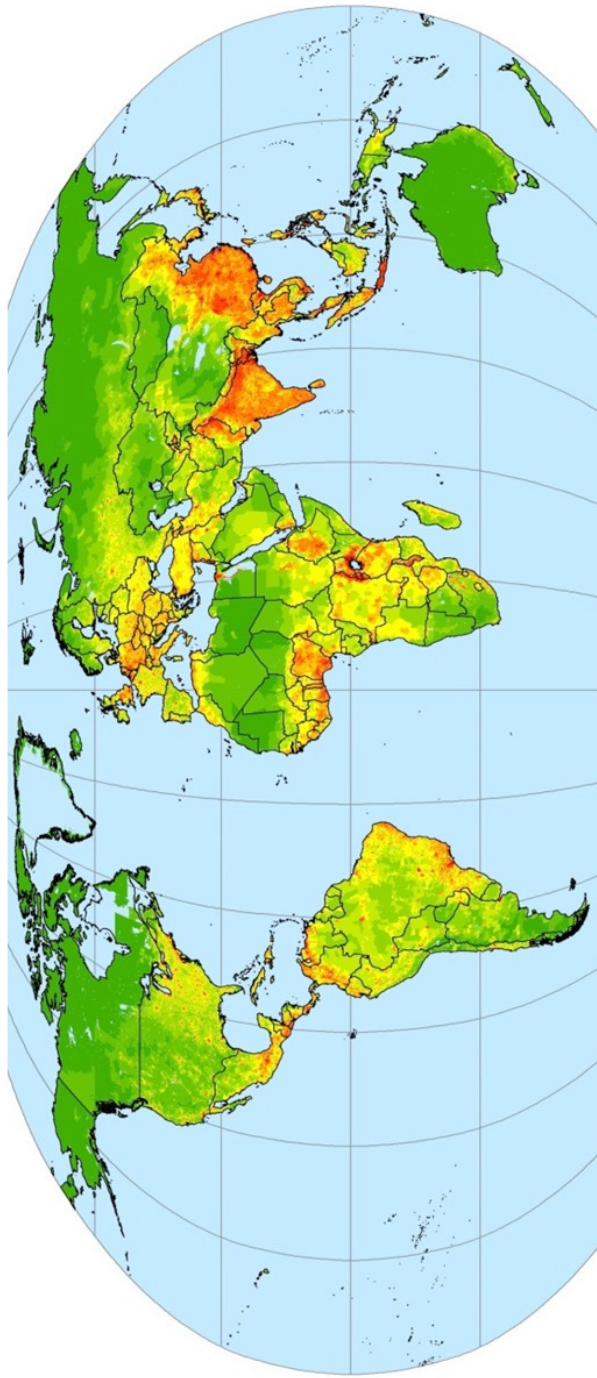


FIGURE WO-27 Global emerging disease "hot spots."
NOTE: Update of model found in Jones et al., 2008, using driver datasets as of 2009 and events as of 2010.
SOURCE: Daszak presentation, 2013 (adapted and updated from Jones et al., 2008).

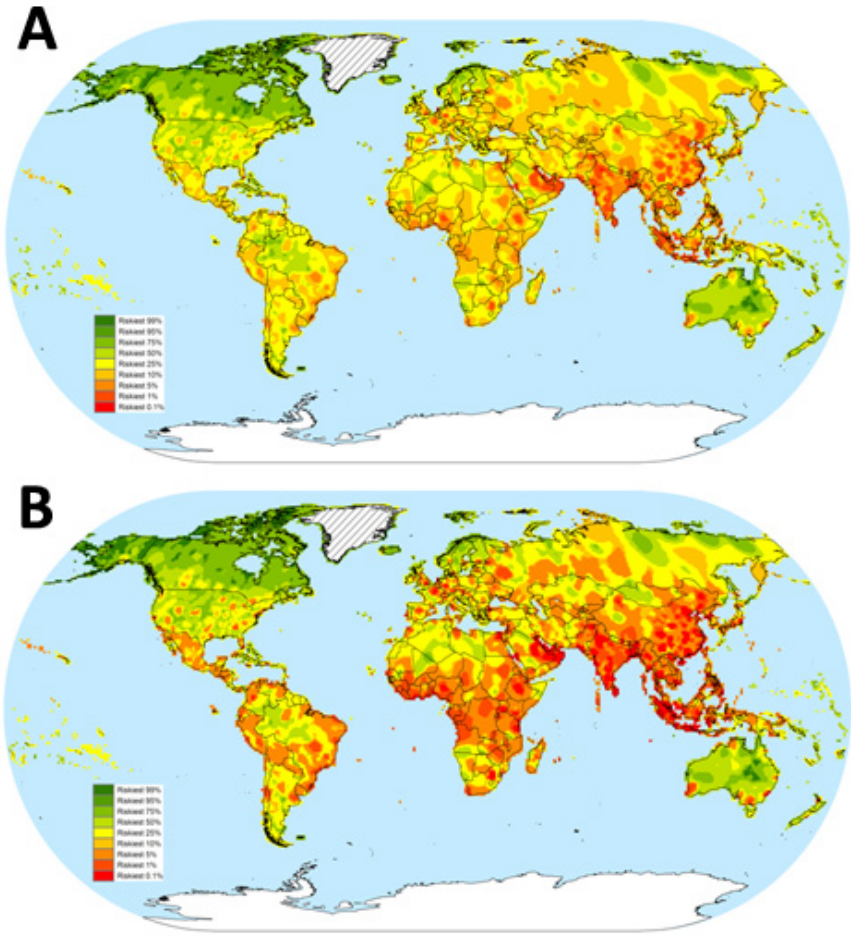


FIGURE WO-28 Global vulnerability from (A) zoonotic EIDS and (B) vector-borne EIDS.
SOURCE: Daszak presentation, 2013.

In pursuit of the first of these unknowns, Daszak and coworkers made use of a standard statistical method for gauging biodiversity in order to estimate the total number of unknown mammalian viruses. They based their calculations on comprehensive viral discovery in 2,000 *Pteropus giganteus* bats[22] from Bangla-

[22] Commonly referred to as a fruit bat.

desh (Anthony et al., 2013). This bat species has become notorious as a carrier of the Nipah virus (discussed in the section "Local-Scale Interventions to Reduce Pandemic Risk" on page 84). Having determined that this species hosts about 58 unknown viruses, and assuming other mammalian species host a similar number of unknown viruses, the researchers calculated that mammals as a group possess about 320,000 unknown viruses. They further estimated that all of these viruses could be identified at a cost of about $6.8 billion (or 85 percent of them could be identified for about $1.4 billion)—cheap compared to the cost of a pandemic such as SARS, which took a $10 to $50 billion toll on the global economy, he noted.

To learn how people make contact with wildlife, Daszak and coworkers are sampling viral diversity in sites representing pristine forest, fragmented habitats, and rural–urban centers in Borneo, Brazil, and Uganda—all hot spots for disease emergence. The researchers are examining known reservoir species in these areas for viruses with pandemic potential; they also use questionnaires to learn about residents' contact with local wildlife.

Determining how likely is it that a newly discovered virus will infect people is a major challenge, Daszak observed. "I think this is where there is a big black box around emerging disease. This is where we really need to think creatively and cleverly," he said. "It is something that is going to involve sequences and proteins and cultures and really good virology."

Halting an already emerging pandemic represents an even more daunting challenge, Daszak noted, especially if it involves an unknown pathogen. Noting that nearly half of past EID events are attributable to land use, he suggested that businesses involved in environmentally disruptive projects—such as mining and logging—associated with risk for infectious disease outbreaks might be persuaded to change their practices if there were a demonstrated financial advantage to do so. "There is a huge economic impact to the extractive industry," he stated. "Ten billion to $40 billion in potential liability if they get blamed for emerging disease." Health impact assessments that demonstrate such costs could reduce destructive land use, and thereby, infectious disease emergence.

Similarly, from the consumer side, people are likely to reject products associated (fairly or not) with the risk of infectious disease, Daszak observed. EcoHealth Alliance has developed a smart phone application, PetWatch, to help people choose exotic pets that do not come from disease hot spots, and that otherwise bear a relatively low risk of spreading infectious disease. The EcoHealth Alliance has also launched a media campaign to discourage illegal trade in wildlife.

A global perspective In considering how resources should be allocated to prevent disease emergence and spread, Daszak and coworkers noted a fundamental problem: the term *emerging* has no universally accepted, empirical definition. It is "rarely backed by quantitative analysis and is often used subjectively," they wrote. "This can lead to over allocation of resources to diseases that are incorrectly labeled 'emerging'—such as salmonellosis in Europe—and insufficient

allocation of resources to diseases for which evidence of an increasing or high sustained impact is strong" (Funk et al., 2013).

Daszak emphasized that a coordinated, global effort to address the threat of emerging diseases is crucial. "From the U.S. point of view . . . this is a biosecurity argument … [and] also an international development argument," he stated. He endorsed the approach taken by the U.S. Agency for International Development (USAID) toward emerging pandemic threats, which emphasizes building capacity for infectious disease surveillance in developing countries in which emergence hot spots are located. "That will help solve the pandemic problem, but also help with building basic capacity for malaria, cholera, and all the other big killers of the tropics," he observed.

Daszak also decried the lack of international coordination evinced in the response to the recent emergence of Middle East respiratory syndrome (MERS; see footnote to Box WO-2). "We have brilliant models where we can predict the spread rapidly when a new disease emerges," but, he observed, the global public health community is dealing with MERS "extremely poorly because of political and cultural differences between Saudi Arabia, other countries in the Middle East, and us here [in the United States], and everybody else. Until we truly are acting as one species, we have a big problem," he warned. This occurred despite the involvement of nongovernmental and multinational organizations, including the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE), the WHO, coupled with the revisions to the International Health Regulations (IHR). The revised IHR were designed to improve response to early outbreaks of emerging diseases, he noted with disappointment. "One has to ask the question: is the IHR really doing anything specifically for MERS now?" he wondered.

"I think that is an overly pessimistic look at progress of global governance," Cetron responded. He credited the revised IHR with improving the global response to MERS, as well as to an outbreak of H7N9 influenza A that occurred in China in April 2013, as compared with the SARS epidemic in 2003 that catalyzed the IHR revisions. "There is not going to be one great universal global governance system that will hold everybody accountable to the same degree," he remarked. "What success looks like may not be fewer outbreaks, but it may be more outbreaks of smaller size with more rapid intervention," he added—and the world has made progress toward that goal under the formal disease reporting structure imposed by the IHR. "It is not perfect, but it is a lot better than where we were [when SARS emerged] in 2003," he concluded.

Daszak agreed with that assessment, noting that the ability for third parties to report outbreaks has increased reporting accuracy for infectious diseases. "One of the things that we will probably see over the next 10 years or so is trying to deal with the underlying drivers of emerging disease," he observed—an area in which global governance could enable swift and effective interventions to reduce pandemic threats. Such an effort would also benefit from involvement by the

private sector, and in particular, multinational corporations involved in large-scale agriculture, logging, and mining, he noted.

Local-Scale Interventions to Reduce Pandemic Risk

To study emerging diseases means looking carefully at pathogens that currently do not cause a high disease burden in humans, but which have the potential for uncontrollable human-to-human transmission, observed speaker Steve Luby, of Stanford University. These include zoonotic pathogens such as the Nipah and H5N1 influenza viruses (Lloyd-Smith et al., 2009; Wolfe et al., 2007). These are diseases that today cause "stuttering" chains of transmission in humans, but with very slight adaptation, could become important new human pathogens, he said.

In response to such threats—and, as he described it, at the risk of taking what might be described as an "under-theorized approach" without "proper disciplinary credentials"—Luby's team applies the following seven-step framework to designing and testing interventions against diseases with pandemic potential:

1. Identify the risks
2. Understand the reasons for the risk
3. Develop interventions that address the underlying reasons
4. Pilot interventions
5. Iteratively revise
6. Scale up
7. Evaluate

His presentation focused on employing this framework to reduce the risk of human-to-human transmission of Nipah virus and H5N1 influenza in Bangladesh.

Case study: Interventions against Nipah virus Since diagnostics for Nipah became available, outbreaks have been regularly identified in Bangladesh, with an average case fatality rate of nearly 80 percent, Luby reported. Not only is Nipah lethal, but some people infected through exposure to the *Pteropus* bats that serve as the virus' reservoir have been shown to have transmitted Nipah to other people (Luby and Gurley, 2012).

According to their framework, Luby and coworkers first investigated how humans became infected with the Nipah virus. Case-control studies in Bangladesh revealed that people who reported drinking raw date palm sap were significantly more likely to be cases than controls. This led to the suspicion that consumption of raw date palm sap may be an important route for human exposure to Nipah. The researchers were then able to make a clear connection between bats, sap, and humans, when they discovered that bats drink at the sap collection points on date palm trees, fouling the sap with saliva (and often, with feces and urine as well) which contain Nipah virus.

FIGURE WO-29 Protective skirts for palm sap collection made from (A) jute; (B) doincha (*Sesbania rostrata*); (C) bamboo; and (D) polyethylene.
SOURCE: Khan et al., 2012 (frames A, B, and D); Luby presentation 2013.

Anthropologists learned from sap harvesters that collecting and selling the highly popular fresh palm sap, which may also be boiled to make molasses (a process that inactivates the virus), is often highly profitable. Luby and coworkers designed two types of interventions to address this risk: a campaign to warn people not to drink raw date palm sap, and several versions of protective "skirts," that sap harvesters could manufacture themselves, to keep bats and other animals out of the sap as it is being collected (see Figure WO-29) (Khan et al., 2012).

Disappointingly, a pilot study to test whether sap harvesters would use the skirts, once informed of Nipah risk and encouraged by increased demand for cleaner sap, found that only about one-quarter of the sap collectors used the skirts during the first year, and fewer than 10 percent continued for a second year (Nahar et al., 2013). On the other hand, preliminary results of the carefully crafted "just say no to raw sap" media campaign suggested that overall raw sap consumption declined by more than half among both men and the women in villages exposed to this message, Luby stated. This result appears quite variable from village to village, however, so he and coworkers plan to launch a two-tiered message campaign—"just say no" and "skirts make sap safer"—in the hope that this dual messaging effort will reduce outbreaks that are still occurring.

Rather than convince sap collectors to use skirts, the key to reducing infection risk "is convincing the date palm sap drinkers that they want to drink sap from a protected tree," Luby observed. "If people ask for that—and this is a local activity, so they can see whether it is done or not—I think that demand will drive and support the behavior change."

Case study: Interventions against H5N1 influenza Bangladesh is a crowded country, in which some 150 million people (the approximate population of the East Coast of the United States) inhabit an area the size of Iowa—along with 183 million chickens and 37 million ducks, according to Luby. More than half of all Bangladeshi households raise their own poultry, keeping them indoors at night to prevent theft; birds are also sold live and slaughtered in open markets.

All of these conditions raise the risk that H5N1 influenza, a strain endemic to Bangladesh and associated with a 60 percent case mortality in humans who have become infected through contact with birds, will emerge as a human-transmitted pandemic disease, Luby warned. If an outbreak of H5N1 in poultry occurs simultaneously with one of human influenza—also common in Bangladesh—there is a risk that a person co-infected with both strains could serve as an incubator for a novel, human-transmitted form of H5N1. Such a pathogen, he said, would constitute "a severe global risk."

People at highest risk for such simultaneous infections are (1) those who raise poultry without regard to biosecurity, as is typical for backyard livestock operations, (2) those who slaughter infected birds, (3) those who work in live bird markets, and (4) those who provide care for avian influenza patients. There are so many risks in Bangladesh that it is difficult to choose one on which to focus, Luby observed—but ending the raising of poultry by individual households is not one of them, because poultry provides significant nutrition and income in this extremely impoverished country (Sultana et al., 2012). Instead, the researchers attempted to design a message campaign to improve slaughtering practices (e.g., not slaughtering sick birds for consumption or sale); this was determined by follow-up anthropological study to be ineffective. Villagers exposed to messages

could recall them and thought they were truthful, he said, but their practices remain largely unchanged.

Another intervention targeted family care-giving practices, which are important even within hospitals (Blum et al., 2009). Family members, rather than nurses, provide physical care and desire close physical contact with hospital patients, especially if they are dying, Luby explained. As a result, hospitals in Bangladesh are crowded; moreover, hand-washing stations tend to be reserved for staff, in part because soap is an expensive commodity in this extremely poor country. So, while hand washing is a highly effective way to control disease transmission, the researchers were forced to focus on other risks more amenable to reduction, such as convincing people not to share beds or face-to-face contact with sick relatives (Gurley et al., 2013). However, Luby added, the team recently launched pilot studies of hand-washing interventions using low-cost soap and alcohol-based gel. "It looks like there is reasonable uptake, but we are interested in continuing to iterate around this to collect data," he said. "We still have many steps to go."

Sound interventions to reduce pandemic risk are feasible, Luby concluded. "They are not simple," he noted. "They require an appreciation of local constraints. They require an iterative scientific process and long-term engagement with multidisciplinary teams."

Lessons learned Many cycles of developing and testing interventions against Nipah and influenza in Bangladesh revealed the critical importance of collaboration between scientists and government, Luby observed. He noted that considerable time and evidence were required to convince government officials that people should be discouraged from the culturally established practice of drinking raw date palm sap. Yet, once persuaded, he continued, these officials also stuck by that message, not wanting to dilute it with the notion that skirt use made raw sap safe; thus even more data were needed to convince them that "just say no" was not sufficiently effective.

"I think a big part of working towards change is generating evidence that policy makers find persuasive," Luby concluded. "[Through] engagement with government, focusing on where the data sends you, we can make meaningful contributions." Such decisions resonate far beyond villages in Bangladesh, he added. "I think it is important to recognize that the problem of reducing the risk of emerging disease is not fundamentally a problem of Bangladesh. It is a problem of humanity."

Modeling Emerging Infectious Diseases

According to speaker Neil Ferguson, of Imperial College, London, mathematical models address several stages of infectious disease emergence. During preemergence, models can assess risk and improve preparedness, he said;

post-emergence, models enable the rapid assessment of epidemiological data and pathogen genetics, predict short-term risk, and inform control policy optimization. In his presentation to the workshop he described his work on two of these applications: estimating risk associated with viral pathogens that have achieved "stuttering" transmission in humans, and the rapid assessment of post-emergence transmission dynamics at the outset of the H1N1 pandemic in 2009 and after the recent emergence of MERS.

Estimating risk for emergence As noted by Daszak and Luby, the preemergence stage of pandemic development is characterized by sporadic human-to-human transmission, described as "stuttering chains of transmission" or "viral chatter" (Antia et al., 2003; Lloyd-Smith et al., 2009). During this stage, mutations accumulate in viral pathogens that eventually allow them to shift from animal-to-human to human-to-human transmission, but there is no selection pressure for viruses to adapt to human hosts until they are readily transmissible among them, Ferguson noted. This process has been modeled many times, he said, but it would be ideal to link this transition to data that reveals the specific changes that enable human-to-human transmission in order to understand the "evolutionary hurdles" a virus would have to cross, and the likelihood that it could do so.

Ferguson and coworkers have approached this challenge using genome-wide association studies, a technique that allows researchers to pinpoint the minimal set of genetic changes that would permit a zoonotic virus to infect humans, and with that knowledge, to determine the probability that these changes would occur (Aguas and Ferguson, 2013; Russell et al., 2012). "If we know something about the mutational barrier a virus needs to cross, the number of end point mutants that need to accumulate, we can use mathematical modeling to say what the probability [is that] this will occur," Ferguson said. "You have to make an awful lot of assumptions, but effectively you are building a model of . . . pathogenesis within a person." From there, he continued, you can estimate how many people need to get infected over a given time period in order for the virus to have a significant chance of emerging. This process is highly speculative, because it includes assumptions about the fitness of the viral intermediates. Nevertheless, he observed, "It gives you some ballpark estimate."

In the case where a virus has already begun to infect humans, such as the swine influenza variant H3N2v, which has caused limited human cases since it was first reported in 2011, one can use epidemiological data to assess whether this virus is more transmissible in humans than other swine strains, and whether it can generate sustained epidemics in humans, Ferguson stated. In collaboration with colleagues at the CDC, his group was able to estimate the relative transmissibility of the variant virus in humans from limited information (they knew the source of infection in detected cases, but lacked examples of complete and representative chains of transmission). "If you imagine a virus is really quite transmissible then most of the cases you will start to see, which you pick up randomly, will

have not had any exposure to swine," he explained. "But if the virus is really not transmissible at all from person to person, then all of the cases can be associated to swine." Their results suggest that H3N2v is more transmissible from person to person than its predecessor (H3N2v is a variant of the H3N2 influenza virus that infected 321 people in the United States in 2011 and 2012), but insufficiently transmissible to cause a sustained epidemic, he stated (Cauchemez et al., 2013a).

Rapid assessment of 2009 H1N1 and MERS "Perhaps the busiest time in the last few years was during the H1N1 pandemic in 2009 where we undertook with collaborators around the world particularly Mexico and the World Health Organization and later with the Centers for Disease Control and Prevention a number of rapid assessments," Ferguson recalled. Early on, the researchers focused on four key questions:

1. How severe is the illness?
2. How far has it spread?
3. How fast is it spreading?
4. What can be done?

Using the "case curve" from Mexico City (showing the number of cases identified each day as the epidemic unfolded, and known to be biased toward severe cases) and case reports from surveillance of travelers at the U.S. and European borders, the illness was quickly determined to be more transmissible than seasonal flu, but less so than the strains that caused any of the three landmark influenza pandemics (in 1918, 1957, and 1968), he reported.

Helpful and reassuring as this information doubtless was, it was not sufficiently accurate to inform the sorts of policy decisions that are needed to control a pandemic in today's world, Ferguson observed. Because their estimates were based on reported disease among people who sought health care for their symptoms, they likely reflected a fraction of the people infected with H1N1. "We did not really know what proportion of an iceberg those reported cases were," he stated, so his group is pursuing analytical approaches that would allow them to impute the number of true cases from those reported. He noted that tracking cases indirectly—through data mining methods such as those employed by Google Flu Trends, HealthMap, and ProMED—could be of limited use in these circumstances. However, such informal data sources are far from definitive, and thus cannot serve as disease-specific surveillance systems, he added.

Similar challenges are now facing Ferguson and coworkers as they attempt to understand—and thereby help to control—the emerging viral disease, MERS-CoV. Since the first human cases of this β-coronavirus were reported in 2012, there have been more than 228 cases of MERS, he reported. Marano previously noted that bats and camels remain suspected—but not confirmed—reservoirs for MERS-CoV.

Ferguson observed that two possible scenarios could account for the current epidemiological data on MERS emergence: reported cases may have largely been transmitted to humans by animals, in which case the virus remains incapable of sustained human transmission; or, human-to-human transmission is already sufficiently facile to support epidemic disease (Cauchemez et al., 2013b,c). Distinguishing between these alternatives is difficult due to the poor quality of available epidemiological data, he said. As they did early on following the emergence of H1N1, the researchers are combining multiple analyses in hopes of resolving a general picture of MERS emergence, rather than a definitive history. One method they have used to do this is to use the number of cases exported out of the affected area in the Middle East as an indicator of the number of cases actually occurring there. With that number (four cases), along with passenger flow information—assuming that visitors and locals bear the same risk of infection—it is possible to calculate how many people in the region must have been infected. "You come up with an answer of around a thousand [cases to date], with big confidence intervals," he reported—a figure similar to one the group obtained using a phylodynamic approach, which estimates viral spread according to sequence divergence.

Neither of these estimates is sufficiently robust to distinguish between the two scenarios he posed, Ferguson stated—although evidence appears to favor significant human-to-human transmission of MERS. Its overall impact remains to be determined, because the relatively few observed cases are almost among the most severe, he observed; however, more accurate fatality rates can be estimated by comparing fatality rates for the first- and second-detected infections in case clusters. He also noted that data from case clusters can be applied to estimate disease transmissibility. Fortunately, in the case of MERS, all case clusters detected to date have been limited, which demonstrates that disease control measures effectively stop transmission once imposed within a case cluster. These results, viewed in concert with estimates of transmissibility based on the case curve itself, and on phylodynamic analysis of viral diversity, depict MERS as it currently exists as a "slow epidemic."

Better data, better models During subsequent discussion, workshop participants considered how several assumptions made in the models Ferguson described might be strengthened. The lack of epidemiological data on MERS is a source of particular concern. Ferguson noted that as a result, in part, of increased attention from researchers, health officials in Saudi Arabia and other affected countries are more consistently performing follow-up investigations of cases, and increasingly detecting milder cases. "The data collected just in the last few weeks very much validates what I presented," he reported. "The evidence is that clearly, if you look harder, you are going to detect more cases. If you are picking up index cases through some sort of random severe disease surveillance system, or doctors testing, then those submitted are likely to be the more akin to the 'iceberg' [of total cases]."

Similarly, knowledge of exposure risks for travelers, as compared with the general population in endemic areas, will improve estimates of disease based on cases among travelers, Ferguson stated—but this information is difficult to obtain, and even more difficult to interpret. "If you assume there is human-to-human transmission, it is entirely likely that there is a certain degree of contact disconnect between travelers in hotels and the local population," he explained. "This sort of estimate would underestimate the scale of the epidemic in Saudi Arabia. Conversely, though, if there is not much human-to-human transmission, and what we are really talking about is exposure to animal reservoir, then tourist-type activities might actually increase your exposure. You would need to do some very difficult studies to resolve that." However, he added, highlighting the need to resolve such issues is an important function of disease models. "Modeling is often about hypothesis generation," he observed: it is not just giving possible interpretations of data, but also feedback to people collecting the data that suggests new studies.

As was discussed in several contexts during this workshop, differences among the various definitions of a disease "case" present a significant challenge to understanding disease transmission dynamics—and this applies as well to models of emerging infections. While increasing work is being done to improve the analysis of surveillance data from multiple sources, Ferguson said, ultimately researchers must recognize that there is not a fixed case definition, and be aware of its implications. "We always recognize we are seeing a partial picture," he observed. "When we do have clinical data, we use it to try and categorize cases. Often, though, we are left with what we have. Modeling is never a substitute for data."

Investigating the Influence of Population Shifts on Disease Dynamics

Disease models typically involve algorithms that estimate dynamic parameters, such as transmission or recovery rates, from information such as the number of infected and susceptible people and their degree of contact. The influence of population dynamics—demography, mobility, and migration—is generally missing from such models, according to speaker Nita Bharti, of Penn State and Stanford Universities (Dr. Bharti's contribution may be found on pages 154–165 in Appendix A). Failing to recognize that these factors are not static hinders our understanding of disease dynamics, as well as our ability to predict or change them, she observed. Rather, what is needed is a "merged understanding of populations and diseases."

Studies of HIV-1 clusters along African road networks (Tatem et al., 2012) and influenza transmission through commuter flows in the United States (Viboud et al., 2006) demonstrate that human mobility and migration impact spatial patterns of disease transmission at different scales, Bharti noted. This point—and its consequences for disease control—was further borne out in her work on measles

transmission dynamics in Niger, which she described in her presentation to the workshop.

Case study: Measles in Niger Annual epidemic measles regularly kill as many as 150,000 children each year in Niger, despite the availability of inexpensive measles vaccine, Bharti reported. To understand the persistence of this disease despite efforts to control it, she and colleagues from Niger's Ministry of Health and Doctors Without Borders investigated the mechanisms underlying these cyclical outbreaks in three major cities: Maradi, Niamey, and Zinder.

The seasonal pattern of measles outbreaks in Niger proved to be unusual in two respects. First, Bharti noted, rather than coinciding with the school term, as is typical, measles strikes Niger during the dry season, and declines significantly with the onset of the rainy season. Secondly, transmission is not correlated with rainfall, as would be expected if transmission rates were determined purely by environmental conditions (Ferrari et al., 2010). Recognizing that labor migration is common in this region, which is economically dependent on agriculture, the researchers attempted to examine the influence of migration patterns on disease dynamics.

First, the researchers tested the hypothesis that population density fluctuates seasonally in the three cities, with large numbers of migrants living in low-density agricultural areas during the rainy season and returning to high-density urban areas during the dry season (Faulkingham and Thorbahn, 1975; Rain, 1999). After considering several different sources of data on population density and location, they chose to use satellite imagery composites of visible, anthropogenic light at night (Bharti et al., 2011; Elvidge et al., 1997; Pozzi et al., 2003). While cumbersome, this analysis had several advantages, Bharti explained: the images are captured daily and available within 48 hours; they are of increasingly high resolution (to 1 kilometer during her study period); they are publicly available; and, they have been collected and archived for several decades, so baselines can be established. While not appropriate for measuring migration in all situations (particularly in small towns and villages), the researchers determined that these images are sufficiently sensitive to reveal population changes in cities such as those that constituted their study area.

"We see that there is a strong decrease in brightness during the rainy season in each of these three cities," Bharti said, "but this is a retrospective study. We could not go back in time and count the people that were there." Thus the researchers attempted to validate their result through close study of the spatial progression of measles within Niamey, during an especially large outbreak in 2003–2004, when cases were recorded daily in each of three city subdivisions known as communes. "If population density was driving the spatial progression of measles through the city of Niamey, then the measles cases and the brightness values should show similar patterns within each commune," she explained. This turned out to be the case: two communes had high brightness, which peaked at the

same time as the measles cases, she reported; the third, less-bright commune had fewer cases. Additional modeling confirmed that with the correctly timed increase and decrease in population size, the researchers could predict the trajectory and peak of measles outbreaks in Niamey (Bharti et al., 2011).

Bharti then described how she and coworkers applied their findings to improve the effectiveness of measles vaccination efforts in Niamey. Following the 2003–2004 epidemic, Niger's Ministry of Health conducted a campaign, which proved only to be marginally effective, so they wanted to know why (Dubray et al., 2006). "We thought that if the variation in the vaccine coverage was due to the seasonal movement of the population, then it should be correlated with . . . changes in brightness that we think are indicating the change in population," she said. They were able to show this was essentially the case.

"Conventional wisdom in measles vaccination strategy tells us that we should vaccinate during the troughs of infection, to get ahead of disease and eliminate some of the nonlinearities in transmission," she noted. Their results, however, suggest that for catch-up campaigns (not reactive interventions) vaccinating during the urban phase of the migratory cycle would be better for increasing regional vaccine coverage, even if it missed the infection trough. This timing is also advantageous, because it is easier to recruit people to be vaccinated when they are not scattered across a rural landscape. "We can take advantage of these rural–urban migration patterns and vaccinate people when they are coming to the cities," Bharti observed.

A clear understanding of population dynamics not only helped to explain the mechanism underlying the dynamics of measles transmission in their study area, but also to inform better disease control, Bharti concluded. She noted that a similar approach could prove valuable in other contexts, such as to investigate the contribution of rainy-season migration to malaria transmission dynamics, and the effects of drought on migration patterns, which in turn could affect the transmission of several infectious diseases.

Integrating and Applying Information on Demography, Health, and Migration

Prominent among the effects of the Great Acceleration in the United States has been a wave of immigration, rivaling that of the early twentieth century. Today, approximately 12 percent of the U.S. population—more than 40 million people—are foreign-born, that is, born outside the country to noncitizen parents, according to Cetron, of the CDC. Foreign-born residents of the United States represent 105 countries, with China, India, Mexico, the Philippines, and Vietnam combined accounting for half of this population (Table WO-3). In 2010, he reported, about 1 million immigrants entered the United States, of whom more than 70,000 were refugees, along with 36 million nonimmigrant visitors and 127 million border-crossing commuters.

TABLE WO-3 Top 15 Source Countries with Largest Populations in the United States as Percent of Foreign Born, 2008

Country	Number of Foreign Born	% of U.S. Foreign-Born Population
Mexico	11,467,856	30.3
China	1,899,643	5.0
Philippines	1,652,430	4.4
India	1,535,038	4.1
Vietnam	1,110,878	2.9
El Salvador	1,078,337	2.9
Korea	1,019,757	2.7
Cuba	958,548	2.5
Canada	824,354	2.2
Dominican Republic	762,511	2.0
Guatemala	718,993	1.9
Jamaica	622,431	1.6
Germany	635,065	1.7
Colombia	596,104	1.6
Haiti	522,678	1.4
Other	12,385,534	32.8
Total of Top 15 Birth Countries:	25,404,623	67.2
Total U.S. Foreign-Born Population:	37,790,157	12.4

SOURCE: American Community Survey, 2006–2008.

Given the significant role of mobility and migration as a driver of infectious disease emergence and spread—along with deep global disparities in health care—it is important to identify pathogens that are likely to be crossing our borders along with visitors and immigrants, Cetron said. For example, he noted, tuberculosis (TB) rates in the United States—including multidrug-resistant disease (MDR-TB)—are 10 times higher among foreign-born residents than among the general population. Until 2007, very little had been done by the CDC to address this health disparity. In that year, the CDC changed its screening policies to increase the effectiveness of both detection and treatment of TB among immigrants, he noted. As a result, TB rates are declining among foreign-born U.S. residents for the first time in several decades.

Disease screening programs for immigrants provide opportunities for surveillance of a range of emerging infectious diseases, some of which may be most effectively addressed through intervention in their countries of origin (see Figure WO-30). "Most of these are events that should never happen, such as vaccine-preventable diseases," Cetron observed. Simply administering anti-malarial or anti-parasitic medications to refugees prior to their arrival in the United States has proved highly effective from both medical and cost standpoints, he stated (Stauffer et al., 2008; Swanson et al., 2012). In Africa, the CDC's Refugee Health program in Kakuma and Dadaab refugee camps in Kenya conducts a wide range

FIGURE WO-30 More than 60,000 children were vaccinated against measles and polio in the Za'atari refugee camp in Jordan during a coordinated and targeted campaign in April 2013.
SOURCE: Cetron presentation, 2013; UK Department for International Development. Photo credit: Peter Millett/British Embassy Jordan.

of public health activities, including TB screening and treatment, syphilis testing, influenza surveillance, measles vaccination, and field investigations of outbreaks. More importantly, this program is building health infrastructure for the ongoing detection, treatment, prevention, and control of infectious diseases, he said. The CDC also provides interventions to control outbreaks of measles and prevent the spread of other infectious diseases among Syrian refugees of civil war living in camps in neighboring countries. During April 2013, more than 60,000 Syrian children in refugee camps were vaccinated against measles and polio.

Introducing BioMosaic The United States will soon accept Syrian women and children refugees, who are likely to benefit—along with their communities and local health care services—from a new tool developed by the CDC called BioMosaic, according to Cetron. A recent fact sheet from the agency describes it as follows (CDC, 2013a):

> BioMosaic is a big data fusion and visualization project that integrates demography (human, animal, and environmental), health (disease profiles and emerging threats) and migration data into a common platform. The platform is linked by GIS coordinates that allows geospatial and temporal visualizations over mobile

and web interfaces. It has numerous applications for retrospective and prospective analyses enabling high-level risk assessment and pandemic threat forecasting to enhance detection, response, and prevention.

BioMosaic has aided international responses to recent global health threats such as H1N1 pandemic influenza, cholera following the Haiti earthquake, H7N9 influenza, and MERS-CoV. When Syrian refugees enter the United States, BioMosaic maps will keep track of their locations at a county level, enabling health officials to target interactions, ensure access to treatment for TB, and continue screening for other health issues as appropriate, Cetron predicted. "We think that this is an opportunity to change the paradigm" of immigrant screening, he observed. Rather than a means of exclusion, information available through BioMosaic provides an opportunity to conduct infectious disease surveillance and outbreak response, and to target interventions for prevention and treatment.

Ultimately, the CDC and its BioMosaic collaborators, the BioDiaspora project of the University of Toronto[23] and HealthMap of Harvard University,[24] anticipate that BioMosaic will integrate data from a range of sources on human health and migration, insect and vector distribution, animal movements and speciation, and environmental data such as temperature, rainfall, and anthropogenic light (as described by Bharti), Cetron stated. Applications have been developed for both Web and iPad. At present, the platform is available only within the CDC and its collaborators. It will include publicly available information on the intersection of demography, migration, and health in the U.S. foreign-born population, he said. The Web version, designed for technical applications by registered users, incorporates a more comprehensive, global set of interfaces and data layers. The range of possible applications of BioMosaic is summarized in Box WO-4.

Case study: BioMosaic investigation of MERS Cetron and colleagues used BioMosaic to study the potential for the international spread of MERS-CoV out of the Arabian Peninsula (Khan et al., 2013). Of particular concern was an annual gathering of millions of Muslims in Mecca, Saudi Arabia, during the pilgrimage known as the Hajj, which in 2013 took place in October. To help cities and countries worldwide assess their potential for MERS-CoV importation following the 2013 Hajj, the researchers examined Hajj-related travel to the area over the previous decade, along with worldwide flight patterns, to predict population movements out of Saudi Arabia and the broader Middle East. They also compared the magnitude of travel to countries, their capacity for timely detection of imported MERS-CoV, and their ability to mount an effective public health response, as indicated by their economic status and per capita health care expenditures.

Figure WO-31 illustrates the result of this analysis, and reveals that Egypt, India, Indonesia, and Pakistan are among the highest-risk countries for MERS-CoV

[23] See http://www.biodiaspora.com (accessed August 6, 2014).

[24] See http://healthmap.org/site/about (accessed August 6, 2014).

introduction, Cetron observed. "The vast majority of these pilgrims are coming from and going back to very-low-income countries where we expect the surveillance capacity to detect the introduction of cases to be quite small," he said. "Understanding this and prioritizing the ranking of those countries really helped us advise WHO and these other countries on where to target early diagnostic surveillance capability, enhanced recognition, nosocomial infection control guidelines, and to prioritize them in areas that are particularly vulnerable by this assessment."[25]

Useful though it is, BioMosaic is not a predictive tool, Cetron insisted. Rather, it reveals patterns that arise from the intersection of multiple data sets and generates hypotheses that must be tested through specific studies that take into account local variations in environmental conditions and population dynamics, he explained. Invoking Stephen Hawking's observation that the greatest enemy of knowledge is not ignorance, but the illusion of knowledge, Cetron warned against confusing the correlations BioMosaic generates with evidence of causation. The purpose of BioMosaic is to distill simple patterns from large amounts of complex information; the interpretation of those truths and patterns remains to be determined experimentally, he concluded.

Conclusion

Cetron's presentation on BioMosaic brought together many recurring themes of the workshop:

- The complex interactions of anthropogenic drivers of infectious disease emergence and spread,
- The usefulness and limitations of maps (along with other quantitative and modeling tools) as a means to characterize and predict those interactions,
- The importance of local and temporal variation in environmental conditions and population dynamics, and
- And the need to distinguish between correlative and causative observations of environmental change and disease dynamics.

In his closing remarks, Forum vice-chair James Hughes, of Emory University, emphasized the challenges researchers, and health officials, face when communicating the need and means to address emerging pathogens to the global community—particularly to people most at risk to bear the burden of infectious disease.

[25] As of December 3, 2013, only two Hajj pilgrims have tested positive for MERS-CoV. According to the *Montreal Gazette* (and as noted in ProMED Mail), the cases of the two women from Spain, who were traveling together, are designated "probable," because tests done by Spanish laboratories have only met part of the WHO's criteria for a confirmed case (Branswell, 2013).

BOX WO-4
What Can BioMosaic Do?

BioMosaic uses layers of information to depict health risks visually through Web and iPad applications. Public health officials can then use the information to detect, respond, and prevent any type of public health emergency. Specifically, BioMosaic can be used for:

- **Surveillance—**By monitoring multiple data sources to identify outbreaks, emerging diseases, events of public health significance, media reports, or other sources, BioMosaic helps predict health threats.

For example, during the cholera outbreaks in Haiti in 2010, the CDC's Division of Global Migration and Quarantine (DGMQ) used BioMosaic to monitor reports of diseases in Haiti to determine what diseases could be introduced into Haiti or brought back to the United States.

- **Evaluation of conditions at the source of a public health event—**By layering information about environmental conditions, animal and human populations, and any changes from historical data in the area where a disease has been identified, BioMosaic provides new insights about health risks.

During the 2013 H7N9 influenza outbreak in China, BioMosaic was used to determine the potential risk of exposure by visually comparing poultry and swine density with the human population density in China.

- **Evaluation of transportation networks from an event source into the United States—**By analyzing flight schedules, flight capacity, and final passenger destination, BioMosaic provides information that can be used for public health responses at entry points to the United States.

During the cholera outbreaks in Haiti in 2010, BioMosaic helped DGMQ effectively target detection, education, and prevention messages at airports where travelers from Haiti were arriving.

"It has never ceased to amaze me over the years: all the ingenious things that we as a species do to aid and abet the microbes," Hughes declared. Indeed, a decade after SARS raised global awareness of emerging diseases, MERS-CoV—another novel coronavirus—serves to remind us of the many ways in which human agency drives pathogens to adapt to our species. Indeed, it is as a species that we must respond to this threat, as Khan and coauthors (2013) note:

- **Evaluation of conditions in the United States—**By visualizing distribution of foreign-born populations and performing demographic analysis (English proficiency, education level, etc.), BioMosaic can map risk areas where interventions should be targeted.

In 2010, DGMQ used BioMosaic in Haiti to collect information on where Haitians lived in the United States and shared that information with state health partners to help inform outreach and communication efforts.

- **Analysis to determine where the CDC intervention is needed—**By considering the layers of information provided through BioMosaic, the CDC can determine the best populations, locations, and timing for public health interventions.

During the CDC's response to the 2013 outbreak of MERS-CoV, BioMosaic provided information about historic trends of travelers attending the Hajj, a religious gathering which draws about 3 million Muslims from around the world, and more than 11,000 Americans each year. BioMosaic also provided peak periods for travel and their countries of origin, which helped DGMQ target communication messages and timing for outreach to Hajj travelers.

- **Building risk models and testing public health hypotheses—**By layering information that has never been pulled together before, BioMosaic may reveal new information on public health problems.

For example, the *Aedes aegypti* mosquito can transmit both dengue fever and yellow fever. However, dengue is found all over the world and yellow fever is limited to a few locations. By looking at layers of information about the environment, populations affected, and regions where dengue and yellow fever exist, BioMosaic may help illuminate something new about the spread of disease.

SOURCE: CDC, 2013a.

The emergence of MERS-CoV requires an internationally coordinated effort to mitigate its potential global health and economic consequences, with particular emphasis on supporting diagnostic and public health response capacity in vulnerable, resource-limited countries. Understanding the most probable pathways for international spread of MERS-CoV could help medical and public health providers worldwide operate in a far more anticipatory and less reactive manner than occurred during SARS.

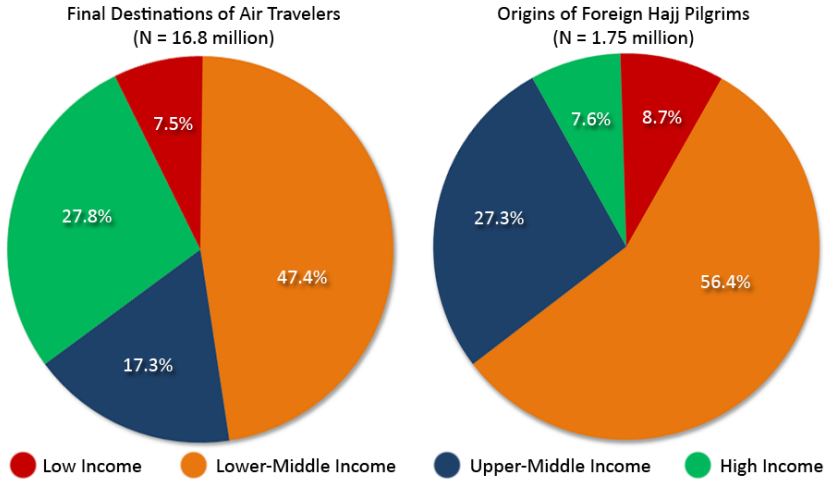


FIGURE WO-31 Final destinations of air travelers departing Saudi Arabia, Jordan, Qatar, and United Arab Emirates from June to November 2012 and origins of foreign Hajj pilgrims by World Bank income classification.
SOURCE: Khan presentation, 2013; data from Khan et al., 2013.

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Appendix A

Contributed Manuscripts

A1

ANIMAL MIGRATION AND INFECTIOUS DISEASE RISK[1]

*Sonia **Altizer**,[2] Rebecca Bartel,[2] and Barbara A. Han[2]*

Abstract

Animal migrations are often spectacular, and migratory species harbor zoonotic pathogens of importance to humans. Animal migrations are expected to enhance the global spread of pathogens and facilitate cross-species transmission. This does happen, but new research has also shown that migration allows hosts to escape from infected habitats, reduces disease levels when infected animals do not migrate successfully, and may lead to the evolution of less-virulent pathogens. Migratory demands can also reduce immune function, with consequences for host susceptibility and mortality. Studies of pathogen dynamics in migratory species and how these will respond to global change are urgently needed to predict future disease risks for wildlife and humans alike.

[1] Originally printed as Altizer et al. 2011. Animal migration and infectious disease risk. *Science* 331(6015):296-302. Reprinted with permission from AAAS.

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Billions of animals from groups as diverse as mammals, birds, fish, and insects undertake regular long-distance movements each year to track seasonal changes in resources and habitats (Dingle, 1996). The most dramatic migrations, such as those by monarch butterflies (Figure A1-1), gray whales, and some shorebirds and dragonflies (Figure A1-2), span entire continents or hemispheres, can take several months to complete, and are accompanied by high energetic demands and extreme physiological changes. The ultimate cause of these seasonal migrations remains debated; most hypotheses focus on avoidance of food scarcity, seeking physiologically optimal climates, and avoiding predation during periods

FIGURE A1-1 Monarch butterflies (*Danaus plexippus*), shown here at a wintering site in central Mexico, undertake one of the longest distance two-way migrations of any insect species worldwide. Monarchs are commonly infected by a debilitating protozoan parasite that can lower the flight ability of migrating butterflies.

Animal		Locations and distance traveled	Major infectious diseases	Major threats to migration
	**Chinook salmon** (*Oncorhynchus tshawytscha*)	3- to 4-year-old adults migrate up to 1500 km from the Pacific Ocean upriver to freshwater spawning sites in the Pacific Northwestern U.S.	Sea lice (*Lepeophtheirus* sp.); Myxozoan (*Henneguya* sp.)	Dam construction; Human-modified water flow; Deforestation; Fish hatcheries
	**Green sea turtle** (*Chelonia mydas*)	Adults migrate over 2300 km to nesting locations in tropical to subtropical areas of the Atlantic Ocean, Gulf of Mexico, Mediterranean Sea, and the Indo-Pacific	Tumor-forming herpesvirus (fibropapillomatosis); Spirorchid cardiovascular flukes	Hunting and egg poaching; Bycatch; Nesting and foraging habitat destruction
	**Western toad** (*Anaxyrus boreas*)	Annual breeding migration up to 6 km from hibernating sites (likely underground) to breeding ponds in high-elevation habitats in the Western U.S.	Chytrid fungus (*Batrachochytrium* sp.); Parasitic trematode (*Ribeiroia* sp.); Oomycete (*Saprolegnia* sp.)	Building of roads; Loss of breeding habitat through deforestation
	**Ruddy turnstone** (*Arenaria interpres*)	Annual migration up to 27,000 km from Arctic nesting grounds to overwintering sites along the coastlines of all continents except Antarctica	Avian influenza virus; West Nile virus; Multiple endoparasitic worms	Habitat loss (due to dams, freshwater extraction); Overharvesting of food resources at stopover sites
	**Flying foxes** (*Pteropus spp.*)	Unknown maximum migratory distances for many species; can range between 50-1000 km across Southeast Asia and Australia	Paramyxoviruses such as Nipah virus and Hendra virus	Loss of feeding grounds through deforestation; Habitat loss through land conversion
	**Green darner** (*Anax junius*)	Exact distances unknown, but adults travel 700 km or more annually from southern Canada and northern U.S. to Central America	Eugregarine protozoan (*Geneiorhynchus* sp.)	Unknown; possibly destruction of freshwater breeding habitats
	**Wildebeest** (*Connochaaetes taurinus*)	In the Serengeti, animals move between wet and dry seasons across an area of 30,000 km^2	Rinderpest (*Morbillivirus* sp.); Brucellolsis (*Brucella*); Foot-and-mouth disease (*Aphtae epizooticae*)	Landcover change (reduction in tree cover); Fire frequency; Exposure to infected domestic livestock
	**Swainson's thrush** (*Catharus ustulatus*)	Migrate up to 10,000 km annually between breeding grounds in Canada/northern U.S. to overwintering sites in Central and South America	West Nile virus; Lyme disease; Blood parasites (*Haemoproteus* and *Plasmodium*)	Habitat loss on breeding and wintering grounds; Building strikes during migration
	**Gray whale** (*Eschrichtius robustus*)	Annual migrations of over 18,000 km from feeding sites in the Bering Sea to winter breeding grounds along the coast of Baja California	Whale lice (cyamid amphipods, *Cyamus* spp.); Barnacles (*Crytolepas*); Multiple endoparasitic worms	Industrial activity near calving lagoons; Oil exploration along migration routes; Vessel harassment

FIGURE A1-2 Representative migratory species, including migration distances and routes, known parasites and pathogens, and major threats to species persistence. Infectious diseases have been examined in the context of migration for some, but not all, of these species. Supporting references and photo credits are provided in the supporting online material (SOM) text.

of reproduction [e.g., (McKinnon et al., 2010)]. Contemporary studies of migration have uncovered mechanisms of animal navigation, energy budgets, resource use, and phenological responses to environmental change; migratory species have also been recognized for their potential to connect geographically distant habitats and transfer large amounts of biomass and nutrients between ecosystems [reviewed in (Bowlin et al., 2010)]. These studies illustrate the profound ecological and evolutionary consequences of migratory journeys for animal populations on a global scale.

Owing to their long-distance movements and exposure to diverse habitats, migratory animals have far-reaching implications for the emergence and spread of infectious diseases. Importantly, most previous work on the role of host movement in infectious disease dynamics has focused on spatially localized or random dispersal. For example, dispersal events give rise to traveling waves of infection in pathogens such as raccoon rabies (Russell et al., 2005), influenza in humans (Viboud et al., 2006), and nuclear polyhedrosis viruses in insects (White et al., 2000). In the context of metapopulations, limited amounts of host movement could actually prevent host extinction in the face of a debilitating pathogen and allow host resistance genes to spread (Carlsson-Granner and Thrall, 2002; Gog et al., 2002). From a different perspective, case studies of species invasions demonstrate that one-time transfers of even a few individuals can transport pathogens long distances and introduce them to novel habitats (Daszak et al., 2000). Yet relatively few studies have examined how regular, directed mass movements that characterize seasonal migration affect the transmission and evolution of pathogens within host populations and the response of migratory species to infection risks.

In this article, we review the consequences of long-distance migrations for the ecological dynamics of host–pathogen interactions and outline key challenges for future work. Ecological processes linked with migration can increase or decrease the between-host transmission of pathogens, depending on host migratory behavior and pathogen traits (Figure A1-3). Moreover, new work shows that for some species, the energetic demands of migration compromise host immunity, possibly increasing susceptibility to infection and intensifying the impacts of disease. Importantly, many migratory species are at risk of future declines because of habitat loss and exploitation, and animal migrations are shifting with ongoing anthropogenic change (Wilcove, 2008). Thus, understanding how human activities that alter migratory patterns influence wildlife–pathogen dynamics is urgently needed to help guide conservation and management of migratory species and mitigate future risks from infectious disease.

What Goes Around Comes Around: Pathogen Exposure and Spatial Spread

An oft-cited but poorly supported assumption is that long-distance movements of migrating animals can enhance the geographic spread of pathogens,

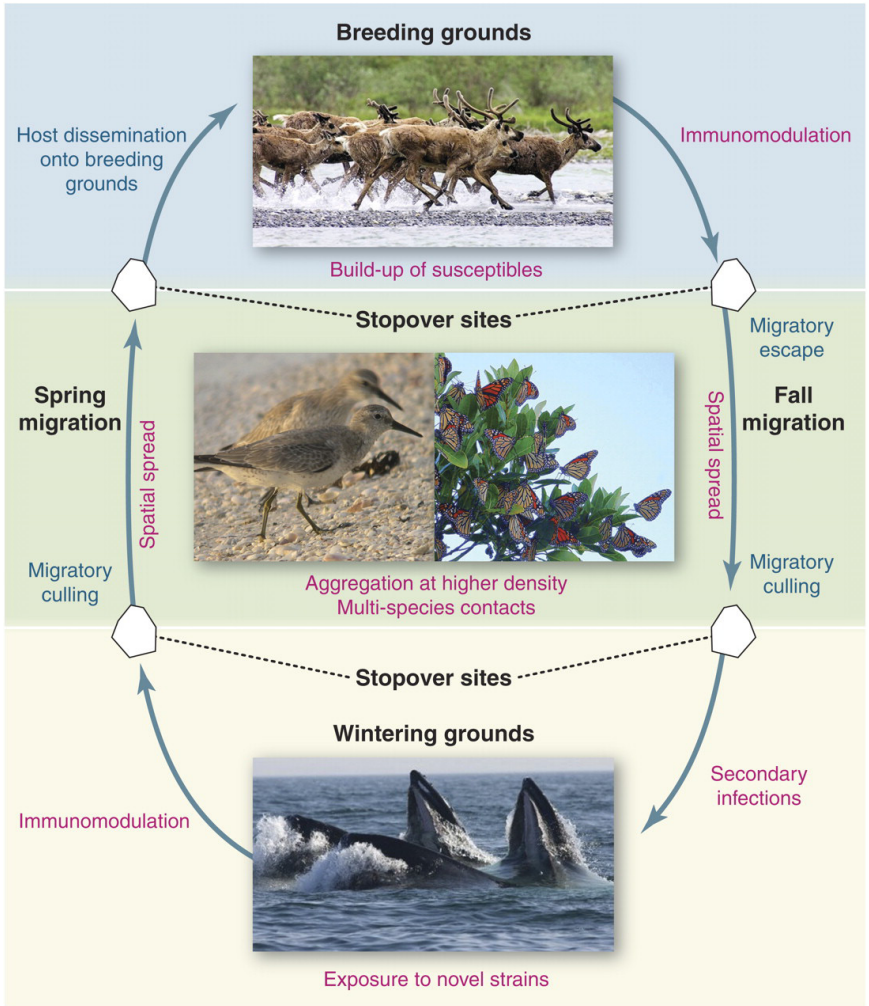


FIGURE A1-3 Points along a general annual migratory cycle where key processes can increase (red text) or decrease (blue text) pathogen exposure or transmission. Behavioral mechanisms such as migratory escape and migratory culling could reduce overall pathogen prevalence. As animals travel to distant geographic locations, the use of multiple habitat types including stopover sites, breeding areas, and wintering grounds can increase transmission as a result of host aggregations and exposure to multihost pathogens. This might be especially true for migratory staging areas where animals stop to rest and refuel. High energetic demands of spring and fall migration can also result in immunomodulation, possibly leading to immune suppression and secondary infections. [Photo credits (clockwise): J. Goldstein, B. McCord, A. Friedlaender, and R. Hall]

including zoonotic pathogens important for human health such as Ebola virus in bats, avian influenza viruses in waterfowl and shorebirds, and Lyme disease and West Nile virus (WNV) in songbirds. For example, WNV initially spread in North America along a major corridor for migrating birds and rapidly expanded from its point of origin in New York City along the Atlantic seaboard from 1999 to 2000 (Rappole et al., 2000). Although experimental work concluded that passerine birds in migratory condition were competent hosts for WNV and could serve as effective dispersal agents (Owen et al., 2006), evidence to show that this expansion resulted from movements of migratory birds remains equivocal. For the zoonotic pathogen Ebola virus, a recent study points to the coincident timing of an annual influx of migratory fruit bats in the Democratic Republic of Congo and the start of human Ebola outbreaks in local villages during 2007 (Leroy et al., 2009). In central Kazakhstan, saiga antelopes (*Saiga tatarica*) become infected with gastrointestinal nematodes (*Marshallagia*) during the course of seasonal migration by grazing on pastures used by domesticated sheep earlier in the season. As migration continues, saiga carry and transmit *Marshallagia* to northern sheep populations, leading to pulses of infection that coincide with annual saiga migrations (Morgan et al., 2007).

The potential for serious disease risks for human and livestock health has raised alarm about the role of migratory species in moving infectious agents to distant locations. Yet surprisingly few examples of long-distance pathogen dispersal by migrating animals have been clearly documented in the published literature, and some studies indicate that migrants might be unfairly blamed for transporting pathogens. As a case in point, wild waterfowl (Anseriformes) and shorebirds (Charadriiformes) represent the major natural reservoirs for diverse strains of avian influenza virus (AIV) worldwide, including the highly pathogenic (HP) H5N1 subtype that can lethally infect humans (Olsen et al., 2006). Although many of these migratory birds can become infected by HP H5N1, recent work incorporating what is known about viral shedding period, host migration phenology, and the geographical distribution of viral subtypes suggests that most wild birds are unlikely to spread HP H5N1 long distances (e.g., between Asia and the Americas) as previously suspected [e.g., (Krauss et al., 2007; Takekawa et al., 2010)]. Central to the question of how far any host species can transport a pathogen are the concepts of pathogen virulence and host tolerance to infection. Specifically, virulence refers to the damage that parasites inflict on their hosts, and tolerance refers to the host's ability to withstand infection without suffering major fitness costs. Thus, host–parasite species or genotype combinations associated with very low virulence or high tolerance should be the most promising candidates for long-distance movement of pathogen strains, a simple prediction that could be explored within migratory species or using cross-species comparisons.

Beyond their potential role in pathogen spatial spread, a handful of studies suggest that migratory species themselves encounter a broader range of pathogens from diverse environments throughout their annual cycle compared with species

residing in the same area year-round (Figure A1-3). One field study showed that songbird species migrating from Europe became infected by strains of vector-borne blood parasites originating from tropical bird species at overwintering sites in Africa (Waldenström et al., 2002), in addition to the suite of parasite strains transmitted at their summer breeding grounds. The authors posited that winter exposure to parasites in tropical locations is a significant cost of migration, because resident species wintering in northern latitudes encounter fewer parasite strains and do not experience year-round transmission. Similarly, the number of parasite species per host was positively related to distances flown by migratory waterfowl (Figuerola and Green, 2000), indicating that migrating animals could become exposed to parasites through encounters with different host species and habitat types.

Although some animals undertake nonstop migrations, most migratory species use stopover points along the migration route to rest and feed. These stopover points usually occur frequently along a journey, although some species like shorebirds fly thousands of kilometers between only a handful of staging areas (Dingle, 1996). Refueling locations are often shared by multiple species, and the high local densities and high species diversity can increase both within- and between-species transmission of pathogens. In one of the most striking examples of this phenomenon, shorebirds such as sanderlings (*Calidris alba*), ruddy turnstones (*Arenaria interpres*; Figure A1-2), and red knots (*Calidris canutus*), which migrate annually between Arctic breeding grounds and South American wintering sites, congregate to feed in massive numbers in the Delaware Bay and the Bay of Fundy to rebuild fat reserves, leading to upwards of 1.5 million birds intermingling, at densities of over 200 birds per square meter (Krauss et al., 2010). This phenomenon creates an ecological hotspot at Delaware Bay, where the prevalence of AIV is 17 times greater than at any other surveillance site worldwide (Krauss et al., 2010).

Leaving Parasites Behind: Migration as a Way of Lowering Infection Risk

Although greater exposure to parasites and pathogens can pose a significant cost of long-distance migration, for some animal species, long-distance migration will reduce infection risk by at least two nonexclusive processes (Figure A1-3). First, if prolonged use of habitats allows parasites with environmental transmission modes to accumulate (i.e., those parasites with infectious stages that can persist outside of hosts, such as many helminths, ectoparasites, and microbial pathogens with fecal-oral transmission), migration will allow animals to escape from contaminated habitats [i.e., "migratory escape" (Loehle, 1995)]. Between intervals of habitat use, unfavorable conditions (such as harsh winters and a lack of hosts) could eliminate most parasites, resulting in hosts returning to these habitats after a long absence to encounter largely disease-free conditions (Loehle, 1995). Empirical support for migratory escape comes from a few well-studied

host–parasite interactions, including research on reindeer (*Rangifer tarandus*), which showed that the abundance of warble flies (*Hypoderma tarandi*) was negatively correlated with the distance migrated to summer pastures from reindeer calving grounds (the main larval shedding area in early spring) (Folstad et al., 1991). This observation prompted researchers to suggest that the reindeers' annual postcalving migration reduces warble fly transmission by allowing animals to leave behind areas where large numbers of larvae have been shed (and where adult flies will later emerge). It is worth noting that escape will be less successful from pathogens with long-lived infectious stages that persist between periods of host absence or pathogens that cause chronic or life-long infections.

Long-distance migration can also lower pathogen prevalence by removing infected animals from the population [i.e., "migratory culling" (Bradley and Altizer, 2005)]. In this scenario, diseased animals suffering from the negative consequences of infection are less likely to migrate long distances owing to the combined physiological demands of migration and infection. Work on the migratory fall armyworm moth (*Spodoptera frugiperda*) suggested that insects infected by an ectoparasitic nematode (*Noctuidonema guyanense*) had reduced migratory ability because few to no parasites were detected in moths recolonizing sites as they returned north (Simmons and Rogers, 1991). More recent work on Bewick's swans (*Cygnus columbianus* bewickii) showed that infection by low-pathogenic avian influenza (LPAI) viruses delayed migration over a month and reduced the travel distances of infected birds compared with those of healthy individuals (van Gils et al., 2007). However, a study of AIV in white fronted geese did not find any difference in distances migrated between infected and uninfected birds (Kleijn et al., 2010), suggesting that, not surprisingly, some species are better able to tolerate infections during long journeys and raising the possibility that migration could select for greater tolerance to infections in some hosts due to the high fitness costs of attempting migration with a debilitating pathogen.

Whether the net effects of migration will increase or decrease prevalence depends in large part on the mode of parasite transmission and the level of host specificity, both of which will affect opportunities for cross-species transmission at staging and stopover sites. Parasites that decline in response to host migration may include specialist pathogens, as well as those with transmission stages that can build up in the environment, pathogens transmitted by biting vectors or intermediate hosts, or for which transmission occurs mainly from adults to juveniles during the breeding season (e.g., Box A1-1). Conversely, migrating hosts could experience higher pressure from generalist parasites if opportunities for cross-species transmission are high at stopover areas or wintering grounds or from specialist pathogens if transmission increases with dense host aggregations that accompany mass migrations. Importantly, effects of migration on pathogen dynamics within host populations should translate to large differences in prevalence across host populations with different migratory strategies. Over the past few years, we have focused on monarch butterflies (*Danaus plexippus*)

as a model system to study the effects of migration on host–pathogen interactions (Box A1-1) and found that both migratory culling and migratory escape can cause spatiotemporal variation in prevalence within populations and extreme differences in prevalence among populations with different migratory strategies. However, we are not aware of intraspecific comparisons of prevalence between migratory and nonmigratory populations for other animal species.

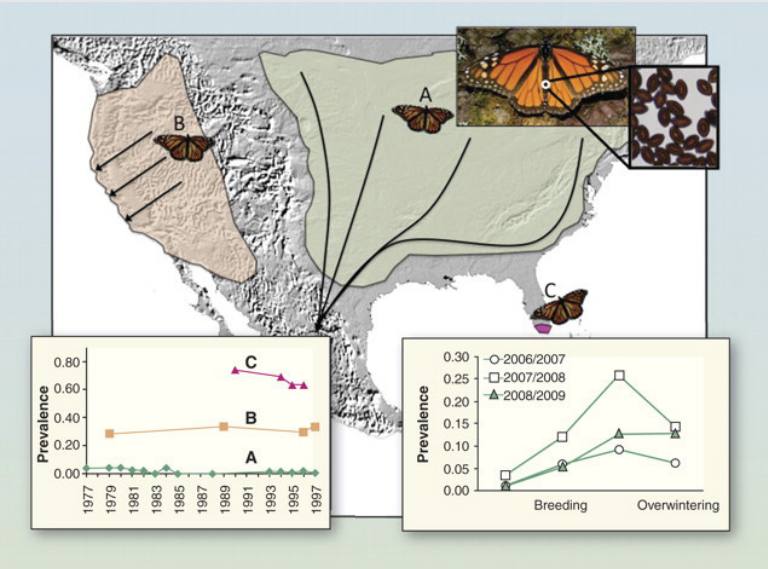
Immune Defense Balanced Against the Demands of Migration

In addition to ecological mechanisms affecting between-host transmission, the physiological stress and energetic demands of migration can alter the outcome of infection within individuals through interactions with the host's immune system (Figure A1-2). More generally, because several immune pathways in both vertebrates and invertebrates are known to be costly (Eraud et al., 2005; Schmid-Hempel, 2005), seasonal demands such as premigratory fattening or strenuous activity will likely lower the resource pool available for mounting an immune response (Weber and Stilianakis, 2007). In anticipation of migration, for example, some animals accrue up to 50% of their lean body mass in fat, increase muscle mass, and atrophy organs that are not essential during migration (Dingle, 1996). Thus, before migration, animals might adjust components of their immune response to a desired level (i.e., immunomodulation), or the energetic demands of migration could reduce the efficacy of some immune pathways (i.e., immunosuppression).

To date, the effects of long-distance migration on immune defenses have been best studied in birds. In a rare study of immune changes in wild individuals during migration, field observations of three species of thrushes showed that migrating birds had lower baseline measures for several components of innate immunity (including leukocyte and lymphocyte counts), and exhibited lower fat reserves and higher energetic stress, relative to individuals measured outside of the migratory season (Owen and Moore, 2006). Captive experiments with Swainson's thrushes (*Catharus ustulatus*; Figure A1-2) later demonstrated that cell-mediated immunity was suppressed with the onset of migratory restlessness (the agitated behavior of birds that would normally precede their migratory departure) (Owen and Moore, 2008a), suggesting that predictable changes in immunity occur in preparation for long-distance flight. In this species, the energetic costs of migration can intensify seasonal immune changes: Migrating thrushes that arrived at stopover sites in poorest condition had the lowest counts of immune cells (Owen and Moore, 2008b).

The extent of altered immunity before and during migration is likely to be both species and resource dependent and will further depend on the specific immune pathway measured. Red knots, for example, exhibited no change in either antibody production or cell-mediated immunity after long flights in a wind tunnel, a result that argues against migration-mediated immunosuppression (Hasselquist

BOX A1-1
Lessons from a Model System: Monarch Migration Drives Large-Scale Variation in Parasite Prevalence



During the past 10 years, we studied monarch butterflies (*Danaus plexippus*) and a protozoan parasite (*Ophryocystis elektroscirrha*) (top-right images) for the effects of seasonal migration on host–pathogen dynamics. Monarchs in eastern North America (A) migrate up to 2,500 km each fall from as far north as Canada to wintering sites in Central Mexico (Brower and Malcolm, 1991). Monarchs in western North America (B) migrate shorter distances to winter along the coast of California (Nagano et al., 1993). Monarchs also form nonmigratory populations

et al., 2007). Another study of captive red knots revealed no declines in costly immune defenses during the annual periods of mass gain (Buehler et al., 2008); however, animals in this study had constant access to high-quality food, which might have negated energetic trade-offs between immune investment and weight gain. Interestingly, barn swallows (*Hirundo rustica*) in better physical condition showed greater measures of cellular immunity during migration, cleared ectoparasites and blood parasites more effectively, and arrived earlier at breeding grounds than birds with poor energy reserves (Møller et al., 2004). These studies suggest that animals in robust condition or with access to resources might tolerate long journeys without significant immunocompromise. Studies of migratory species to date also emphasize the need for a more detailed understanding of the

that breed year-round in southern Florida (C), Hawai'i, the Caribbean Islands, and Central and South America (Ackery and Vane-Wright, 1984). Because monarchs are abundant and widespread and can be studied easily both in the wild and in captivity, field and experimental studies can explore effects of annual migrations on host–pathogen ecology and evolution. A recent continent-scale analysis showed that parasite prevalence increased throughout the monarchs' breeding season, with highest prevalence among adults associated with more intense habitat use and longer residency in eastern North America, consistent with the idea of migratory escape (bottom-right graph) (Bartel et al., 2010). Experiments showed that monarchs infected with *O. elektroscirrha* flew shorter distances and with reduced flight speeds, and field studies showed parasite prevalence decreased as monarchs moved southward during their fall migrations (Bartel et al., 2010; Folstad et al., 1991), consistent with the idea of migratory culling. Parasite prevalence was also highest among butterflies sampled at the end of the breeding season than for those that reached their overwintering sites in Mexico (bottom right graph). Collectively, these processes have likely generated the striking differences in parasite prevalence reported among wild monarch populations with different migratory behaviors (bottom-left graph) (Altizer et al., 2000). Laboratory studies also showed that parasite isolates from the longest-distance migratory population in eastern North America (A) were less virulent than isolates from short-distance (B) and nonmigratory (C) populations (de Roode and Altizer, 2010; Altizer, 2001), suggesting that longer migration distances cull monarchs carrying virulent parasite genotypes. Work on this model system illustrates how multiple mechanisms can operate at different points along a migratory cycle and highlights the role that migration plays in keeping populations healthy. Monarch migrations are now considered an endangered phenomenon (Brower and Malcolm, 1991) due to deforestation of overwintering grounds, loss of critical breeding habitats, and climate-related shifts in migration phenology. If climate warming extends monarch breeding seasons into fall and winter months, migrations may eventually cease altogether. Evidence to date indicates that the loss of migration in response to mild winters and year-round resources could prolong exposure to parasites, elevate infection prevalence, and favor more virulent parasite genotypes. Images reproduced from (Bartel et al., 2010; Altizer et al., 2000). [Photos by S. Altizer]

mechanisms linking nutrient intake and metabolic activity to innate and adaptive immune measures, a step that is essential to predicting how different immune pathways will respond to physiological changes that occur before and during long-distance migrations.

Perhaps most importantly, immune changes that accompany long-distance migration could lead to a relapse of prior infections and more severe disease following exposure to new pathogens, increasing the likelihood of migratory culling and lowering the probability of spatial spread. This possibility was investigated for Lyme disease in redwings (*Turdus iliacus*) (Gylfe et al., 2000). Consistent with results showing negative effects of migratory status on immunity, migratory restlessness alone was sufficient to reactivate latent Borrelia infections in captive

birds. Thus, the demands of migration could ultimately lead to more severe infections and greater removal of infected hosts. Together, these results point to a role for migration-mediated immune changes in the dynamics of other wildlife pathogens, including zoonotic agents such as WNV (Owen et al., 2006) and bat-transmitted corona and rabies viruses (Li et al., 2005; Messenger et al., 2002).

Effects of Anthropogenic Change and Climate

Changes to the ecology of migratory species in the past century (Figure A1-2) could have enormous impacts on pathogen spread in wildlife and livestock, as well as altering human exposure to zoonotic infections. As one example, habitat loss caused by urbanization or agricultural expansion can eliminate stopover sites and result in higher densities of animals that use fewer remaining sites along the migration route (Wilcove, 2008). Although the resulting impacts on infectious diseases remain speculative, dense aggregations of animals at dwindling stopover sites might create ecological hot spots for pathogen transmission among wildlife species, as illustrated in the case of AIV in migrating shorebirds at Delaware Bay (Krauss et al., 2007). Moreover, continuing human encroachment on stopover habitats increases the likelihood of contact and spillover infection from wildlife reservoir hosts to humans and domesticated species.

For some animal species, physical barriers such as fences (terrestrial species) or hydroelectric dams (aquatic species) impede migration (Berger et al., 2008), leaving animals to choose between navigating a narrow migratory corridor or forming nonmigratory populations. Consequently, pathogen prevalence could increase when animals stop migrating and become confined to smaller habitats, if parasite infectious stages build up with more intense use of a given habitat. Attempts to control cattle exposure to brucellosis from bison (*Bison bison*) and elk (*Cervus elaphus*) in the Greater Yellowstone Ecosystem illustrate these risks. Due to the potential threat of *Brucella* transmission from bison to cattle, bison are routinely culled if they leave the confines of Yellowstone National Park (Bienen and Tabor, 2006). Elk migration is less restricted, but there is evidence that supplemental feeding areas encourage the formation of dense nonmigratory populations that support higher prevalence of brucellosis, with 10 to 30% seroprevalence in animals at the feeding grounds compared with 2 to 3% seroprevalence in unfed elk ranging the park (Cross et al., 2010). High population densities in elk also correlate with higher gastrointestinal parasite loads at feeding grounds (Hines et al., 2007), suggesting that high densities of nonmigrating hosts lead to increasing intraspecific transmission of multiple parasites.

More generally, human activities that discourage long-distance animal movements and encourage the formation of local year-round populations can cause the emergence of zoonotic pathogens in humans. For example, human-meditated environmental changes facilitated outbreaks of two zoonotic paramyxoviruses

carried by flying foxes (*Pteropus* fruit bats; Figure A1-2): These animals are highly mobile and seasonally nomadic in response to local food availability (Daszak et al., 2006). Anthropogenic changes such as deforestation and agricultural production likely influenced the emergence of lethal Nipah and Hendra virus outbreaks in humans in Australia and Malaysia in two key ways: by resource supplementation and habitat alteration limiting migratory behaviors of fruit bats and by facilitating close contact with domesticated virus-amplifying hosts (pigs and horses). In Malaysia, resident flying foxes foraging on fruit trees on or near pig farms transmitted Nipah virus to pigs, probably via urine or partially consumed fruit with subsequent spread from pigs to humans [(Daszak et al., 2006) and references therein]. Human activities are also thought to increase the risk of Hendra virus outbreaks in Australia by driving flying foxes from formerly forested areas into urban and suburban areas (Plowright et al., 2008), where they form dense nonmigratory colonies that aggregate in public gardens containing abundant food sources.

In marine systems, aquaculture increases exposure to parasites in wild fish species, particularly in salmonids. Migration normally protects wild juvenile salmon from marine parasites in coastal waters by spatially separating them from infected wild adults offshore (Krkošek et al., 2007), but densely populated salmon farms place farmed fish enclosures adjacent to wild salmon migratory corridors, increasing the transmission of parasitic sea lice (*Lepeophtheirus salmonis*) to wild juveniles returning to sea (Krkošek et al., 2007).

Finally, climate change will alter infectious disease dynamics in some migratory species (Harvell et al., 2009). To survive, many migratory species must respond to climate changes by shifting migratory routes and phenology in response to temperature and the availability of key resources (i.e., flowering plants, insects) [e.g., (Saino et al., 2010)]. It is possible that changes in the timing of migration could disrupt the synchronicity of host and parasite life cycles, much in the way that ecological mismatch in migration timing or altered migratory routes could impact whether suitable food and habitat are available when migrants arrive. For example, the spawning periodicity of whale barnacles in calving lagoons of gray whales is a classic example of a parasite synchronizing its reproduction to overlap with a host's migratory cycle (Rice and Wolman, 1971). If the timing of whale migrations and barnacle reproduction shift in response to different environmental cues, this could result in reduced infections over time. On the other hand, altered migration routes might facilitate contact between otherwise geographically separated host species, leading to novel pathogen introductions and increasing disease risks for some wildlife species (Harvell et al., 2009). One example of this phenomenon involves outbreaks of phocine distemper virus in harbor seals (*Phoca vitulina*) in the North Sea, which was likely introduced by harp seals (*Pagophilus groenlandicus*) migrating beyond their normal range and contacting harbor seal populations (Jensen et al., 2002). Moreover, if climate

warming extends hosts' breeding seasons, migrations may cease altogether, with year-round resident populations replacing migratory ones (Box A1-1), leading to greater pathogen prevalence through a loss of migratory culling and escape.

Outlook and Future Challenges

Understanding the mechanisms by which long-distance movements affect host–pathogen systems offers exciting challenges for future work, especially in the context of global change and evolutionary dynamics. In terms of basic research, there remains a great need to identify conditions under which migration will increase host exposure to infectious agents versus cases where migration can reduce transmission, with the ultimate goal of predicting the net outcomes for host species where multiple mechanisms operate on the same or different pathogens (e.g., Box A1-1). To that end, mechanistic models are needed to examine how migration affects infectious disease dynamics and to explore the relevance of possible mechanisms. Such models must combine within-season processes (including host reproduction, overwintering survival, and pathogen transmission) with between-season migration (Figure A1-4). For example, to examine the importance of environmental transmission for the dynamics of LPAI in North American birds, Breban et al. (Breben et al., 2009) modeled a waterfowl population migrating between two geographically distant sites, with transmission dynamics occurring at both breeding and wintering grounds. Similarly, models describing interconnected networks of metapopulations could be useful in investigating disease dynamics between habitats linked through seasonal migrations (Keeling et al., 2010). Although currently uncommon in the literature, epidemiological models can also be extended to capture mechanisms such as migratory culling and migratory escape and to include multiple infectious agents to explore questions of coinfection and multihost transmission dynamics (Figure A1-4).

One outstanding question is whether parasites can increase the migratory propensity of their hosts by favoring the evolution of migratory behaviors. Long-distance migration has previously been hypothesized to reduce predation risks for ungulates and birds, with the general rationale being that the survival costs of migration should be outweighed by fitness benefits associated with reproduction. In support of this idea, field studies of wolf predation on North American elk at their summer breeding grounds (Hebblewhite and Merrill, 2007) and nest predation on migrating songbirds (McKinnon et al., 2010) showed that animals traveling farthest experienced the lowest predation risk. Similar observational studies could ask how the prevalence, intensity, virulence, and diversity of key parasites change with migratory distances traveled. To that end, comparing infection dynamics between migratory and nonmigratory populations of the same species offers a powerful test of both pattern and process (e.g., Box A1-1), although researchers will need to keep in mind that climate differences (e.g., milder climates for habitats used by nonmigratory populations) could confound some comparisons.

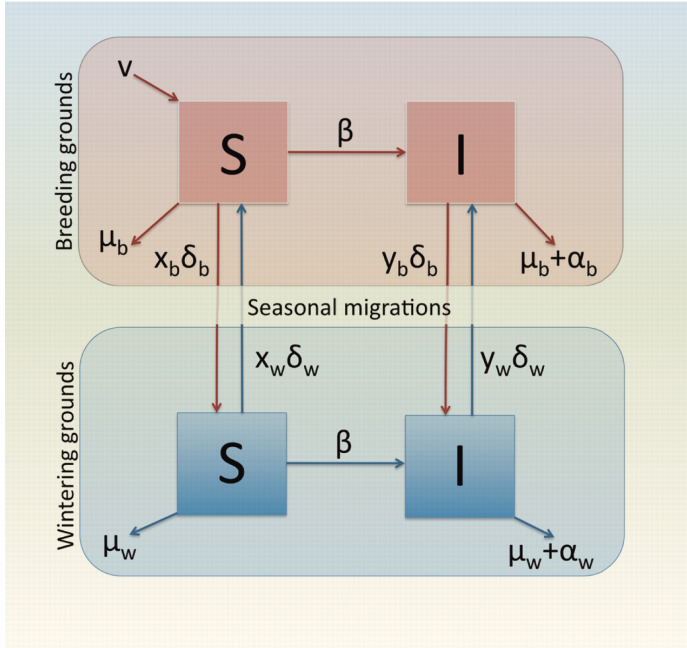


FIGURE A1-4 A compartmental model illustrating infectious disease dynamics (S-I model) in a migratory host population moving between geographically distinct breeding and overwintering habitats. Susceptible hosts (S) in the breeding grounds are born (v), die (μ_b) because of background mortality, and become infected at a rate, β. Infected hosts (I) suffer disease-induced mortality (α_b). Different fractions of susceptible (x_b) and infected hosts (y_b) survive migration from the breeding habitat and arrive successfully at an overwintering habitat at some rate (δ_b). Here, natural (μ_w) and disease-induced mortality (α_w) are both influenced by a different set of environmental conditions that characterize wintering grounds. The fraction of hosts surviving the spring migration the following year ($x_w\delta_w$, $y_w\delta_w$) will return to the breeding grounds to reproduce. A simple model like this can be readily modified to accommodate different parasite species and their transmission modes, host recovery, host age structure, and cross-species transmission.

Modeling approaches are also needed to explore how seasonal migration might respond evolutionarily to parasite-driven pressures, similar to other studies that examined effects of within-site competition, costs of dispersal, and variation in habitat quality on random dispersal strategies (McPeek and Holt, 1992).

Another question related to host evolution is whether the combined demands of migration and disease risk could select for greater or lower investment in resistance or immunity. Field and laboratory studies have already documented between-season changes in immune investment, suggesting that some migratory species suppress specific immune responses before or during migration (Owen

and Moore, 2006). The reduction in investment in immune defense could be an adaptive response to lower risks from certain parasites in migratory species (beyond issues related to energetic trade-offs) and might affect adaptive immunity (shown to be costly for many vertebrate species) more strongly than innate defenses. Over longer time scales, long-distance migration could select for greater levels of innate immunity in migratory species or populations, especially if migrating animals encounter more diverse parasite assemblages (Møller and Erritzøe, 1998). With this in mind, comparisons of adaptive and innate immune defense and resistance to specific pathogens between migratory and nonmigratory populations represent a challenge for future work that could be especially tractable with invertebrate systems (Altizer, 2001).

Pathogens might also respond to migration-mediated selection, with ecological pressures arising from migration leading to divergence in virulence. There is some evidence to show that less-virulent strains circulate in migratory populations than in resident populations. The negative correlation between virulence and host migration distance, illustrated in the monarch system (Box A1-1), highlights the troubling possibility that pathogens infecting other migratory species could become more virulent if migrations decline. Moreover, dwindling migrations might affect host life history by altering pathogen virulence in once-migratory hosts. For example, a theoretical study showed that even moderate increases in virulence can change host breeding phenology to stimulate hosts to develop more quickly and breed earlier before they have a chance to become heavily infected (Restif et al., 2004). The recent facial tumor disease devastating Tasmanian devil populations provides a striking empirical example of high disease-induced mortality shifting host reproductive strategy from an iteroparous to a semelparous pattern through precocious sexual maturity in young devils (Jones et al., 2008). Although the hosts in this example are nonmigratory, they illustrate how virulent pathogens can generate longer-term fecundity costs beyond their direct impacts on host survival.

Studying the migratory process in any wildlife species poses exceptional logistical challenges, in part because distances separating multiple habitats can sometimes span thousands of kilometers, making sampling for infection or immunity intractable for field researchers. One problem is that historically, large numbers of animals have been sampled and marked at migratory staging areas, but for many species their subsequent whereabouts remain unknown (Webster et al., 2002). Tracking animals over long time periods and across vast distances has become more feasible with technological innovations such as radar and satellite telemetry for larger animals and ultra-light geolocators, stable isotopes, and radio tags to record or infer the movements of smaller animals (Robinson et al., 2010). Furthermore, physiological measurements such as heart rate, wing beat frequency, and blood metabolites can be obtained remotely for some species, enabling scientists to examine how infection status influences movement rates and the energetic costs of migration (Robinson et al., 2010).

Interdisciplinary studies to connect the fields of migration biology and infectious disease ecology are still in the early stages, and there are many exciting research opportunities to examine how infection dynamics relate to animal physiology, evolution, behavior, and environmental variation across the annual migratory cycle. Most evidence comes from studies of avian-pathogen systems, especially viruses. Although this is not surprising given the relevance of pathogens such as avian influenza and WNV to human health, there remains a great need to explore other systems. Good places to start would be to make connections between disease and migration for species such as sea turtles, wildebeest, bats, dragonflies, and whales (Figure A1-2). Parasite infections and movement ecology in species in each of these groups have been well studied separately but not yet bridged. Taking a broad view of diverse host life histories and parasite transmission modes will allow future studies to identify ecological generalities and system-specific complexities that govern the mechanistic relationships between host movement behavior and infectious disease dynamics.

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A2

CLIMATE CHANGE AND INFECTIOUS DISEASES: FROM EVIDENCE TO A PREDICTIVE FRAMEWORK[3]

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Abstract

Scientists have long predicted large-scale responses of infectious diseases to climate change, giving rise to a polarizing debate, especially concerning human pathogens for which socioeconomic drivers and control measures can limit the detection of climate-mediated changes. Climate change has already increased the occurrence of diseases in some natural and agricultural systems, but in many cases, outcomes depend on the form of climate change and details of the host–pathogen system. In this review, we highlight research progress and gaps that have emerged during the past decade and develop a predictive framework that integrates knowledge from ecophysiology and community ecology with modeling approaches. Future work must continue to anticipate and monitor pathogen biodiversity and disease trends in natural ecosystems and identify opportunities to mitigate the impacts of climate-driven disease emergence.

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The life cycles and transmission of many infectious agents—including those causing disease in humans, agricultural systems, and free-living animals and plants—are inextricably tied to climate (Garrett et al., 2013; Harvell et al., 2002). Over the past decade, climate warming has already caused profound and often complex changes in the prevalence or severity of some infectious diseases (Figure A2-1) (Baker-Austin et al., 2013; Burge et al., 2014; Garrett et al., 2013;

FIGURE A2-1 Animal–parasite interactions for which field or experimental studies have linked climate change to altered disease risk. (A) Black-legged ticks, *Ixodes scapularis*, vectors of Lyme disease, attached to the ears of a white-footed mouse, *Peromyscus leucopus*, show greater synchrony in larval and nymphal feeding in response to milder climates, leading to more rapid Lyme transmission. (B) Caribbean coral (*Diploria labyrinthiformis*) was affected by loss of symbionts, white plague disease, and ciliate infection during the 2010 warm thermal anomaly in Curaçao. (C) Malformed leopard frog (*Lithobates pipiens*) as a result of infection by the cercarial stage (inset) of the multihost trematode *R. ondatrae*; warming causes nonlinear changes in both host and parasite that lead to marked shifts in the timing of interactions. (D) Infection of monarchs (*D. plexippus*) by the protozoan *O. elektroscirrha* (inset) increases in parts of the United States where monarchs breed year-round as a result of the establishment of exotic milkweed species and milder winter climates. (E) Infection risk with *O. gruehneri* (inset shows eggs and larvae) the common abomasal nematode of caribou and reindeer (*R. tarandus*), may be reduced during the hottest part of the Arctic summer as a result of warming, which leads to two annual transmission peaks rather than one (e.g., Figure A2-3C). Photo credits (A to E): J. Brunner, E. Weil, D. Herasimtschuk, S. Altizer, P. Davis, S. Kutz.

Harvell et al., 2009). For human diseases, vector-control, antimicrobial treatments, and infrastructural changes can dampen or mask climate effects. Wildlife and plant diseases are generally less influenced by these control measures, making the climate signal easier to detect (Harvell et al., 2009). For example, although the effects of climate warming on the dynamics of human malaria are debated, climate warming is consistently shown to increase the intensity and/or latitudinal and altitudinal range of avian malaria in wild birds (Garamszegi, 2011; Zamora-Vilchis et al., 2012).

Predicting the consequences of climate change for infectious disease severity and distributions remains a persistent challenge surrounded by much controversy, particularly for vector-borne infections of humans [boxes S1 and S2 (available as supplementary materials on *Science* Online)]. Work using climate-based envelope models has predicted that modest climate-induced range expansions of human malaria in some areas will be offset by range contractions in other locations (Rogers and Randolph, 2000). An alternative approach, based on mechanistic models of physiological and demographic processes of vectors and pathogens (Ruiz-Moreno et al., 2012), predicts large geographic range expansions of human malaria into higher latitudes (Martens et al., 1995). Both approaches have their limitations (Garrett et al., 2013), and the challenge remains to accurately capture the contributions of multiple, interacting, and often nonlinear underlying responses of host, pathogen, and vector to climate. This challenge is further exacerbated by variation in the climate responses among host–pathogen systems arising from different life history characteristics and thermal niches (Molnár et al., 2013).

A decade ago, Harvell et al. (2002) reviewed the potential for infectious diseases to increase with climate warming. Since then, the frequency of studies examining climate–disease interactions has continued to increase (Figure A2-2), producing clear evidence that changes in mean temperature or climate variability can alter disease risk. Some of the best examples of climate responses of infectious diseases to date are from ectothermic hosts and from parasites with environmental transmission stages that can persist outside the host (Figure A2-1). Indeed, first principles suggest that the rates of replication, development, and transmission of these pathogens should depend more strongly on temperature relative to other host–pathogen interactions. The next challenges require integrating theoretical, observational, and experimental approaches to better predict the direction and magnitude of changes in disease risk. Identifying the contribution of other environmental variables, such as precipitation, humidity, and climate variability remains a challenge (Paijmans et al., 2009; Raffel et al., 2013).

Here, we review the individual, community, and landscape-level mechanisms behind climate-induced changes in infectious disease risk and illustrate how a quantitative, ecophysiological framework can predict the response of different host–pathogen relations to climate warming. We mainly focus on changes in temperature, which have been more thoroughly explored both empirically and

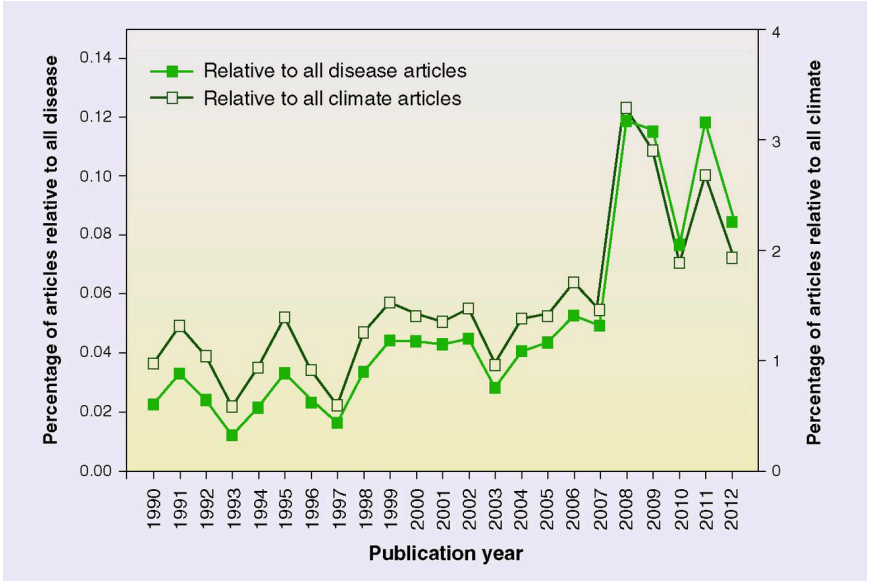

FIGURE A2-2 Rising interest in climate–disease interactions. Research focused on associations between infectious disease and climate change has increased steadily over the past 20 years. After correcting for total research interest in climate change (open symbols) or infectious disease (closed symbols), the frequency of papers referencing a climate–disease link in the title has nearly doubled over this period, based on long-term publication trends following a Web of Science search of article titles (1990 to 2012). Search criteria and statistical analyses are provided in the supplementary materials, and the total number of climate change–infectious disease papers identified by our search criteria ranged from 5 to 117 publications per year.

theoretically, relative to other environmental variables. We consider impacts of climate change on human diseases and on pathogens affecting species of conservation or economic concern, including agroecosystems [box S3 (available as supplementary materials on *Science* Online)]. A crucial need remains for long-term ecological studies that examine the consequences of climate-disease interactions for entire communities and ecosystems, as well as for efforts that couple effective disease forecasting models with mitigation and solutions.

Ecophysiology of Host–Pathogen Interactions

More than a century of research has firmly established that temperature and other climatic variables strongly affect the physiology and demography of free-living and parasitic species [e.g., (Walther et al., 2002)], with effects on behavior, development, fecundity, and mortality (Parmesan and Yohe, 2003). Because these

effects can be nonlinear and sometimes conflicting, such as warmer temperatures accelerating invertebrate development but reducing life span, a central challenge has been to identify the net outcomes for fitness (Harvell et al., 2002). For infectious diseases, this challenge is compounded by the interactions between at least two species—a host and a pathogen—and often vectors or intermediate hosts, which make the cumulative influence of climate on disease outcomes elusive [e.g., (Lafferty, 2009; Rohr et al., 2011)].

Immune defenses are physiological processes crucial for predicting changes in disease dynamics. Warmer temperatures can increase immune enzyme activity and bacterial resistance for insects, such as the cricket *Gryllus texensis* (Adamo and Lovett, 2011). Positive effects of temperature on parasite growth and replication, however, might outweigh greater immune function of the host. In gorgonian corals, for example, warmer temperatures increase cellular and humoral defenses (Mydlarz et al., 2006), but because coral pathogens also replicate faster under these conditions, disease outbreaks have coincided with warmer sea temperatures in the Caribbean (Figure A2-1) (Burge et al., 2014; Harvell et al., 2009). Warm temperatures also can lower host immunity; for example, melanization and phagocytic cell activity in mosquitoes are depressed at higher temperatures (Murdock et al., 2012). In addition, increased climate variability can interfere with host immunity, as illustrated by decreased frog resistance to the chytrid fungus *Batrachochytrium dendrobatidis* (*Bd*) in response to temperature fluctuations (Raffel et al., 2013). Even though *Bd* grows best in culture at cooler temperatures, which suggests that warming should reduce disease, incorporating variability-induced changes in host resistance suggests a more complex relation between climate change and *Bd*-induced amphibian declines (Rohr and Raffel, 2010). These issues are important for predicting the immunological efficiency of ectotherms outside of their typical climate envelope.

One promising approach for predicting how host–pathogen interactions respond to climate warming involves infusing epidemiological models with relations derived from the metabolic theory of ecology (MTE). This approach circumvents the need for detailed species-specific development and survival parameters by using established relations between metabolism, ambient temperature, and body size to predict responses to climate warming (Brown et al., 2004). One breakthrough study (Molnár et al., 2013) used MTE coupled with traditional host–parasite transmission models to examine how changes in seasonal and annual temperature affected the basic reproduction number (R_0) of strongylid nematodes with direct life cycles and transmission stages that are shed into the environment. By casting R_0 in terms of temperature-induced trade-offs between parasite development and mortality, this approach facilitated both general predictions about how infection patterns change with warming and, when parameterized for *Ostertagia gruehneri*, a nematode of caribou and reindeer (Figure A2-1), specific projections that corresponded with the observed temperature dependence of parasite stages. Moreover, this model predicted a shift from one to two peaks

in nematode transmission each year under warming conditions (Figure A2-3C), a result consistent with field observations (Hoar et al., 2012; Molnár et al., 2013).

In some cases, ecophysiological approaches must consider multiple host species and parasite developmental stages that could show differential sensitivity to warming. Such differential responses can complicate prediction of net effects, especially for ectothermic hosts with more pronounced responses to temperature. For instance, because both infectivity of a trematode parasite (*Ribeiroia ondatrae*) and defenses of an amphibian host (*Pseudacris regilla*) increase with

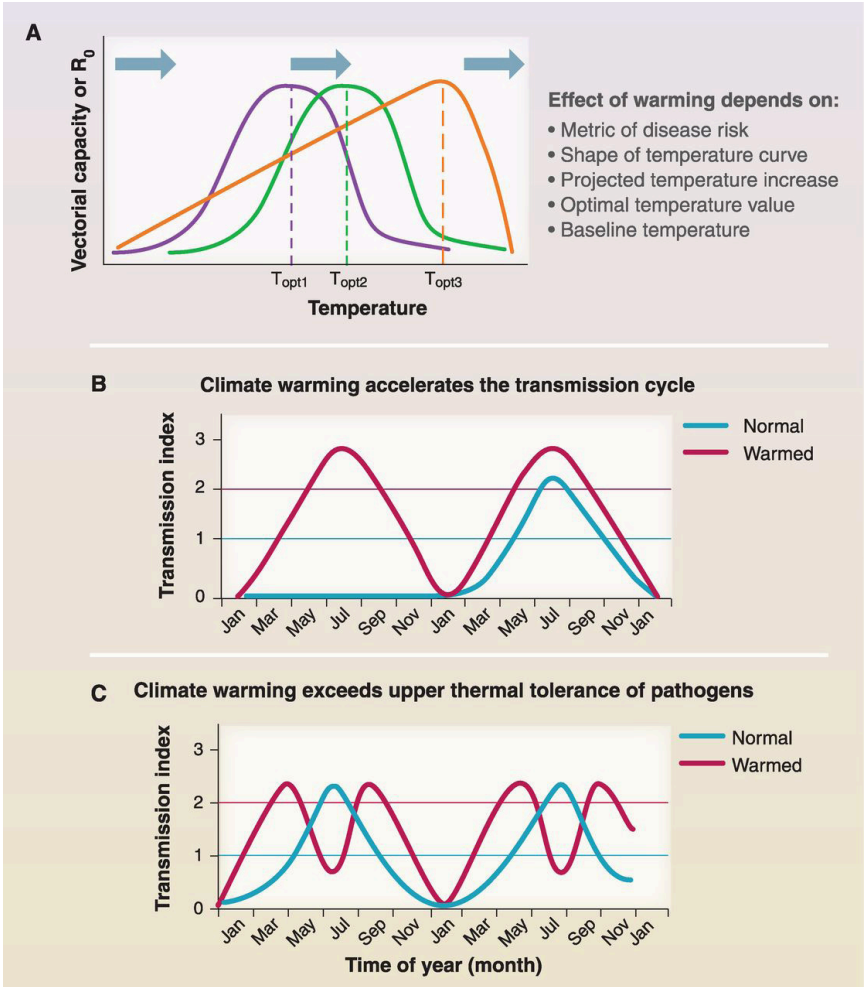

FIGURE A2-3 Theoretical underpinnings and categorization of disease responses to climate change.

temperature; maximal pathology (limb malformations) (Figure A2-1) occurs at intermediate temperatures (Paull et al., 2012). Other work showed that the virulence of both a coral fungus (*Aspergillus sydowii*) and protozoan (*Aplanochytrium* sp.) increased with temperature, probably because pathogen development rate continued to increase in a temperature range where coral defenses were less potent (Burge et al., 2013). Thus, the ideal approach will be an iterative one that combines metabolic and epidemiological modeling to predict general responses and to identify knowledge gaps, followed by application of models to specific host–pathogen interactions.

Pathogen responses to climate change depend on thermal tolerance relative to current and projected conditions across an annual cycle. (A) Gaussian curves relating temperature to a metric of disease risk suggest symmetrical temperature zones over which warming will increase and decrease transmission, whereas left-skewing [a common response for many terrestrial ectotherms, including arthropod vectors (Deutsch et al., 2008)] indicates greater potential for pathogen transmission to increase with warming [box S2 (available as supplementary materials on *Science* Online)]. Bold arrows represent geographic gradients that span cool, warm, and hot mean temperatures, which indicate that the net effect of warming (at point of arrows) depends on whether temperatures grow to exceed the optimum temperature (T_{opt}) for disease transmission. Projected changes in disease will further depend on the starting temperature relative to T_{opt}, the magnitude of warming, measurement error, adaptation, and acclimation. (B) Pathogens at their northern or altitudinal limits might show range expansion and nonlinear shifts in their life cycle in response to warmer temperatures (red) relative to baseline (blue). For example, a shift from 2- to 1-year cycles of transmission has occurred for the muskox lungworm (Kutz et al., 2009). This outcome could generate sporadic disease emergence in a naïve population (if extremes in temperature allow only occasional invasion and/or establishment), or could gradually increase prevalence and establishment. (C) At the low-latitude or low-altitude extent of a pathogen's range, where temperature increases could exceed the pathogen's thermal optimum, transmission might be reduced, or we might see the emergence of a bimodal pattern whereby R_0 peaks both early and late in the season, but decreases during the midsummer [as in the case of the arctic *O. gruehneri*–reindeer example (Molnár et al., 2013)]. In (B) and (C), the lower blue line represents $R_0 = 1$, above which the pathogen can increase; values above the pink line represent severe disease problems owing to a higher peak of R_0 and a greater duration of time during which $R_0 > 1$.

Community Ecology, Biodiversity, and Climate Change

Host–pathogen interactions are embedded in diverse communities, with climate change likely leading to the loss of some host–pathogen interactions and the gain of novel species pairings. In some cases, pathogen extinction and the loss of

endemic parasites could follow from climate change, potentially reducing disease or conversely releasing more pathogenic organisms from competition. In other cases, multiple pathogens can put entire host communities at risk of extinction. Although ecosystems of low biodiversity, such as occur in polar regions, can be particularly sensitive to emerging parasitic diseases (Kutz et al., 2009), most knowledge of community-wide responses stems from tropical marine systems. For example, the wider Caribbean region is a "disease hot spot" characterized by the rapid, warming-induced emergence of multiple new pathogens that have caused precipitous coral declines with ecosystem-wide repercussions (Rogers and Muller, 2012; Ruiz-Moreno et al., 2012). Impacts of climate-induced changes in disease can be especially large when the host is a dominant or keystone species. For example, near extinction of the once-dominant, herbivorous abalone (genus *Haliotis*) by warming-driven rickettsial disease caused pervasive community shifts across multiple trophic levels (Burge et al., 2014). Similarly, seagrass (*Zostera marina*) declines caused by infection with the protist *Labyrinthula zosterae*, which correlates positively with warming, have degraded nursery habitats for fish and migratory waterfowl and caused the extinction of the eelgrass limpet (Hughes et al., 2002).

Microbial communities, which are often part of the extended phenotype of host defenses, are also likely to respond to climate changes. For instance, warming sea-surface temperatures in coral reefs can inhibit the growth of antibiotic-producing bacteria, sometimes causing microbial communities to shift from mutualistic to pathogenic (Ritchie, 2006). In agroecosystems, higher temperatures can suppress entomopathogenic fungi and antibiotic production by bacterial mutualists in plants (Humair et al., 2009). Warming also underlies bacterial shifts from endosymbiotic to lytic within host amoebas that live in human nasal passages, increasing the potential risk of respiratory disease (Corsaro and Greub, 2006). Thus, effects of warmer temperatures on the diversity and function of commensal or mutualist microbes could promote pathogen growth and pest outbreaks.

From a broader perspective, biodiversity loss is a well-established consequence of climate change (Jetz et al., 2007; Parmesan and Yohe, 2003) and can have its own impact on infectious diseases. For many diseases of humans, wildlife, and plants, biodiversity loss at local or regional scales can increase rates of pathogen transmission (Cardinale et al., 2012; Johnson and Hoverman, 2012; Keesing et al., 2010). This pattern can result from several mechanisms, including the loss of the dilution effect (Johnson and Hoverman, 2012). For example, lower parasite diversity could allow more pathogenic species to proliferate when endemic and competing parasites are lost from a system (Johnson and Hoverman, 2012). Climate warming can also weaken biotic regulation of disease vectors by inhibiting their predators (Hobbelen et al., 2013) and competitors (Farjana et al., 2012). Interactions between biodiversity and infectious disease underscore the need to put climate–disease interactions into the broader context of other forms

of global change, such as land-use change and habitat loss, when extending predictions from focused host–pathogen interactions to larger spatial and taxonomic scales.

Shifts in Behavior, Movement, and Phenology of Hosts and Parasites

Changes in climate are already affecting the phenology of interactions between plants and pollinators, predators and prey, and plants and herbivores (Parmesan and Yohe, 2003). Climate-induced shifts in phenology and species movements (Chen et al., 2011) will likely affect disease dynamics. Many species are already moving toward higher elevations or latitudes (Hickling et al., 2006), and an open question is whether these shifts could disrupt established interactions or bring novel groups of hosts and pathogens into contact (Morgan et al., 2004). For instance, the range expansion of the Asian tiger mosquito (*Aedes albopictus*) across Europe and the Americas has created the potential for novel viral diseases such as Chikungunya to invade (Ruiz-Moreno et al., 2012); this pathogen is already expanding in geographic range, and a recent outbreak in Europe emphasizes the need for surveillance and preparedness. Along eastern North America, warming sea temperatures and changes in host resistance facilitated a northward shift of two oyster diseases into previously unexposed populations (Burge et al., 2014).

Migratory species in particular can be sensitive to climate change (Hickling et al., 2006), with the routes and timing of some species' migrations already shifting with climate warming (Parmesan and Yohe, 2003). Long-distance migrations can lower parasite transmission by allowing hosts to escape pathogens that accumulate in the environment or by strenuous journeys that cull sick animals (Altizer et al., 2011). In some cases, milder winters can allow previously migratory host populations to persist year-round in temperate regions (Bradshaw and Holzapfel, 2007); this residency fosters the build-up of environmental transmission stages, and mild winters further enhance parasite over-winter survival (Garrett et al., 2013). A case study of monarch butterflies (*Danaus plexippus*) and the protozoan parasite *Ophyrocystis elektroscirrha* (Figure A2-1) provides support for climate-warming shifts in migration and disease. Monarchs typically leave their northern breeding grounds in early fall and fly to Mexican wintering sites. Milder winters, combined with increased planting of exotic host plants, now allow monarch populations to breed year-round in parts of the United States (Howard et al., 2010). Relative to migratory monarchs, winter-breeding monarchs suffer from higher rates of infection (Altizer et al., 2011). Similarly, migration is considered an important parasite avoidance strategy for barren-ground caribou (Hoar et al., 2012), but the loss of sea ice with climate warming will likely inhibit migrations and prevent them from seasonally escaping parasites (Post et al., 2013). Thus, diminishing migration behaviors among animals that use seasonal habitats can increase the transmission of infectious diseases.

Changes in the timing of vector life stages and feeding behavior can also arise from interactions between climate and photoperiod. For several tick-borne infections (Figure A2-1), pathogens are sequentially transmitted from infected vertebrate hosts to naïve larval tick vectors, and from infected nymphal ticks to naïve vertebrate hosts. Asynchrony in the seasonal activity of larval and nymphal ticks can delay transmission and select for less virulent strains of the Lyme bacterium *Borrelia burgdorferi* (Kurtenbach et al., 2006), whereas synchrony allows for more rapid transmission and the persistence of virulent strains. In the case of tick-borne encephalitis (TBE), viral transmission occurs directly between cofeeding ticks; thus, viral maintenance requires synchronous larval and nymphal feeding (Randolph et al., 1999). Because synchrony of larval and nymphal ticks characterizes milder winter climates, climate change could increase tick synchrony and the transmission and virulence of several tick-borne infections.

Changes in the timing of shedding or development of environmental transmission stages could result from climate warming. Some parasites could experience earlier hatching, exposure to hosts earlier in the season, and encounters with earlier (and often more sensitive) life stages of hosts. For example, a long-term data set of lake plankton showed that warming shifted fungal prevalence patterns in diatom hosts from acute epidemics to chronic persistence, in part because of faster transmission and more widespread host population suppression under warmer temperatures (Ibelings et al., 2011). In contrast, Brown and Rohani (Brown and Rohani, 2012) argued for the opposite outcome with respect to avian influenza (AI) in reservoir bird hosts. Climate-driven mismatch in the timing of bird migration and their prey resources (e.g., horseshoe crab eggs) amplified variability in epidemiological outcomes: Although mismatch increased the likelihood of AI extinction, infection prevalence and spillover potential both increased in cases where the virus persisted.

Plasticity in parasite traits could allow parasites with environmental transmission stages to respond more rapidly to climate warming. For example, arrested development (hypobiosis) of the nematode *O. gruehneri* within its caribou host is a plastic trait more commonly expressed in areas with harsher winters as compared with milder climates (Hoar et al., 2012). This arrested state prevents wasted reproductive effort for the parasites, because eggs produced in late summer in colder regions are unlikely to develop to infective-stage larvae by fall. Ultimately, plasticity in life history traits could speed parasite responses to changing environments and allow parasites to deal with climate instabilities (e.g., a series of severe winters interspersed by mild), relative to the case where selection must act on genetically variable traits (Moritz and Agudo, 2013). For example, if climate warming extends the transmission season for *O. gruehneri* on tundra, a rapid decrease in the frequency of nematode hypobiosis could shorten the life cycle and increase infection rates.

Consequences for Conservation and Human Health

Climate change is already contributing to species extinctions, both directly and through interactions with infectious disease (Thomas et al., 2004). Roughly one-third of all coral species and the sustainability of coral reef ecosystems are threatened by human activities, including climate warming and infectious diseases (Burge et al., 2014). In contrast to tropical marine systems, the Arctic is a less diverse and minimally redundant system that is warming at least twice as fast as the global average (International Panel on Climate Change, 2007) and simultaneously experiencing drastic landscape changes from an expanding human footprint. Altered transmission dynamics of parasites, poleward range expansion of hosts and parasites, and disease emergence coincident with climate warming or extremes have all been reported in the Arctic (Kutz et al., 2009; Laaksonen et al., 2010). Together, these phenomena are altering host–parasite dynamics and causing endemic Arctic species—unable to compete or adapt rapidly enough—to decline (Gilg et al., 2012). Changes in wildlife health can also compromise the livelihoods and health of indigenous people who depend on wildlife for food and cultural activities (Meakin and Kurvitz, 2009).

In humans, exposure to diarrheal diseases has been linked to warmer temperatures and heavy rainfall (Pascual et al., 2002). Human infections of cholera, typically acquired through ingestion of contaminated water (in developing countries) or undercooked seafood (in the developed world), affect millions of people annually with a high case-fatality rate. Coastal *Vibrio* infections are associated with zooplankton blooms, warmer water, and severe storms (Baker-Austin et al., 2013). For example, in the Baltic Sea, long-term warming and temperature anomalies have been linked to increased disease from *Vibrio vulnificus*, which was first reported in 1994 along the German coast after an unusually warm summer (Baker-Austin et al., 2013). Long-term sea surface warming can increase the geographic range, concentration, and seasonal duration of *Vibrio* infections, as seen in coastal Chile, Israel, and the U.S. Pacific Northwest. Modeling approaches indicate that *Vibrio* illnesses from the Baltic region could increase nearly twofold for every 1°C increase in annual maximum water temperature (Baker-Austin et al., 2013).

Human mosquito-borne diseases, such as malaria and dengue fever, are frequently proposed as cases where vector and disease expansion into the temperate zone could follow from climate warming (Mills et al., 2010). However, some researchers have argued that ranges will shift with warming, rather than expand, and that the best predictors of infection risk are economic and social factors, especially poverty (Lafferty, 2009; Randolph, 2010). Controversy has also arisen over which climatic variables are most important in delimiting the distributions of these diseases [boxes S1 and S2 (available as supplementary material on *Science* Online)]. Detecting impacts of climate change on human vector-borne diseases remains difficult, in part, because active mitigations, such as vector-control, antimicrobials, and improved infrastructure, can complicate detection of a climate

signal. Several unresolved issues include identifying conditions under which climate warming will cause range expansions versus contractions, understanding the impact of increasing variability in precipitation, and determining the additional economic costs associated with increased disease risk caused by warming.

Ultimately, the societal implications of climate-driven shifts in diseases of humans, crops, and natural systems will demand solutions and mitigation, including early-warning programs. Recently, a forecasting system linking global coupled ocean-atmosphere climate models to malaria risk in Botswana allowed anomalously high risk to be predicted and anticipatory mitigations to be initiated (Thomson et al., 2006). Forecasting is well established in crop disease management and leads to improved timing of pesticide application and deployment of planting strategies to lower disease risk [box S3 (available as supplementary material on *Science* Online)]. Modeling efforts to better predict crop loss events are also tied to improved insurance returns against losses (Garrett et al., 2013). Similarly, accurate forecasting programs for coral bleaching have become a mainstay of marine climate resilience programs (Eakin et al., 2010) and are leading to the development of coral disease forecasting algorithms (Maynard et al., 2011). Appropriate management actions under outbreak conditions include reef closures to reduce stress and transmission, culling of diseased parts of some colonies, and increased surveillance (Beeden et al., 2012). In the ocean, efforts are also under way to increase the resilience of marine ecosystems to disease, including developing no-fishing zones and reducing land-based pollution that can introduce new pathogens (Burge et al., 2014).

Outlook and Future Challenges

Climate change will continue to limit the transmission of some pathogens and create opportunities for others. To improve predictions and responses we need to deepen our understanding of mechanistic factors. Although the initial climatic drivers to be explored should be temperature variables (both mean and variability), because the data are available and we understand the mechanisms at work, future work must concurrently explore the effects of precipitation, relative humidity, and extreme events. In particular, models are needed that combine the principles of ecophysiology and MTE (Brown et al., 2004) with epidemiological response variables, such as R_0 or outbreak size, and that are designed to accommodate distinct pathogen types (e.g., vector-borne, directly transmitted, or complex life cycle) and host types (ectotherm versus endotherm) (Molnár et al., 2013). These models should be applied, by using climate-change projections, to evaluate how broad classes of pathogens might respond to climate change. Building from this foundation, the next step is to extend such general models to specific pathogens of concern for human health, food supply, or wildlife conservation, which will require empirical parameterization, with attention to the on-the-ground conditions. Modeling efforts should be integrated with experiments to

test model predictions under realistic conditions, and with retrospective studies to detect the "fingerprint" of climate-induced changes in infection.

Scientists still know relatively little about the conditions under which evolution will shape host and pathogen responses to climate change. Although evolutionary change in response to climate warming has been reported for some free-living animals and plants, the evidence remains limited (Moritz and Agudo, 2013). Even less is known about how climate change will drive host–pathogen evolution. Corals have multiple levels of adaptation to intense selection by thermal stress that could also affect resistance to pathogens, including symbiont shuffling of both algae and bacteria, and natural selection against thermally intolerant individuals (Howells et al., 2011). In oysters (*Crassostrea virginica*), warming might have contributed to increased resistance to the protozoan multinucleated sphere X (MSX) disease (Ford and Bushek, 2012), but climate variability might also slow the evolution of oyster resistance (Powell et al., 2012). In cases where increased rates of transmission follow from warming, selection could favor higher pathogen virulence, although examples are now unknown.

A persistent challenge involves the ability to detect changes in disease risk with climate across different systems. In the oceans, for example, impacts of disease on sessile hosts like corals, abalones, and oysters are readily apparent, and for terrestrial systems, clear impacts are seen for plant diseases and some wildlife-helminth interactions. But for highly mobile species and many human diseases, detecting signals of climate change remains problematic. For these less tractable systems, long-term ecological studies that examine the past distributions of pathogens, important hosts, and severity of diseases are indispensable. Permanent repositories of intact physical specimens, as well as their DNA, can provide records of diversity that will be critical resources as new methodologies become available (Fernandez-Triana et al., 2011; Hoberg, 2010). Moreover, new technologies can detect variability in physiological processes and gene expression and can improve climate projections from global circulation models. Sophisticated experimental designs conducted under appropriate ranges of environmental conditions and retrospective studies to identify past climatic effects on disease (Burge et al., 2014; Hoverman et al., 2013) will help advance predictive power.

An additional key challenge is predicting the impacts of climate–disease interactions for human societies and gauging how these compare with other components of climate change, such as the loss of arable land. By affecting food yields and nutrition, water quality and quantity, social disorder, population displacement, and conflict, past climate changes have long influenced the burden of infectious disease in many human societies (McMichael, 2012; Wheeler and von Braun, 2013). Predicting the regions where humans and natural systems are most vulnerable to pressures from infectious disease and how these pressures will translate to changes in global health and security constitute critical research priorities (Myers and Patz, 2009). Building a mechanistic understanding of climate–disease interactions will allow public health interventions to be proactive and will

facilitate effective responses to new or expanding health threats. Surveillance programs capable of detecting pathogen or disease emergence are essential and, in many instances, predicting and detecting local-scale impacts might be more important than predicting global-scale changes. To this end, the value of engaging local communities in disease surveillance is increasingly recognized, with the goal of advancing science on climate–disease linkages for practical solutions to protecting human and wildlife health.

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A3

MIGRATION, CIVIL CONFLICT, MASS GATHERING EVENTS, AND DISEASE

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Introduction

Human agency can drive infectious disease establishment, adaptation, and spread, which can subsequently have profound impacts on the health of individuals, communities, and populations. Civil conflicts and the complex humanitarian emergencies they generate are widespread, common, and may increase in context of current global environmental change (Hsiang et al., 2013). Conflict, civil disruption, and the implicit migration that comes with both can compromise our ability to understand, track, respond, and mitigate infectious disease threats making their impact on human health even more difficult to address.

With increased migration and mobility of peoples, a concurrent increase in exposure to multiple infectious diseases can occur. Populations mixing from the movement of individuals, groups, and sometimes whole communities can allow for a greater mixing of infectious diseases and heightened vulnerability to those diseases. Work by our group in Eastern Burma documented much higher rates of childhood and adult malaria, water-borne diarrheal diseases, childhood malnutrition, and land mine injuries among displaced populations in civil conflict zones than among stable and nondisplaced communities (Richards et al., 2009).

More than just increasing the exposure to infectious diseases, migration can allow for greater acquisition and transmission of the diseases. Studies performed in South Africa, Kenya, Guinea-Bissau, and Nepal show an increased odds of HIV acquisition and infection among migratory groups, including rural to urban migration or migration out of the country (Beyrer et al., 2006). Migratory peoples

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seldom receive proper health care, particularly undocumented migrants who have left home countries. They can experience treatment delays and gaps, barriers to access and care, and lack many protective commodities such as bed nets, water filters, and condoms that would decrease further exposures.

Given a lack of treatment and access to trained health care workers, morbidity and mortality can increase among migratory and mobile populations. Additional limited access to essential medications can increase disease severity and the likelihood of onward transmission—sustaining cholera outbreaks, for example, as has occurred in Zimbabwe and Haiti among displaced populations (Piarroux et al., 2011; Sollom et al., 2009).

The increase in infectious disease exposure and transmission within migratory groups does not only affect those within the group, but it can also affect those with whom the group comes into contact (Beyrer and Lee, 2008). A study performed in China showed that cities with a higher number of immigrants per 1,000 people also had a greater incidence of STDs (Tucker et al., 2005). Therefore, in order to protect the health of the displaced peoples and those they come into contact with, the underlying rights of these mobile groups and their access to adequate care must be protected and preserved. Often, particularly in the context of civil conflict, this does not happen. The flawed response to Cyclone Nargis, an enormous cyclone, which struck Burma/Myanmar, helps illustrate these issues—and demonstrates how climate change and human agency can interact in complex and challenging pathways—extracting heavy tolls on vulnerable populations. The conflict in Côte d'Ivoire illustrates another challenge—the loss of health care workers in conflict and our subsequent diminished capacity to both understand and address the health impacts of conflicts on populations.

Conflict and Complex Humanitarian Emergencies

Humanitarian emergencies can arise from many possible causes, but one of the more common causes, conflict, creates very complex problems. Conflict leads to displaced and marginalized people, as do many humanitarian crises. The political and social unrest that accompanies conflict is what makes the associated humanitarian issues much more difficult to right. Threats to humanitarian assistance are much more likely if conflict is ongoing, and the deliberate politicization of aid by forces in conflict is an increasing reality which can undermine responses and expose relief workers and beneficiaries to violence and intimidation, a feature of relief efforts in Sudan, DR Congo, and Burma (Lischer, 2006).

The First Ivorian Civil War erupted in Côte d'Ivoire during 2002 with attacks by rebel forces on the government. These rebels took hold of the northern regions of the country, while the government maintained its claim to the southern regions, making the central region of the country a barrier zone. The conflict continued until 2007, despite numerous attempts at peace throughout the ensuing 4 years.

Before the First Ivorian Civil War, around 2001, a sizeable number of health care staff worked around the country. In the north, there were 38 doctors and 257 nurses; in the central region, there were 127 doctors and 471 nurses; and, in the west, there were 69 doctors and 310 nurses. After the conflict started and had been going on for a few years, around 2004, these numbers changed dramatically. In the north, there were 2 doctors and 82 nurses; in the central region, there were 3 doctors and 67 nurses; and, in the west, there were 6 doctors and 42 nurses (Betsi et al., 2006). Access to care then arose as a major problem for everyone living within the borders of Côte d'Ivoire.

While the health staff dwindled, the prevalence of STIs markedly rose. Baseline measurements around 2002 showed that 24,636 people in Côte d'Ivoire had been infected, making the prevalence risk at that time 10.1 per 1,000 people. Around 2004, the infection rate increased. Measurements taken showed that 29,688 people now lived with an STI, making the new prevalence risk 21.5 per 1,000 people. Within just a few years, not forgetting the conflict that started in 2002, the prevalence had doubled. This increase in STIs is not rare in conflict situations. With decreased access to and use of reproductive health services, the normalization of sexual predation and violence, and increased population mixing, among others, the increase is hard to combat (Mills et al., 2006).

The First Ivorian Civil War not only left the country with very little health care infrastructure, but it also started a massive spread of STIs, making many health issues much more complicated. While the issues here discussed may be somewhat specific to Côte d'Ivoire, the complex nature of the humanitarian crisis, causing rapid displacement, is something shared by all conflicts. The current strife in Syria, with over 100,000 dead and over 2 million refugees, shows that the problems are indeed not isolatable.

Natural disasters add additional challenges to these health threats. According to the Brookings-Bern Report (Brookings-Bern Project on Internal Displacement, 2008), the human rights of disaster victims are often not taken into account and include:

- Unequal access to assistance
- Discrimination in aid provision
- Enforced relocation
- Sexual and gender-based violence
- Loss of documentation
- Recruitment of children into fighting forces
- Unsafe or involuntary return or resettlement
- Property restitution

These problems are additional to the many consequences of a natural disaster felt by its victims. The tsunamis, hurricanes, and earthquakes, which hit parts of Asia and the Americas in 2004/2005, highlighted the multiple human rights

challenges victims of disasters may face, but the 2008 Cyclone Nargis and the response of the Myanmar government best shows the overwhelming problem of human rights within the context of conflict and natural disasters.

Case Study: Cyclone Nargis and Burma/Myanmar

In May of 2008, Cyclone Nargis hit the southwest corner of Myanmar and sent a massive storm surge into the Irrawaddy Delta. At least 146,000 died, 2.4 million were displaced, and 700,000 homes were destroyed in the wake of this enormous storm. The cyclone washed over some 5,000 km, and radically altered the geography of the Irrawaddy Delta itself. Much of what was rice fields and farmlands before the storm is now open water. As a consequence, 60 percent of Burma's rice crop was obliterated.

Myanmar is no stranger to civil conflict. At the time of Cyclone Nargis' landfall, a military dictatorship or junta, the State Peace and Development Council (SPDC), headed by Senior General Than Shwe, held power. Cyclone Nargis and the response of the Myanmar government to international aid revealed what many had known for decades: The regime of Senior General Than Shwe was incompetent, corrupt, and focused on political survival.

On the third day after Cyclone Nargis hit, May 5, the BBC reported a death toll of 351 and that the toll was likely higher. In Labutta, a southwestern township, 75 percent of buildings were said to have collapsed. MRTV, a state-owned television station, reported that 222 people were dead in Irrawaddy and 19 were dead in Rangoon. No official cleanup crews existed, and the Burmese embassy in Thailand closed for a (Thai) holiday. A Rangoon trishaw driver questioned, to the Associated Press, "Where are all the uniformed people who are always ready to beat civilians?"

On day 4, the official death toll rose to 3,394, with 2,879 missing, which was later increased to 22,000 dead and 41,000 missing. Reports arose of looting in Rangoon from a lack of food and clean water. The European Union called the aftermath a "massive disaster . . . with destruction [of some communities] close to 100 percent."

International aid forces began to assemble as it became clear that the loss of life was enormous, and the response by the ruling junta clearly inadequate. UN Secretary General Ban Ki Moon put a UN Disaster Assessment & Coordination team on standby in Thailand to assist the Burmese government as soon as necessary. The United States released $250,000 of cyclone aid funds and also has a disaster relief team on standby, awaiting permission. The WHO had "officers [who were] on the ground and ready for rapid assessment, surveillance, and mobilization," including medical teams. The only thing holding all of these groups back was permission from the Burmese government to supply visas and allow the aid to enter the country. Unfortunately, as Jean Maurice Ripert, French

ambassador to the UN, noted, they were "not able to [deliver aid] because they [wouldn't] give visas to humanitarian workers."

On day 6, many top leaders in the government disappeared. No responses to world leaders' condolence messages came in. Most importantly the government did not answer Ban Ki Moon's calls to discuss aid restrictions. Images of monks helping in cyclone cleanup and relief were banned, while only aid from the SPDC aired on state television. The government asked for direct donations of cash and supplies. All international aid workers still awaited visas.

On day 8, the junta proceeded with its long planned constitutional referendum, evicting all storm refugees from any polling places. The UN and the U.S. government, among others, had strongly urged the junta not to proceed with the referendum, and to focus on the relief effort. But the generals proceeded, and reported greater than 94 percent voter participation. To no one's surprise, the referendum passed overwhelmingly. The SPDC rejected international monitors and barred international relief from the delta. The government went out of their way to ensure that all aid went through them. By day 10, the death toll had risen to 31,938 dead with 29,770 missing.

It was not until the 16th day after the cyclone that Than Shwe visited show camps. All of the relief supplies still sat perfectly wrapped and unopened. A Myanmar newspaper reported that "the government took prompt action to carry out the relief and rehabilitation work after the storm" despite the differing report from the UN stating that only 20 percent of survivors had received some rudimentary aid. The Burmese regime then requested $11.7 billion for rehabilitation and reconstruction with no needs assessment, saying that the first phase of emergency relief was over and that they were moving into the rebuilding phase. Finally, on the 21st day after Cyclone Nargis hit, Than Shwe met with Ban Ki Moon, who had personally come to the country to break the block on assistance, and agreed to allow in aid workers.

While it is certainly difficult to ascribe the power and scale of Cyclone Nargis to climate change, land use patterns and environmental destruction did likely play more measureable roles in the storm's impact and loss of life. The Irrawaddy Delta is a very large, low-lying coastal marsh region, once protected from the open sea by dense mangrove forests. Under British rule in the nineteenth century, the delta was drained, and a century of intensive rice paddy cultivation and population in-migration followed. By the time Nargis hit, the delta was a densely populated region producing more than 50 percent of Burma's wet rice crop, and the protective mangroves and coastal marshes had been decimated. This exposed rural and remote coastal communities to the full force of the storm, and many communities were washed over in the first, massive storm surge. Military misrule limited the humanitarian response to this natural disaster, but climate change and land use patterns exposed communities and led to enormous losses of life.

Instability Bias

In times of conflict, diseases and health problems do not subside. In fact, as we have discussed, the opposite is true. Research of all kinds, including health research and disease surveillance, however, can markedly decline when conflict arises. This problem, which we have characterized, is known as instability bias and makes it difficult to assess health outcomes related to conflict.

During the rule of Mobutu Sese Seko from 1965 to 1997, the Democratic Republic of the Congo or Zaire, as it was known at the time, faced corruption, state violence, and internal conflict. Zaire was also an epicenter of the emergence of HIV/AIDS, and a key country in early efforts to investigate and understand this newly emerging human pathogen. New HIV/AIDS studies in DR Congo peaked from 1986–1988 at 16 studies per year and then started to decline (Figure A3-1). New malaria studies also peaked from 1986–1988 (Figure A3-2). In 1994, Mobutu ordered that international collaborative research stop (Beyrer and Pizer, 2007).

Seventeen peer-reviewed publications on HIV/AIDS in the Democratic Republic of the Congo came out in 1990. In 2002, none were published (Beyrer and Pizer, 2007). Of course, the issue of HIV/AIDS had not been resolved in DRC. Instead, the political unrest within the country halted the research.

The example of research in the Democratic Republic of the Congo shows not only the power that conflict can have on controlling the amount of research

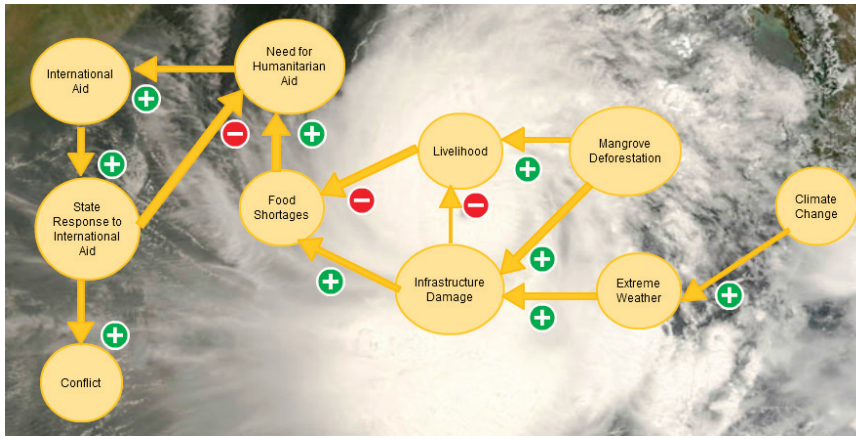

FIGURE A3-1 Causal loop diagram of Cyclone Nargis. The causal loop diagram illustrates the relationship between climate change, international and national governance, and conflict in Myanmar in the aftermath of Cyclone Nargis in 2008.
SOURCE: Naples, 2011.

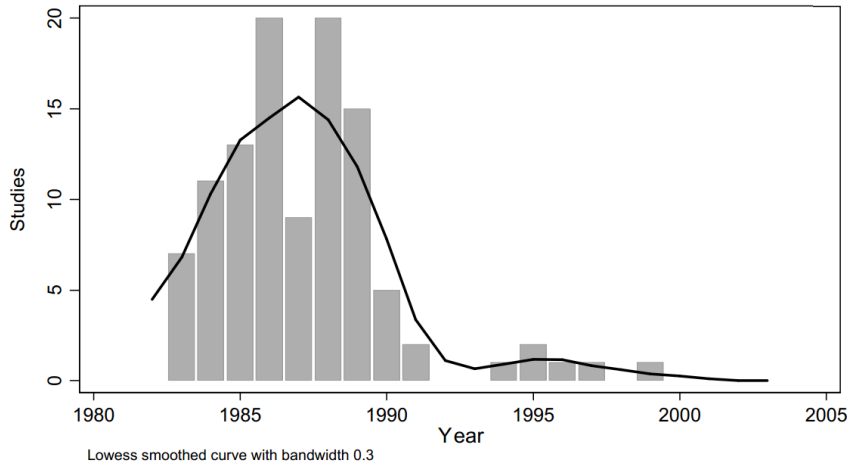

FIGURE A3-2 Bibliometric analysis of HIV publications, Democratic Republic of Congo, 1982–2004.
SOURCE: Beyrer and Pizer, 2007.

produced, but also the power of the ruling class. Researchers must utilize creative methods such as expanding community engagement practices (Amon et al., 2012). Otherwise, research on issues such as infectious diseases will continue to be sparse on conflict zones.

Ways Forward

According to an ICE case study, "The Intergovernmental Panel on Climate Change (IPCC) predicts an increase in extreme weather events such as tropical cyclones in the Southeast Asian region. Cyclone Nargis, which struck Myanmar on May 2, 2008, illustrates the potential for extreme weather events to contribute to conflict" (Naples, 2011). In this same case study, the ICE proposed a framework that outlines how human agency in the form of climate change can lead to natural disasters and the outcome of conflict (Figure A3-3). Taking into account what we know about the impact of conflict on the spread of infectious disease and what we have learned from Cyclone Nargis and Myanmar, we must begin to recognize human agency and its interactions with global infectious disease threats.

To better address this researchers can partner with grassroots organizations and human rights groups in country and internationally. More importantly, partnering with those we seek to serve facing these complex and overlapping threats and again expanding community engagement practices can provide opportunities for more effective health efforts in conflict zones (Amon et al., 2012).

Migration, civil conflicts, and climate change are all likely to be more common, and to interact with the well-being of communities and populations in the

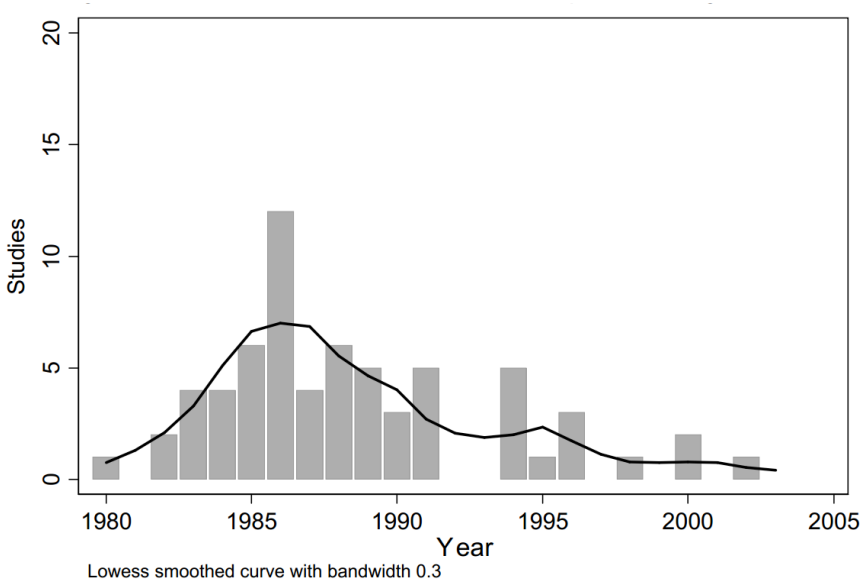

FIGURE A3-3 Malaria studies initiated, Democratic Republic of Congo, 1980–2004. SOURCE: Beyrer and Pizer, 2007.

years and decades to come. Relief efforts must be prepared for complex crises, and new approaches to delivery of relief will likely be required to address these emerging threats.

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A4

THE IMPORTANCE OF MOVEMENT IN ENVIRONMENTAL CHANGE AND INFECTIOUS DISEASE

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Abstract

Global environmental changes directly impact human movement and mobility, which in turn drive infectious disease dynamics and pathogen transmission. In addition to establishing the importance of movement in disease dynamics, characterizing the mechanistic relationship between environment, host behavior, and pathogen transmission is becoming increasingly necessary. Environmental systems are diverging from previous patterns while continuing to mediate individual and group movements as well as the complex interactions between population dynamics and disease dynamics.

Introduction

Movement and Disease

The effects of environmental changes on infectious diseases are most often discussed in their direct links to wildlife diseases and vector borne pathogens. However, a closer look into the complexity of infectious disease systems reveals

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that environmentally driven host movements are a critical element in infectious disease dynamics. Movement and mobility are known to be important underlying mechanisms driving the spatiotemporal dynamics of infectious diseases, both within and between populations (Altizer et al., 2011; Bharti et al., 2010; Bradley and Altizer, 2005; Gray et al., 2009; Loehle, 1995; Morgan et al., 2007; Tatem et al., 2009, 2012; Viboud et al., 2006). Examples of environmentally mediated movements include movement motivated by food and water security and seasonal migration patterns.

The links between host movement and infectious diseases have been studied in the context of animal migrations (Altizer et al., 2011). Data show that long-distance mass animal migrations can either reduce disease via "migratory escape" (Loehle, 1995) or "migratory culling" (Bradley and Altizer, 2005) or increase disease by creating new or high density contacts at stopovers and destinations (Morgan et al., 2007). In addition to recognizing the importance of mobility, these examples from animal migrations illustrate why it is necessary to develop a mechanistic understanding of the relationship between movement and contact patterns as environmental changes occur.

Despite establishing the importance of host movement in infectious disease dynamics (Bharti et al., 2010; Gray et al., 2009; Tatem et al., 2009, 2012; Viboud et al., 2006), many aspects of mobility remain difficult to measure, particularly in humans. Epidemiologically important patterns of movement can remain unknown or poorly understood outside of local knowledge. As a result, it can be challenging to incorporate these movements into public health planning and disease prediction efforts. Improved knowledge and quantification of movement patterns would help in planning and implementing more effective public health interventions (Camargo et al., 2000).

We investigate the role of seasonal human movement in pathogen transmission, disease incidence, and immunization programs. Specifically, we investigate measles dynamics in three cities in the West African nation Niger from 1995 to 2005 as an example of an environmentally driven migration impacting pathogen transmission and control in urban areas. We intentionally use an inherently simple disease, measles, to understand the complex dynamics of populations and disease.

Population Dynamics and Disease

Measles is a strongly immunizing, directly transmitted human disease with no vector, no animal reservoir, and no direct interaction with the environment. Recorded cases of measles in prevaccination industrialized nations are among the richest disease data sets (Fine and Clarkson, 1982). These data demonstrate the highly regular annual and multiennial cycles of measles incidence (Anderson and May, 1991; Cliff et al., 1993). Detailed demographic and measles case records clearly linked population dynamics to disease dynamics; births replenished the susceptibles in the population (Grenfell et al., 2002), the birth rate determined

the periodicity of outbreaks (Bartlett, 1957), and the aggregation of susceptibles increased contact rates raised transmission rates and triggered measles outbreaks (Fine and Clarkson, 1982). In prevaccination Europe and England this aggregation took place in classrooms, and measles outbreaks were seasonally forced onto school terms with a mean age of infection around 5 years (Fine and Clarkson, 1982).

After a vaccine was developed, mathematical analyses showed that the most effective time to vaccinate the population was during the troughs of infection (London and Yorke, 1973; Yorke et al., 1979). This reduced the density of susceptibles prior to the start of school terms, preventing epidemics from taking off. This strategy was successful and became conventional practice in measles immunization. Throughout large regions of the world, similar preventative vaccination campaigns targeted during the troughs of infection were extremely effective in achieving and maintaining high levels of coverage and interrupting local chains of transmission (Cliff et al., 1993). Many high-income nations have maintained greater than 90 percent vaccination coverage for decades, locally eliminating measles infections during these periods (Cliff et al., 1993).

In particular, the Pan American Health Organization (PAHO) has been widely commended for implementing a highly successful vaccination strategy that focused on age-specific routine vaccinations and catch-up campaigns at regular intervals to keep immunization levels consistently high (Castillo-Chavez et al., 2011). PAHO's strategy largely eliminated measles in the Americas and was heralded as an example that would pave the way for measles eradication. The African Health Observatory (AHO) adopted a similar strategy for the African region's measles control initiative. However, the program has not been as succcessful as it was in the Americas, and measles outbreaks continued to cause morbidity and mortality across the continent (Simons et al., 2012). So why was a strategy highly effective in one place yet failed to produce similar results in another? In contrast to the American region, the African region had a completely different geography along with higher levels of diversity and population movements that were not considered in PAHO's vaccination strategy but were likely major contributors to its significantly reduced efficacy in the African region.

Measles in Niger

Today, measles continues to persist across many areas of the globe, but nowhere more than Asia and Africa (*The case of measles*, 2011; Simons et al., 2012), particularly in places with high birth rates (Bongaarts and Caterline, 2012). Throughout the past decades, Niger put forth significant public health efforts to reduce the national burden of measles. In addition to routine immunizations and catch-up campaigns, the Ministry of Health maintained detailed records of measles cases and vaccine coverage. Despite significant investments, measles epidemics persisted, with the biggest cities at risk for particularly large outbreaks (Ferrari et al., 2008).

Niger's measles outbreaks are strongly seasonal, occurring only during the annual dry season. Although the magnitude of outbreaks can vary greatly between years, the timing is extremely consistent (Ferrari et al., 2008). We focus on measles epidemics in the three largest cities in Niger—Niamey, Maradi, and Zinder (Figure A4-1A)—where the seasonal forcing in transmission is stronger than previously observed anywhere else, including prevaccination cities (Ferrari et al., 2010). The strong seasonal forcing causes the outbreaks to subside; epidemics are not self-limiting due to an exhaustion of susceptible individuals, as is often the case with measles (Cliff et al., 1993; Ferrari et al., 2008, 2010; Grenfell and Bolker, 1998).

Despite frequent recurrences, measles is not endemic in Niger, often disappearing completely during the rainy season, even from the largest cities (Bartlett, 1957; Bjornstad and Grenfell, 2008; Ferrari et al., 2008; Grenfell and Bolker, 1998). The very high birth rates rapidly replenish the supply of susceptibles, creating the potential for frequent or large outbreaks in the absence of high vaccination levels (Bartlett, 1957; Ferrari et al., 2008; Grenfell et al., 2002). The median age of measles infection in Niger is around 2 years, which is too young for transmission to be focused in schools (Ferrari et al., 2008).

The observed seasonal outbreaks of measles in Niger had also been noted in other parts of the region. The underlying reason, though definitively unknown, was hypothesized to be the result of agricultural labor migrations (Ferrari et al., 2008). During the rainy season in this highly agricultural economy, it is not uncommon to disperse to rural areas for agricultural work and then aggregate in urban areas during the dry season (Faulkingham and Thorbahn, 1975; Rain, 1999).

Measuring Movement and Interpreting Its Role

Epidemiologically important movements within a familiar context may be relatively easy to detect; in western societies this may include weekday work commutes (Viboud et al., 2006), long-distance travel (Tatem et al., 2012), and travel around major holidays. It can be much more problematic to identify movement patterns found only outside of one's own culture, including different livelihoods and the embedded movement patterns. In this case, inhabitants of western societies may be unfamiliar with nomadic pastoralism (Dyson-Hudson and Dyson-Hudson, 1980) or cyclical regional migration (Byerlee, 1974). In some cases, these types of movements are studied in an ethnographic context with relatively small sample sizes. Careful ethnographic research has detailed seasonal movement patterns for agricultural work in Niger (Faulkingham and Thorbahn, 1975; Rain, 1999). After detection, these movements must be measured and, to explain the observed city-level measles dynamics, the seasonal movements of small groups must be scaled to match large urban areas. However, extracting large-scale data from small-scale samples or scaling down movement data from large data sets, such as a national census, is simply not possible.

Fortunately, advances in technology and methodology have improved our abilities to measure movement patterns at high spatiotemporal resolution. Various aspects of human presence can be captured and traced by satellite imagery (Elvidge et al., 1997, 2009; Sutton et al., 1997, 2001), including changes in urban population density and spread (Bharti et al., 2011).

Remote Measures of Changing Urban Populations

To assess the relationship between changes in population density and measles epidemics, it was necessary to quantify urban populations across seasons. These data could not be extracted from existing ethnographic studies and census data, as mentioned earlier. Other existing data sources, such as composite satellite imagery, often present annually or biannually aggregated information. Commercial flight records illustrate high-temporal-resolution movements but track only long-distance movements. Lastly, there are no functioning railways in Niger; movement occurs along roads, but seasonal measurements of road use and traffic are not recorded.

To quantify seasonally varying high-resolution spatial changes in populations in these three cities in Niger, we developed a method using noncomposited serial nighttime light satellite images. These images capture anthropogenic visible light at night during low moon and cloud-free conditions (Bharti et al., 2011; Elvidge et al., 1997). We created an annual signature of brightness values for each city using 155 images, concurrent with the time period of measles data collection (Bharti et al., 2011; see supporting online materials 1 for method details). We found a consistent, pronounced dip in brightness in each city during the rainy season and a peak during the dry season (Figure A4-1B-D), illustrating that population fluctuations were strongly correlated to the measles transmission curve specific to each city (Figure A4-1B-D) (Bharti et al., 2011; Sutton, 1997).

To look more closely at the spatial relationship between brightness and measles cases, we focused on the three communes within the city of Niamey (Figure A4-2A, inset). Daily case records at the commune level from a 2004 outbreak showed that the epidemic appeared earliest in the two largest communes, where 90 percent of the cases in the city occurred, and appeared last with the fewest cases in the smallest commune (Bharti et al., 2011; Dubray et al., 2006) (Figure A4-2A). The brightness curves for these three communes displayed a similar pattern: the two largest communes increased and peaked earlier with very high brightness values, and the third commune increased and peaked later with a relatively lower brightness value (Figure A4-2B) (Bharti et al., 2011).

A Dynamic Model

In simple theoretical models, migration may be thought of as a source of infected individuals. The dynamics of measles epidemics in the cities of Niger

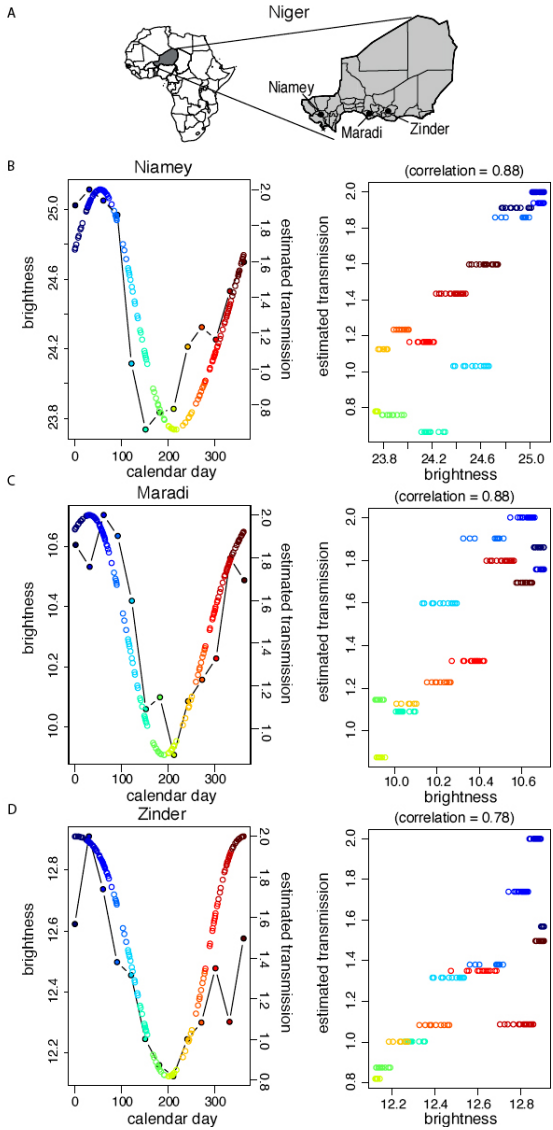

FIGURE A4-1 Measles transmission rates and brightness for three cities in Niger (adapted from Bharti et al., *in prep*). Top left: map of Africa, Niger shaded; top right: map of Niger showing three largest cities and national health districts. B. Niamey. Left: annual brightness pattern against day of year shown in open circles. Color corresponds to time (blue to red = January to December); estimated measles transmission rates for biweekly time steps shown in circles connected by dark lines. Right: estimated transmission rates against brightness values; colors correspond to time of year as on left. C. Same as B for Maradi. D. Same as B for Zinder.

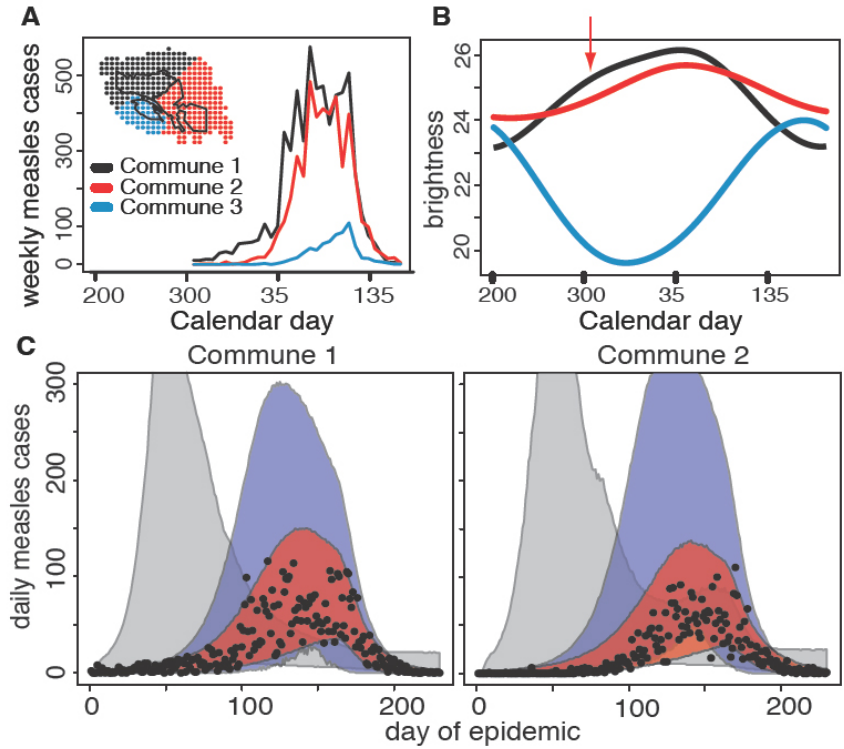

FIGURE A4-2 Measles and brightness in the communes of Niamey (adapted from Bharti et al., 2011). A. *Inset:* map of city of Niamey showing pixels of the city color-coded by commune. Formal boundaries of each commune are shown with black outlines. Time series of weekly reported measles cases for Niamey's 2003–2004 outbreak by commune. B. Time series of brightness values, colors by commune as in A. Red arrow indicates onset of measles epidemic in Niamey. C. Left: commune 1, right: commune 2. Points show daily reported measles cases, shading gives central 95 percent of predicted measles incidence from 25,000 model simulations from nighttime lights-informed model (red), no immigration model (blue), and constant immigration model (gray). The x-axis spans the duration of the epidemic: day 307 of 2003 to day 153 of 2004.

suggested that migration was also an important source of susceptible individuals as well as a critical driver of changes in population density and contact rates (Bharti et al., 2011; Ferrari et al., 2008).

To determine whether the satellite-derived quantified changes in population density could drive the seasonal forcing of the observed measles epidemics in each commune of Niamey, we adapted an SIR model that included fluctuations in the total population size. Conventional SIR models of measles have included seasonal forcing in the transmission rate, a single rate that encompasses (1) the

probability of a contact event occurring between an infected and a susceptible person, and (2) the probability of a transmission event occurring, given such a contact (Begon et al., 2002). We separated these two probabilities and assessed them independently. In the communes of Niger, the per capita rate of contacts between susceptible and infected individuals is unlikely to change across seasons. Instead, the *number* of contact events increases with the overall population density. So while more contacts occur during the dry season, the proportional number of contacts between susceptible and infected individuals does not change. Secondly, the probability of transmission, given a contact between a susceptible and infectious individual, does not change between seasons. Measles outbreaks consistently occur with host aggregation and have been historically observed across all seasons (Cliff et al., 1993). Thus, instead of including seasonality in the transmission term, we allowed the total population size to change with the derivative of the brightness curve for each commune (Bharti et al., 2011).

In addition to the model with migration informed by commune-level changes in brightness, we fit two additional models for comparison. For each commune, we also fit (1) an SIR model with a constant migration rate, and (2) a model with no migration (static population size) to the daily measles case reports.

The model results showed that for communes 1 and 2, where 90 percent of the measles cases within the city occurred, the brightness-informed changes in population size were required to produce the correct rate of increase and decrease of cases as well as the timing and height of the peak of cases (Figure A4-2C) (Bharti et al., 2011). Although commune 3 had far fewer cases, the model with brightness-informed population fluctuations was better than the other two at replicating the correct timing of the peak as well as the increase and decrease in cases (Bharti et al., 2011).

The model illustrates that in order to reach the observed height at the peak of each commune's epidemic, susceptible individuals must be added over the course of the epidemic's increase. If the population starts with the necessary number of susceptible individuals to sustain the epidemic, the number of cases increases far too quickly and the peak appears much sooner than observed before declining exceptionally more rapidly than that of the recorded outbreaks. In the absence of population fluctuations, the epidemic trajectory in each of Niamey's three communes would look very different (Bharti et al., 2011).

Vaccination

Often overlooked, migration has a strong impact on health care and immunization programs. In several instances, movement and mobility have been definitively identified not only as the underlying drivers of spatiotemporal epidemic patterns, but also as important disregarded elements in public health interventions. Within São Paulo, Camargo et al. (2000) showed that risk factors related to a 1997 measles epidemic included migration from other states and rural–urban

migration within the state and determined that movement should be considered when planning a measles vaccination strategy. Relocating also increased the risk that a child would miss a vaccination for polio in India, Angola, and Pakistan (Unicef, 2013). Perhaps most specifically, seasonal migration in Niger was identified as a high-risk factor for children lacking measles vaccination in a 1990–1991 outbreak in Niamey (Malfait et al., 1994).

In a place like Niamey, population fluctuations are not only strongly seasonal and pronounced, they are also the mechanism underlying measles outbreaks. This means that the troughs of infection align with troughs in population size and, contrary to conventional wisdom, may not be the most effective time to vaccinate the population. Practiced in Niger, this strategy would vaccinate fewer individuals than would be present in urban areas during other times of the year. This also means that individuals from hard to reach or remote locations are not opportunistically vaccinated when they are easily accessible in urban areas.

Planning successful intervention strategies relies heavily on understanding local patterns of mobility. Instead of characterizing populations as static entities that can be described with relatively constant values of size and density, we may benefit from considering them to be more fluid with changing membership. It is possible to use fluctuations in populations as opportunities to immunize or provide access to health care to groups and individuals who might otherwise be difficult to reach. Understanding population fluctuations is also important in estimating the population size at the time of an intervention so that the correct number of vaccine doses can be provided.

Previous research has illustrated the merits of regional coordination in infectious disease interventions in this area due to common transnational movement patterns (Bharti et al., 2010, 2012). When looking specifically at urban regions, this is an even more valid argument. Seasonal or rural–urban movements are not always contained within a state's or nation's borders, and regionally coordinated vaccination efforts will reduce the gaps in coverage created by population movements.

Conclusion

Though perhaps unintentionally, we often consider populations to be relatively stable and static in size and density. We know with certainty that this is not only an overly simplistic representation of human populations, it also overlooks the massive impact that movement has on health. This perspective inadvertently inhibits our ability to understand geographically varying important underlying mechanisms of pathogen transmission and epidemic spread as well as access to health care.

Understanding the relationship between human movement patterns and diseases has presented unique challenges. Although known to be central in disease transmission and spatiotemporal patterns of disease dynamics, epidemiologically

important patterns of movement can be difficult to identify and measure. Interdisciplinary research and technological and methodological advances have made immense progress towards enhancing our understanding of movement and mobility in the context of the environment and health. Mobility traces from cell phones (Bengtsson et al., 2011; Gonzalez et al., 2008; Tatem et al., 2009), satellite imagery (Bharti et al., 2011; Checchi and Grundy, 2012), and high-resolution aerial photography as well as ground-truthing some of these proxy measures (Min et al., 2013) have already greatly advanced the methods and data behind understanding populations and their movements across a wide range of geographic areas, environmental settings, and health concerns. Measuring the many aspects of mobility and interpreting their prevalence across spatiotemporal scales is a difficult task, but it is a necessary step towards reducing disease and informing intervention strategies.

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A5

TOWARD A COUNTY-LEVEL MAP OF TUBERCULOSIS RATES IN THE U.S.[12]

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Introduction

Active tuberculosis (TB) is a reportable communicable disease in all 50 states, but nationwide, county-level data are not released publicly. The CDC's Online Tuberculosis Information System (OTIS) provides public surveillance data only by state. Owing to an agreement with the states, the CDC cannot publicly

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release TB data at the county level, precluding the development of publicly available, county-level maps of TB cases and incidence rates.

The lack of a more granular nationwide data set has limited the study of TB trends and socioeconomic risk factors to states (Holtgrave and Crosby, 2004), Metropolitan Statistical Areas (Greenwood and Warriner, 2011), or census tracts within a single state (Myers et al., 2006). A nationwide county-level data set of TB rates provides opportunities to examine TB-related trends across multiple states, metropolitan areas, and across counties with similar demographic characteristics, such as the number of people deemed to be at high risk (Cain et al., 2008).

Methods

TB statistics were generated after extracting publicly available data from state health department websites and requesting public but unpublished county-level data from state TB programs. States providing TB data assented to their use and presentation. The data set, metadata, and sources are published on an interactive map with downloadable data at healthmap.org/tb.

TB incidence rates were calculated using 5-year county-level case counts with corresponding (2006–2010) population estimates from the American Community Survey (ACS). Specifically, the total county-level case counts for 2006–2010 were divided by five to obtain the average number of cases per year. This average was divided by the average population in the county in those 5 years, and finally multiplied by 100,000 to calculate the incidence rate (cases/ 100,000). Therefore, "rates" reported in Table A5-1 and Figure A5-1 represent average annual incidence during the 5-year period.

Counties were cross-classified by four U.S. regions (Midwest, Northeast, South, and West) and by urban/rural classification (metropolitan [urban area of ≥50,000]; micropolitan [urban area of 10,000–49,999]; and rural), according to the Office of Management and Budget classifications. ANOVA was performed to assess differences in means across these 12 cross-classifications. ANOVAs were examined using Welch two-sample t-tests with Bonferroni adjustment for 42 comparisons ($\alpha = 0.0012$); significant comparisons were defined as $p < 0.0012$. Maps were created using ESRI ArcMap, version 10.3, and statistical analyses were performed using R, version 2.14.2.

Data were available on a year-by-year basis for 2,892 (92.0%) counties; supra-county health district level for 161 (5.1%) counties; and only multi-year aggregated data for 90 counties (2.9%). Collectively, these data enabled the creation of a U.S. map depicting 5-year average TB incidence rates (Figure A5-1) and a corresponding data set of 3,006 counties for analysis. Henceforth, we use the term "county" to refer collectively to counties; county-equivalents (e.g., boroughs); and health districts.

TABLE A5-1 Comparison of Average Annual TB Rates of U.S. Counties and Regions by Urban (Rural/Micropolitan/Metropolitan) Classification, 2006–2010[a]

Number of counties, county equivalents, and health districts

Region	Rural	Micropolitan	Metropolitan	Total
Midwest	486	218	259	963
Northeast	41	53	123	217
South	594	297	570	1,461
West	165	82	118	365
Total	1,286	650	1,070	3,006

Median annual TB rates per 100,000 by county and urban classification

Region	Rural	Micropolitan	Metropolitan	All Classes
Midwest	0	0.805	0.95	0.33
Northeast	0.52	0.90	1.78	1.10
South	1.67	2.49	2.305	2.16
West	0	1.28	2.21	1.22
All regions	0	1.38	1.78	1.28

Mean annual TB rates per 100,000 by county and urban classification, 2006–2010, M (SD)

Region	Rural	Micropolitan	Metropolitan	All Classes
Midwest	1.01 (3.06)	1.30 (2.28)	1.26 (1.64)	1.14 (2.57)
Northeast	0.68 (0.82)	0.94 (0.67)	2.49 (2.57)	1.77 (2.16)
South	3.07 (6.21)	3.72 (5.86)	2.90 (2.70)	3.14 (5.06)
West	1.70 (3.95)	1.81 (1.88)	3.33 (3.34)	2.25 (3.46)
All regions	2.04 (4.93)	2.44 (4.40)	2.50 (2.66)	2.29 (4.14)

Annual TB rates per 100,000 by region and urban classification, 2006–2010

Region	Rural	Micropolitan	Metropolitan	All Classes
Midwest	0.95	1.17	2.70	2.32
Northeast	0.63	0.99	4.50	4.14
South	3.09	3.43	4.60	4.33
West	2.33	1.95	5.64	5.31
All regions	2.20	2.27	4.48	4.11

Significant difference of M pairs from Table 1C[b]

Within regions

Northeast: Metro versus rural or micro ($p < 0.0001$)

West: Metro versus rural or micro ($p < 0.001$)

Between regions

National: South versus all other regions ($p < 0.0001$); Midwest versus all other regions ($p < 0.001$)

Rural: South versus all other regions ($p < 0.001$)

Micro: South versus all other regions ($p < 0.0001$); Northeast versus West ($p < 0.001$)

Metro: Midwest versus all other regions ($p < 0.0001$)

[a]Region and metropolitan/micropolitan classifications follow Office of Management and Budget definitions. Rural counties are those not defined as either metropolitan or micropolitan.

[b]Significant according to Welch two-sample t-test and Bonferroni adjustment, where $\alpha = 0.0012$. Number of comparisons = 42.

TB, tuberculosis

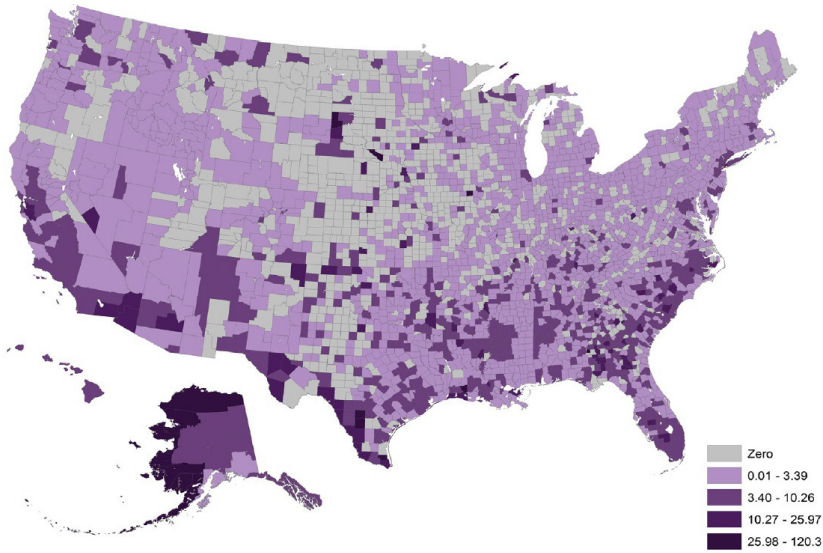

FIGURE A5-1 Average annual tuberculosis rate per 100,000 population, 2006–2010, by county tuberculosis data from publicly available sources. Population estimates from U.S. Census American Community Survey, 2006–2010.

Results

More than 600 counties have TB rates above the 2011 national rate of 3.4 cases per 100,000 people (Miramontes et al., 2012). The top 15 counties exceeded a rate of 20 cases per 100,000 (range = 20.9–120.3 cases); nine of these were rural, and eight were in the Southern region. TB case rates were generally highest in U.S. metropolitan areas; the South had the highest mean and median rates among U.S. regions (Table A5-1). Only the Northeast and West had statistically different mean rates when metropolitan counties were compared with micropolitan and rural means.

Discussion

A publicly available, county-level TB data set enables analysis of TB rates (per 100,000) at the sub-state level. Although TB rates in the U.S. are expected to be high in urban areas (Oren et al., 2011) that have large at-risk foreign-born populations (Liu et al., 2009), certain rural areas also have high TB rates, particularly in Southern states.

Publicly available county-level TB data can assist TB surveillance and control efforts. TB "hotspots" that cross state borders can be identified. Socioeconomic variables can now be tested to identify nationwide trends in at-risk populations for targeted prevention efforts. Thus, we encourage all states to publish county-level TB data online.

Additional demographic information distinguishing cases by birth country will help researchers and public health officials understand emerging TB trends. Although TB data should be interpreted within a local context, these data will facilitate more efficient identification of locales where high rates of TB cross state lines, facilitate collaboration between states to jointly target those areas, and allow health departments to discern regional and nationwide trends.

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A6

ASSESSING THE ORIGIN OF AND POTENTIAL FOR INTERNATIONAL SPREAD OF CHIKUNGUNYA VIRUS FROM THE CARIBBEAN[16]

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Abstract

Background: For the first time, an outbreak of chikungunya has been reported in the Americas. Locally acquired infections have been confirmed in fourteen Caribbean countries and dependent territories, Guyana and French Guiana, in which a large number of North American travelers vacation. Should some travelers become infected with chikungunya virus, they could potentially introduce it into the United States, where there are competent Aedes mosquito vectors, with the possibility of local transmission.

Methods: We analyzed historical data on airline travelers departing areas of the Caribbean and South America, where locally acquired cases of chikungunya have been confirmed as of May 12th, 2014. The final destinations of travelers departing these areas between May and July 2012 were determined and overlaid on maps of the reported distribution of Aedes aeygpti and albopictus mosquitoes in the United States, to identify potential areas at risk of autochthonous transmission.

Results: The United States alone accounted for 52.1% of the final destinations of all international travelers departing chikungunya indigenous areas of the Caribbean between May and July 2012. Cities in the United States with the highest volume of air travelers were New York City, Miami and San Juan (Puerto Rico). Miami and San Juan were high travel-volume cities where Aedes aeygpti or albopictus are reported and where climatic conditions could be suitable for autochthonous transmission.

Conclusion: The rapidly evolving outbreak of chikungunya in the Caribbean poses a growing risk to countries and areas linked by air travel, including the United States where competent Aedes mosquitoes exist. The risk of chikungunya importation into the United States may be elevated following key travel periods in the spring, when large numbers of North American travelers typically vacation in the Caribbean.

Introduction

Chikungunya virus is a mosquito-transmitted alphavirus endemic to sub-Saharan Africa and South and East Asia. In recent years, chikungunya has been appearing outside of its endemic zone as a result of increasing international travel (Enserink, 2007; Tomasello and Schlagenhauf, 2013). Concurrently, the geographic ranges of *Aedes aeygpti* and *albopictus*—the primary vectors for chikungunya virus—have been expanding, a phenomenon thought to be a consequence of climate change and globalization (Reiter et al., 2006). The combination of international travel by potentially infected persons and the increasing geographic availability of competent vectors has set the stage for the introduction and spread

of Chikungunya to previously unaffected areas. In recent years, autochthonous transmission of chikungunya has occurred in non-endemic areas such as the 2007 outbreak in Italy and 2010 outbreak in France, and most recently, in multiple Caribbean Islands where competent *Aedes* mosquitoes exist (Tomasello and Schlagenhauf, 2013).

The geographic dispersion of chikungunya virus may occur in instances where susceptible travelers in endemic areas are bitten by infected female *Aedes* mosquitoes (Powers and Logue, 2007). After the typical incubation period of 3-7 days (range 2-12 days), infected individuals become viremic (Borgherini et al., 2007; Sissoko et al., 2008). Among those who develop illness, common symptoms include fever, headache, rash, and severe symmetrical polyarthralgia. The potential for an infected individual to then transmit chikungunya virus to a susceptible *Aedes* mosquito is greatest during the first 2-6 days of illness, during the viremic phase (Appassakij et al., 2013).

For the first time in the Americas, chikungunya was reported among non-travelers on the Caribbean island of St. Martin in December 2013 (CDC, 2013). Since then, locally acquired cases have been reported in multiple countries and territories in the region for a total count of over 4,000 probable or confirmed cases, raising concerns that this virus could spread into and within neighboring areas, including parts of the United States (Gibney et al., 2011; Reiskind et al., 2008).

Every year, large numbers of North American tourists vacation in the Caribbean during spring and summer months. After returning home, these individuals could potentially introduce chikungunya virus into areas where the conditions necessary for autochthonous transmission exist. We used a novel approach combining a number of datasets related to travel routes, volumes of travelers, historic temperature data and zoonotic distribution of *Aedes* mosquitoes in order to model the recent outbreak in the Caribbean and the risk of spread to other countries via international travel. Due to the large travel volume between the Caribbean and the U.S. we conducted an analysis to determine the vulnerability of U.S. cities and states to the importation of chikungunya virus and subsequent local transmission due to favorable environmental conditions.

Methods

We accessed anonymized, worldwide, passenger-level flight itinerary data for 2012 from the International Air Transport Association (IATA). The IATA dataset represents an estimated 93% of the world's commercial air traffic at the passenger level. Flight itinerary data includes information on the airport where the traveler initiated their trip, and where relevant, connecting flights leading up to their final destination.

Using this dataset, we first analyzed the origins of all air travelers departing chikungunya endemic areas of the world (as defined by the U.S. Centers

for Disease Control and Prevention, [2014a]) that had final destinations in the Caribbean region (as defined by the United Nations [2014]) during the period from October to December 2012 (to assess potential origins of chikungunya virus introduction into the Caribbean in December 2013).

Next, we analyzed the final international destinations of all travelers (between May and July 2012) departing areas of the Caribbean where locally acquired cases of chikungunya have been confirmed as of May 12th, 2014 (i.e. Aruba, Anguilla, Antigua, British Virgin Islands, Dominica, Dominican Republic, French Guiana, Guadeloupe, Haiti, Martinique, St. Barthelemy, St. Kitts and Nevis, and St. Martin, Sint Maarten, St. Vincent and the Grenadines).

We then calculated the volume of travelers departing these indigenous areas of the Caribbean between May and July 2012 with and their countries of final destination. We also calculated city-level volumes of travelers with final destinations in North America. These monthly city-level travel data were mapped and overlaid with the geographic extents of *Aedes aeygpti* and *Aedes albopictus* mosquitoes across the United States (CDC, 2014b). We then determined the average monthly temperature of each state between May and July using 60 years of historical data (WeatherBase, 2014). While there are many unknowns regarding the climatic conditions necessary for *Aedes aeygpti* and *albopictus* mosquitoes to transmit chikungunya virus (Ruiz-Moreno et al., 2012), an average temperature of 20° Celsius was identified as an important threshold in the 2007 chikungunya outbreak in Italy (Charrel et al., 2008; Fischer et al., 2013; Tilston et al., 2009).

Results

While the specific origin of the Caribbean chikungunya epidemic is not precisely known, we found that five countries were the source of 84.4% of all international air travelers departing chikungunya endemic areas of the world with final destinations in the Caribbean region between the months of October and December 2012. These countries included South Africa (4,348 travelers; 23.4% of all travelers from chikungunya endemic areas of the world), India (4,012 travelers; 21.6%), China (2,561 travelers; 13.8%), Philippines (2,555 travelers; 13.7%) and the French territory of Réunion (2,218 travelers; 11.9%).

With respect to the possibility of receiving an imported case via international air travel, the final destinations of travelers departing areas of the Caribbean where locally acquired cases of chikungunya have been confirmed (as of May 12th, 2014), over the three-month period from May to July 2012 are shown in Table A6-1. Three countries represented the final destinations of 70.0% of all travelers worldwide. The United States, including Puerto Rico, had the strongest links through international air travel (1,071,658 travelers; 52.1% of the global total), followed by France (298,921 travelers; 14.5%), and the Netherlands Antilles, not including Sint Maarten (68,604 travelers; 3.3%). By comparison, ten cities represented the final destinations of 49.0% of all travelers. These included

TABLE A6-1 Leading Destination Countries for Travelers Departing Chikungunya Indigenous Areas of the Caribbean

Country	Traveler Volume*	Global Total (%)	Cumulative Total (%)
United States†	1,071,658	52.2	52.2
France	298,921	14.5	66.7
Netherland Antilles	68,604	3.3	70.0
Canada	64,736	3.2	73.2
Spain	55,329	2.7	75.9
Venezuela	42,774	2.1	78.0
Germany	36,984	1.8	79.8
United Kingdom	28,480	1.4	81.1
Italy	27,159	1.3	82.4
St. Lucia	24,102	1.2	83.6
Panama	23,576	1.2	84.8

*Between May and July 2012.
†Includes Puerto Rico.

New York (283,224 travelers; 13.8% of the global total), Paris (240,204 travelers; 11.7%), Miami (161,430 travelers; 7.8%), San Juan, Puerto Rico (80,571 travelers; 3.9%), Curacao (48,594 travelers; 2.4%), Fort Lauderdale (45,076 travelers; 2.2%), Madrid (41,286 travelers; 2.0%), Boston (40,829 travelers; 1.9%), Toronto (36,162 travelers; 1.7%), and Caracas (29,973 travelers; 1.4%).

Discussion

Global forces from climate change to surging worldwide air travel are contributing to the globalization of vector-borne diseases such as West Nile virus, dengue and chikungunya (Fischer et al., 2013; Greer et al., 2008; Sutherst, 2004; Tatem et al., 2006). In December 2013, chikungunya virus was identified for the first time in the Americas, where it has since caused over four thousand locally acquired cases across numerous Caribbean islands in addition to the South American nations of Guiana and French Guiana. While the origins of chikungunya introduction in the Caribbean are not precisely known, molecular diagnostics have determined that the strain currently circulating in the region belongs to the subtype CHIKV-JC2012 and closely resembles a strain found in China, the Philippines and Micronesia (Laniciotti and Valadere, 2014). Our analysis suggests that five chikungunya endemic countries account for the vast majority of international air travel into the Caribbean region in the months leading up to the first reported cases, with China and the Philippines accounting for 27.5% of all such travelers. However, the probability of importation into the Caribbean is a function not only of travel volumes but also of chikungunya incidence in the origin countries.

Our analyses indicate that the United States is the final destination of over half of all travelers departing chikungunya indigenous areas of the Caribbean,

followed by France, which accounts for almost 15% of all travelers. The United States has never reported local transmission of chikungunya virus, despite the presence of *Aedes aeygpti* and *albopictus* mosquitoes across the southeastern region of the country, while autochthonous transmission of chikungunya has previously been documented in southeastern France in 2010, where *Aedes albopictus* is known to exist (Vega-Rua et al., 2013). Furthermore, many North American travelers vacationing in the Caribbean will return to areas of the United States where the climate may be suitable for autochthonous transmission.

We found that New York City, Miami and San Juan are the leading U.S. destination cities of travelers from chikungunya indigenous areas of the Caribbean between May and July. Healthcare providers in these locations should familiarize themselves with the clinical presentation of chikungunya, which overlaps significantly with dengue fever. The early detection of chikungunya is particularly important in areas such as San Juan, Miami, and Charlotte where competent mosquito vectors could become infected through bites of viremic travelers (Reiskind et al., 2008). Symptomatic individuals with suspected or confirmed chikungunya infection should take special measures to avoid mosquito bites in the week following the onset of their illness (when viremia is greatest) to decrease the potential for autochthonous spread.

Although there are many unknowns about the biology of *Aedes* mosquitoes and the specific climatic conditions that would support autochthonous transmission, warmer weather is thought to shorten the interval between the time when an *Aedes* mosquito is infected by a viremic patient and when that mosquito can transmit the virus to another susceptible human host (i.e. the *extrinsic incubation period*) (Liu-Helmersson et al., 2014). Since the 2013-2014 winter season has been unseasonably cool across many parts of the United States, this could favor longer extrinsic periods, and consequently a lower probability of viral transmission from vector to human host. Although belonging to a different strain from the one currently circulating in the Caribbean, of potential concern is the chikungunya E1-A226V mutation identified during the 2005-2006 Réunion epidemic, which facilitated more efficient transmission specifically in *Aedes albopictus* mosquitoes (Schuffenecker et al., 2006; Tsetsarkin et al., 2007). This mutation was subsequently imported to Italy, and has since appeared in China and Papua New Guinea (Bordi et al., 2008; Horwood et al., 2013; Schuffenecker et al., 2006; Wu et al., 2013). However, this mutation does not appear to dominate in the major chikungunya outbreaks that occurred in India 2006-2010 (Kumar et al., 2014).

Our analysis has several important limitations. First, we are relying on accurate identification of indigenous chikungunya cases in the Caribbean region to conduct our analyses of population movements through air travel. Some countries in the Caribbean may have limited infectious disease surveillance capacity, particularly for a newly emerging pathogen such as chikungunya. Our transportation analysis was also limited to commercial air travel despite the fact that many individuals vacationing in the Caribbean may travel on cruise ships or other means of

transport. This limitation would presumably lead to an underestimate of travelers arriving in U.S. port cities that face the Caribbean islands, though the length of travel by sea may exclude them spreading disease further. Similarly, we analyzed commercial air travel data from 2012, which may not reflect forthcoming patterns of travel in 2014. While we found a highly consistent seasonal pattern of travel between the United States and chikungunya indigenous areas of the Caribbean in earlier years (analyses not shown), travel behaviors this year could be influenced by evolving news of chikungunya in the media. We also relied on accurate vector surveillance data for *Aedes aeygpti* and *albopictus* to identify areas at risk of potential autochthonous transmission. While such vector surveillance has limitations, we used contemporary data reported by the U.S. Centers for Disease Control and Prevention as of January 2014 (CDC, 2014b). Finally, the environmental factors necessary to support autochthonous transmission of chikungunya are complex and influenced not only by the type of vector, but also chikungunya virus characteristics. The climatic conditions required for efficient viral transmission are still under investigation; however, it is likely that warmer temperatures are more favorable. Therefore climatic conditions that evolve over the next several months will likely play a significant role in either hindering or supporting autochthonous transmission of chikungunya.

At a time when locally acquired cases of dengue (also transmitted by *Aedes aeygpti* and *albopictus* mosquitoes) have recently been reported in southern regions of the United States (Adalja et al., 2012; Bouri et al., 2012; Effler et al., 2005; Radke et al., 2012; Ramos et al., 2008), our findings highlight the risk for introduction and potential autochthonous transmission of chikungunya virus in selected areas of the country. The effectiveness and efficiency of interventions to mitigate these risks could be optimized through a combination of public education, early detection by medical providers, and the strategic use of public health resources in areas of greatest risk.

Author Contributions

Kamran Khan and Isaac Bogoch jointly developed the design of the study, oversaw the completion of all analyses, and produced the first draft of the manuscript. Jennifer Miniota, Wei Hu, and Adrian Nicolucci conducted reviews of the literature, performed all transportation and spatial analyses, created figures and cartograms, and edited the final version of the manuscript. John Brownstein contributed epidemiological data pertaining to chikungunya in the Caribbean and made significant content contributions and edits to the final manuscript. Marisa Creatore, Martin Cetron and Annelies Wilder-Smith made significant content contributions to the initial draft of the manuscript and edits to the final draft of the manuscript.

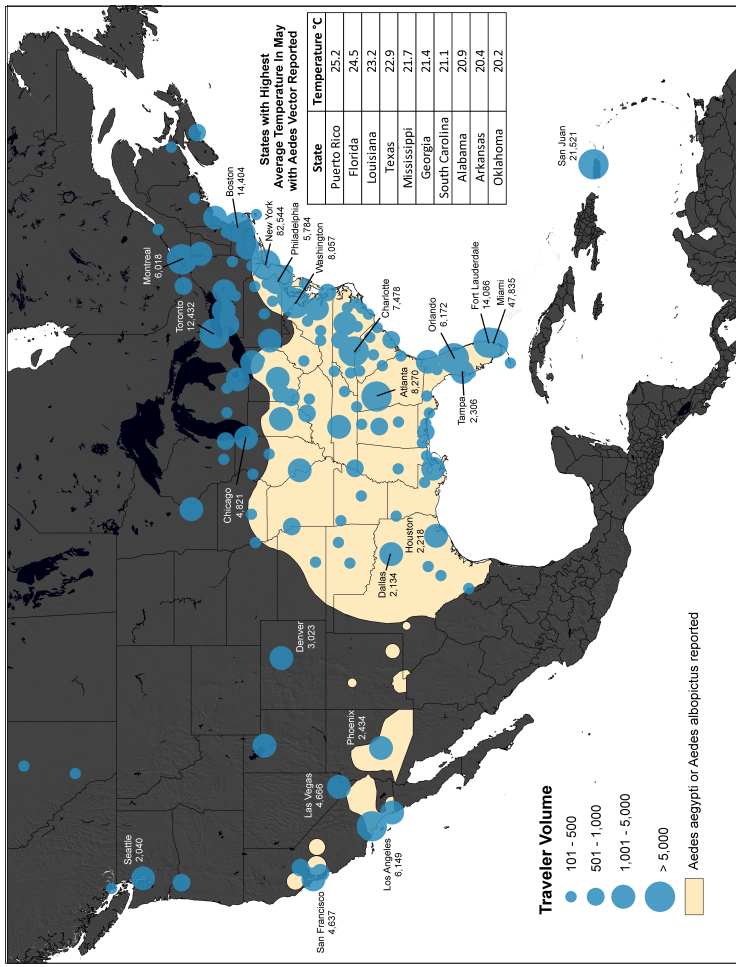

FIGURE A6-1 Volume of travelers from chikungunya indigenous areas of the Caribbean* to the United States and Canada in May†.
*As of May 12th 2014.
†Using historic air travel data from May 2012.

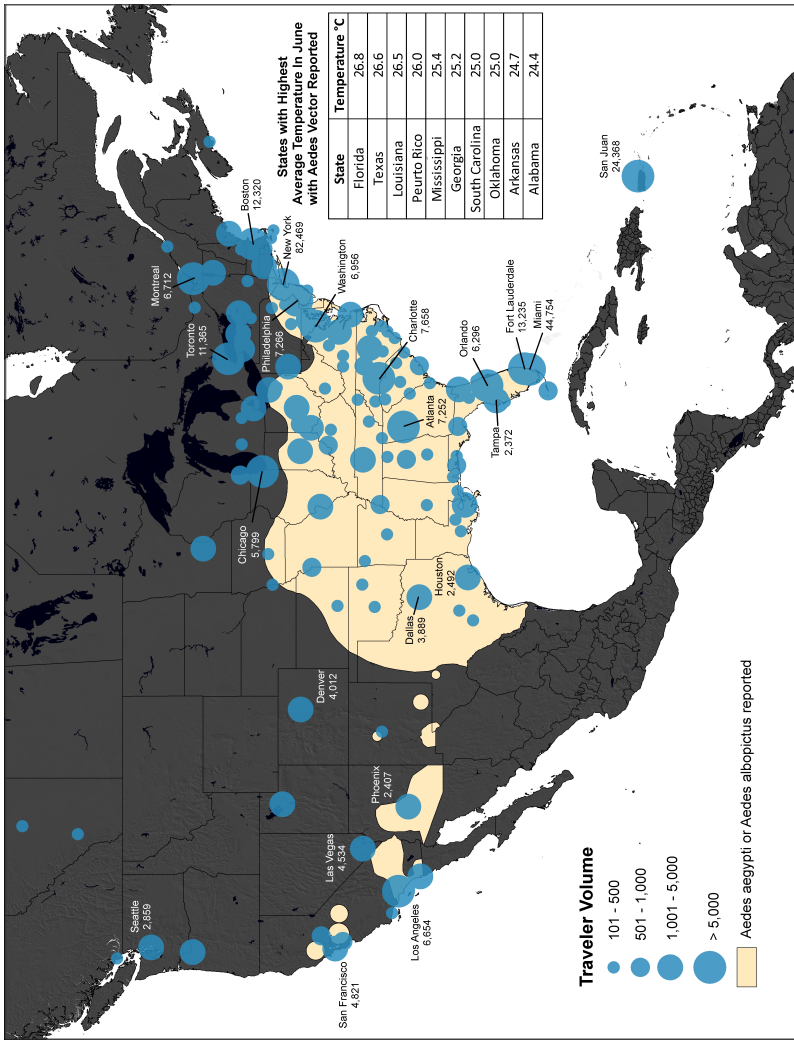

FIGURE A6-2 Volume of travelers from chikungunya indigenous areas of the Caribbean* to the United States and Canada in June†.
*As of May 12th 2014,
†Using historic air travel data from June 2012.

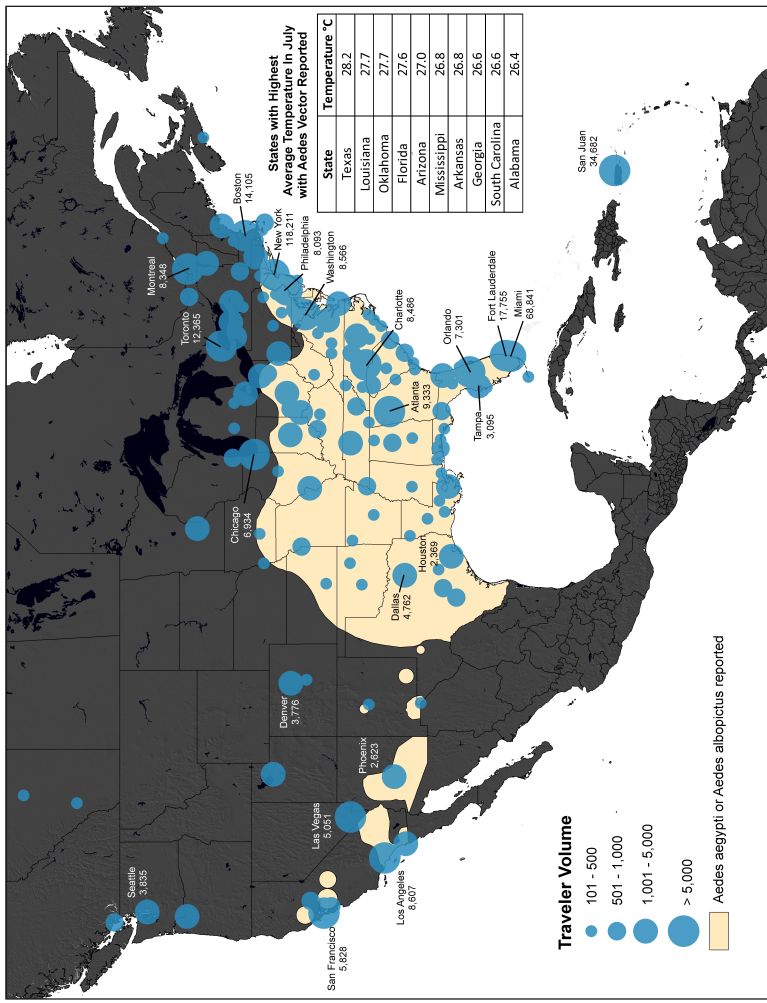

FIGURE A6-3 Volume of travelers from chikungunya indigenous areas of the Caribbean* to the United States and Canada in July†.
*As of May 12th 2014.
†Using historic air travel data from July 2012.

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A7

EIGHT CRITICAL QUESTIONS FOR PANDEMIC PREDICTION

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Introduction

Like hurricanes or earthquakes, pandemics are rare events that can be extremely devastating, causing substantial mortality and economic damages. However, unlike hurricanes or earthquakes, efforts to identify where pandemics are most likely to originate, and to intervene and preempt their impact, are in their nascence. Here, we review recent advances in disease ecology, virology, and biogeography that move the field towards these goals and pose a series of critical questions that must be addressed to sufficiently improve our predictive capacity. This provides a framework for pandemic prediction that may allow us to better allocate our global resources to mitigate this threat.

Because the majority of recent pandemics are zoonotic in origin, most involving wildlife reservoirs, we consider this group specifically. The emergence of pandemic zoonoses reflects a complex interplay of socioeconomic, ecological, and biological factors and can be thought of as a three-stage process (Morse et al., 2012). Initially, pathogens with pandemic potential exist only in their natural reservoirs. In the first stage, *pre-emergence*, our encroachment into a reservoir's natural habitat, often related to changing land use, may bring these pathogens into contact with livestock or humans or otherwise alter the ecological system in which it and its host exist. In the second stage, *localized emergence*, initial transmission to humans occurs, directly from a wildlife host or via domesticated animals. Some of these events may involve small chains of person-to-person transmission. When a pathogen achieves sustained person-to-person transmission, the right confluence of circumstances can lead to *pandemic emergence*, ultimately with large outbreaks propelled internationally by the movement of people and disease vectors.

Each of these stages is itself driven by a plethora of socioeconomic, ecological, and biological factors (e.g., change in land use, migration, agricultural intensification) that alter pathogen dynamics and expose human populations to increasing risk of zoonotic disease emergence, amplification, and spread. It follows that to predict and pre-empt pandemics, we must improve our understanding of how these factors drive increased risk of each stage of the pandemic process (Morse et al., 2012). The complexity of these processes is daunting, but the interplay of ecology, demography, virology, and biology provides a wide range of new tools and approaches that can be used in pandemic prediction and prevention.

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These include strategies to analyze prior outbreaks, model future trends in pandemic drivers, conduct targeted surveillance in wildlife and human populations, and probe the depth of the zoonotic "pool" from which novel EIDs arise. Here we review some of these by posing eight critical questions for pandemic prediction.

Eight Critical Questions for Pandemic Prediction

Are Emerging Infectious Diseases (EIDs) Really on the Rise?

The literature on emerging infectious diseases, and concern among policy makers and the public, has grown substantially in recent years (IOM, 1992, 2003). Does this reflect a public health threat that is also growing, or is this trend driven by increased surveillance, or simply better reporting of outbreaks as they occur? To test this, we expanded and updated a database of all known emerging infectious disease, first collated by Mark Woolhouse's group (Taylor et al., 2001). We focused on "EID events," which we defined as "the first temporal emergence of a pathogen in a human population . . . related to the increase in distribution, increase in incidence or increase in virulence or other factor which led to that pathogen being classed as an emerging disease" (Jones et al., 2008). For each event, we collected data on location, time, and host and/or vector, as well as on associated ecological, biological, and sociodemographic drivers of disease emergence, and performed a number of temporal and spatial regression analyses.

Our analyses showed that the number of EID events has increased over time, peaking in the 1980–1990 decade. This peak was associated with increased susceptibility to infection due to the HIV/AIDS pandemic. Like Taylor et al. (2001), we found that zoonoses comprised the majority of EID events (60.3 percent), and that almost 71.8 percent of zoonotic EIDs were from wildlife (43.3 percent of all EID events). Furthermore, zoonoses from wildlife were increasing as a proportion of all EID events—in the last decade analyzed (1990–2000), 52.0 percent of EID events were zoonoses with known a wildlife origin. We attempted to correct for increasing infectious disease reporting effort over time by including in our regression model the number of articles published in the *Journal of Infectious Diseases* (which gives a crude measure of research effort for infectious diseases generally, not just EIDs) for each decade as an offset. Controlling for reporting effort gave further support to the conclusions that EID events are becoming more common, that zoonoses comprise the majority of EID events, and that zoonoses are rising significantly faster as a proportion of all EID events.

Are There Predictable Patterns to Disease Emergence?

The first step in predicting a biological phenomenon is to look for patterns that underlie previous events. This approach underpins hurricane forecasting and the identification of earthquake zones, and is a logical strategy for pandemic

prediction. Both hurricane forecasting and the identification of earthquake zones look to the underlying drivers of these phenomena to identify patterns. We used a similar approach for disease emergence, focusing on the hypothesized drivers of zoonotic disease emergence. We assigned geographic coordinates to EID events and, using a logistic regression, tested associations between subsets of EID events and a small selection of hypothesized drivers. We found that drug-resistant and vector-borne pathogens, and zoonoses with wildlife and non-wildlife origins, differed in their global patterning and in their associations with different drivers. In particular, all categories of EID events were strongly associated with human population density, which we have suggested ". . . supports previous hypotheses that disease emergence is largely a product of anthropogenic and demographic changes. . . ." Human population growth—taken as a broad proxy for change in socio-economic factors—predicts zoonoses from non-wildlife and the emergence of drug-resistant pathogens. However, zoonoses from wildlife are alone in their association with wildlife host species richness—patterns of wildlife diversity. The overall predicted risk from different categories was differentially distributed across the globe. For instance, wildlife zoonoses and vector-borne pathogens were more likely to have originated in lower-latitude, developing countries (Jones et al., 2008) (Figure A7-1). Describing these patterns provides the first step towards pandemic prediction: predictive models exist of future trends in socio-economic and demographic drivers, and may be used to derive predictive models of the future trends in disease emergence.

The analyses of Jones et al. (2008) show that EID emergence is driven by socioeconomic as well as biological factors, but they are somewhat preliminary, and substantial gaps remain. For example, what aspects of human population density drive disease emergence? Is it anthropogenic environmental changes (e.g., road building, deforestation, land use change)? Is it increased contact with wildlife, or the perturbation of pathogen transmission dynamics in wildlife? Or do dense human populations simply provide an "amplification zone" that allows more frequent recognition of new EIDs otherwise lost to our analyses? Efforts to tease apart the mechanisms underlying these patterns will involve ecological, virological, and biological disciplines collaborating in exciting new ways (Murray and Daszak, 2013). Finally, it is interesting to note that the Jones et al. (2008) models leave 85 percent of the variation in global patterns of disease emergence unexplained. This emphasizes the magnitude of the problem, sets the bar for future studies, and highlights that efforts to gradually improve the model's power need to be prioritized if we are to accurately predict the next pandemic.

Where Will the Next Pandemic Originate?

There are significant geopolitical and logistical constraints to pandemic prevention. Newly emerged pathogens often originate in remote areas that are difficult to access, and in resource-constrained countries that cannot afford to

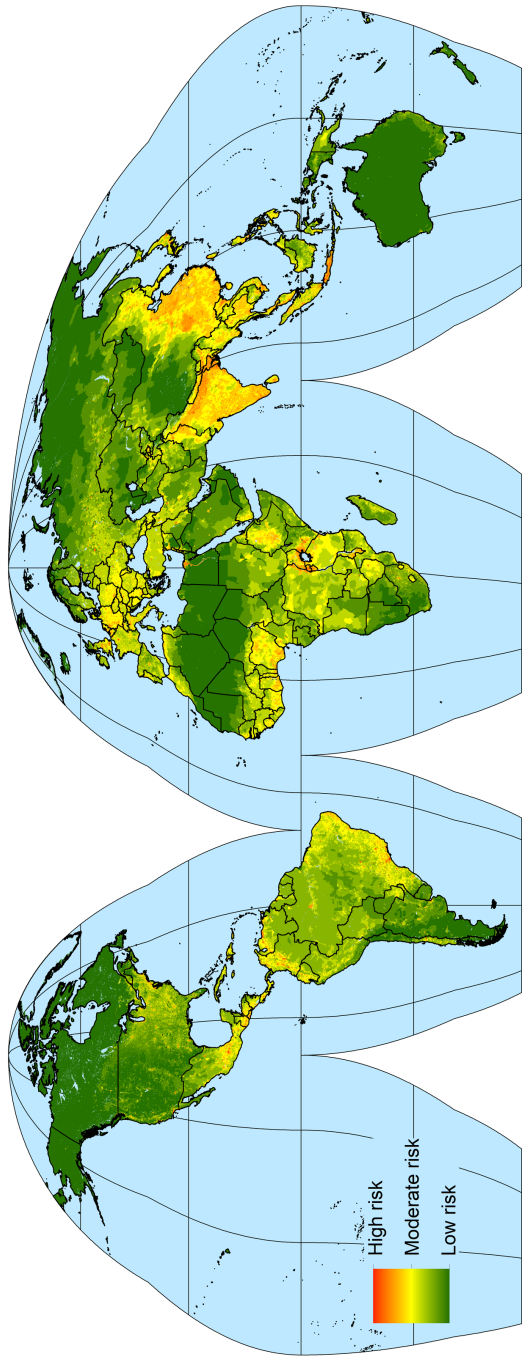

FIGURE A7-1 Map of relative risk of a zoonotic disease of wildlife origin emerging in people. Because almost all prior pandemics, and the majority of emerging infectious diseases, are zoonotic in origin, with the majority of these having a wildlife host, this map acts as a potential basis for future targeted surveillance and the pre-empting of potential pandemics.

systematically identify novel pathogens in their early stages of emergence. Once emerging diseases become pandemic, the large number of cases and wide geographic distribution make response programs costly and complicated by geopolitical issues. Given the finite global capacity for pandemic preparedness, and a limited global budget, can we reconfigure where our resources are spent, based on a scientific understanding of where novel diseases emerge and where our current effort is lacking in relation?

To this end, our previous "EID hotspots" analysis attempts to correct for bias caused by this unequal distribution of surveillance resources and to make recommendations about where surveillance should be increased in response to predicted disease emergence risk. We can draw two conclusions from this work. First, reporting effort significantly influences where we observe EID events. This implies that EID events of a similar scale are occurring, unobserved, in locations with weaker disease reporting infrastructure. Second, reporting infrastructure is stronger in developed countries, in northern latitudes, whereas wildlife zoonoses more commonly emerge in lower latitudes, in countries with weaker reporting effort. The implications are that our resources to rapidly identify novel EIDs poorly match their likely occurrence, and that this can be remedied by improving infrastructure in EID hotspot developing countries to identify pathogens spilling over from wildlife into people.

It is important to note that our analysis, while suggestive, is preliminary. Reporting effort is likely more collinear with population density than a country-level measure can show, and the *Journal of Infectious Diseases* may not be the most accurate measure of where infectious disease reporting is strongest. Constructing higher-fidelity maps of infectious disease reporting effort would allow us to better correct for the lens through which we view disease emergence and identify areas with the greatest need for increased surveillance. Furthermore, the EID hotspot maps are relevant only at large spatial scales. New approaches are needed to identify where, within a region, country, or landscape, the highest risk of a new disease originating exists. One approach is to conduct targeted surveillance efforts at specific wildlife–human interfaces such as people living in remote villages close to forests in EID hotspots, or people engaged in hunting bushmeat, producing livestock, selling live animals in markets, or butchering them in abattoirs or restaurants. Better analysis of the spatial distribution and relative risk of these interfaces is likely to be a productive research line. Finally, with the growing availability of "big data," increasing ease by which it can be manipulated and analyzed, and new models that predict future trends in the underlying drivers of EIDs, hotspot models will become more rigorous, accurate, and based on concrete hypotheses about biological mechanisms.

How Many Unknown Pathogens Are There?

The perfect pandemic prevention program would prevent spillover of pathogens from wildlife to human hosts before they have the opportunity of infecting

people, amplifying their transmission, and becoming pandemic. This approach is theoretically possible. If we target surveillance of *wildlife* to EID hotspot countries and conduct pathogen discovery in these species, we can identify pathogens with pandemic potential before they emerge and target prevention efforts to block their spillover. This is the basis for a number of new programs, including the USAID Emerging Pandemic Threat (EPT) program (Morse et al., 2012) and research programs that target pathogen discovery in bats and other zoonotic disease reservoirs (Drexler et al., 2012; Marsh et al., 2012; Wacharapluesadee et al., 2013).

However, even when we have narrowed down interfaces and locales of interest, two significant challenges remain. Firstly, the diversity of unknown pathogens may be so high that it is not cost effective to identify them all. Indeed, until recently there was no systematic attempt to predict the unknown viral diversity in any single species, let alone all wildlife. Using samples collected and tested through the USAID EPT PREDICT program, we have recently published the first attempt at a strategy to estimate unknown viral diversity. We did this using incidence-based species richness estimators, which have their origin in the "mark-recapture" modeling approach used by conservation biologists to estimate the density of rare animals in a patch of land. In this method, animals are captured, tagged, and released, and the number of recaptures of tagged individuals relative to the number of untagged individuals gives a way to statistically predict the total number of individuals in a region. For pathogen discovery, we repeatedly sampled a large population of *Pteropus giganteus*, a bat species known to carry zoonotic viruses, collecting high-quality samples from around 2,000 unique individual bats. We then used degenerate viral family-level primers (12,793 separate consensus PCR assays) to discover 55 viruses from nine viral families known to harbor zoonoses (Anthony et al., 2013). We then used statistical approaches to estimate the total viral richness of these nine families in this single species. Our analysis suggests that this bat species harbors 58 viruses (i.e., 3 not yet discovered) in these viral families, and if this is extrapolated simplistically to all 5,517 known mammal species, we estimate that there are at least 320,000 mammalian viruses awaiting discovery in these nine viral families. This is a large number, but using the PREDICT program costs of field and lab work, we estimate the cost to uncover 100 percent of virodiversity in this critical group of wildlife reservoirs to be $6.8 billion, and to uncover 85 percent of virodiversity to be only $1.4 billion, considering the exponentially diminishing returns of continued sampling. The latter figure is less than the cost of a single SARS-scale pandemic and, if spread over a decade, a small portion of current global pandemic prevention spending.

Which Wildlife Species Harbor the Next Pandemic Pathogen?

The second challenge to wildlife pathogen discovery as a pandemic prevention strategy is knowing which wildlife are the highest-risk reservoirs (i.e., which species to sample so that we can maximize the discovery of pathogens

with zoonotic, and pandemic, potential). Species differ in the composition of their viral diversity and in the propensity of those pathogens to infect people, but the genetic, behavioral, and ecological rules that underpin these relationships are poorly understood (Bogich et al., 2012b). A recent analysis of the literature found that sampling effort, IUCN threat status, and population genetic structure of bat species were the best predictors of how many viral species they harbored, independent of their phylogenetic relationships (Turmelle and Olival, 2009). Among mammal groups, rodents and bats host a particularly large number of zoonotic pathogens: Rodents have a larger diversity, while bats host more per species (Luis et al., 2013). Within bat and rodent species, those with greater sympatry (range overlap) with other related species host more viral diversity, and bats with smaller litters, greater longevity, and more litters per year tended to host more zoonoses. These are tantalizing glimpses of ecological and evolutionary patterns that likely drive viral speciation and zoonotic risk, and may ultimately inform which species we target for viral discovery. However, there is much more to learn. For example, a logical assumption is that viruses are more able to infect more closely related species, due to the sharing of host cell receptors, for example. Thus, mammals are the source of the majority of zoonotic EIDs (Jones et al., 2008; Taylor et al., 2001) and across all mammal-virus associations, more closely related mammals are more likely to share virus species (Bogich et al., 2012b). However, when two unrelated species have extensive, intimate contact over long periods of time (e.g., humans and domesticated mammals), does this phylogenetic rule still hold? If we continue to expand the wildlife trade, bringing more diverse animals from different regions into close contact with people, will we see pathogens emerging that would normally have difficulty successfully infecting humans?

Can We Predict the Pandemic Potential of a Newly Discovered Pathogen?

With targeted improvements in public health infrastructure and surveillance for pathogen discovery, we can increase our odds of catching a zoonotic outbreak in its nascence or discovering novel pathogens of pandemic potential. But will we be able to identify which ones, out of the hundreds of thousands of new species of virus to be discovered in wildlife, will be able to infect humans? With most of these potential zoonoses being identified by only a short RNA or DNA sequence, is there a logical strategy to identify their potential pandemicity? Identifying which novel pathogens in a wildlife species are most likely able to infect, replicate in, cause cycles of human-to-human infection, and then amplify into pandemics remains one of the biggest challenges to pandemic prevention.

Morse et al. (2012) reviewed some of the known factors that affect whether a particular virus can infect a species and what gaps remain. In some pathogens, receptor specificity and other biological characteristics may be used to predict host range and potential pathogenicity to humans. However, animal models, human cell cultures, and similar methods cannot empirically validate a pathogen's

capacity to infect humans. Some characteristics that may yield improvements in our predictive ability include the effects of host relatedness, relatedness of a virus to known human viruses, host range and evolutionary capacity, and predictive capacity of virulence in humans (some pathogens can infect humans but cause no disease, whereas others cause severe illness) (Morse et al., 2012). As we work towards a better understanding of these factors, we can use a few simple heuristics to prioritize certain pathogens. Certainly, if a pathogen exists at a zoonotic interface, and if there has been documented human infection, it should be prioritized. Pathogens that cause small chains of human-to-human infection with a basic reproductive number (R_0) approaching or higher than 1 should be considered "prime epidemics in waiting," as small evolutionary changes could boost their transmissibility and enable them to cause epidemics.

In fact, though none of the models outlined above can tell us exactly how dangerous a pathogen is, they all contribute valuable information to a risk assessment. Whether a pathogen exists at an interface of interest, how closely related it is to known human pathogens, how closely related to humans its reservoir host is, and various viral traits all convey information about a particular pathogen. Future work may involve testing the zoonotic potential of wildlife pathogens by sequencing receptor binding domains, producing pseudo-type viruses with these proteins expressed, and conducting binding assays, *in vitro* culture assays, and ultimately animal infections with transgenic animals that express human cell surface receptors. This work has already shown the capacity to identify high-priority potential zoonoses for SARS-like viruses in bats, which bind to human, civet, and bat ACE2 (Ge et al., 2013).

Can We Predict How, and to Where, a New EID Will Spread?

The emergence of triple reassortant A/H1N1 influenza in 2009 highlighted how rapidly diseases can spread once they have achieved capacity for effective human-to-human transmission. Targeting these diseases may be effective if we can accurately predict their likely pattern of spread out of a region and strategically allocate resources to respond. Analyses of travel and trade data have shown that predicting spread is relatively straightforward and can provide accurate estimates of spread and case numbers when applied to prior outbreaks (e.g., of SARS (Hufnagel et al., 2004) and A/H1N1 influenza (Hosseini et al., 2010)). This approach has been used to analyze recent historical spread of vectors through shipping trade, and their likely routes of spread via air travel (Tatem, 2009; Tatem et al., 2006a,b). It has also been used to predict the spread of ongoing emergence events such as the MERS-CoV outbreak in Saudi Arabia (Khan et al., 2010). It has particular relevance in zoonotic disease spread when patterns of wildlife migration and trade are implicated, and where policy can be rapidly set to prevent importation. This approach has been used to examine the likely cause of past spreading events for A/H5N1 influenza and to predict and set policy for its likely

route of introduction to the New World (Kilpatrick et al., 2006a). Finally, it has been used effectively in Hawaii and the Galapagos Islands to allocate resources to reduce the risk of West Nile virus introduction via the most likely pathway of mosquitoes transported via air travel (Kilpatrick, 2011; Kilpatrick et al., 2004, 2006b). As in all predictive models, their rigor improves as the quality of data on travel and trade pathways and volumes, on biological characteristics of pathogen and host, and on the human contact networks that allow transmission also improves. For example, the capacity and willingness of countries to identify and report outbreaks early are critical to make accurate predictions about spread, once a pandemic has begun. Analyses of the spread of the 2009 H1N1 influenza showed that two key factors influenced the pandemic's arrival time—a country's global accessibility through air travel, and the percentage of GDP per capita spent on health care (a proxy for testing and reporting capacity) (Hosseini et al., 2010). Again, gaps in this approach remain, including the need for a better understanding of the role of intra-country human movement in disease spread. Newly available datasets on road infrastructure, migration, and human network connectivity will increasingly illuminate this area.

Can We Eventually Stop Pandemics from Emerging?

The new approaches described above to identifying novel pathogens in emerging disease hotspots, and predicting their pandemic potential and likely spread, have likely improved our global pandemic preparedness. But what progress has been made in using this approach to prevent pandemics? One significant shift is in the way pandemic prevention programs are funded and managed. Traditionally, outbreak threats were dealt with by state and national agencies, the World Health Organization, and field laboratory networks funded through these programs. The emergence of H5N1 influenza via small-scale outbreaks, which suggested chronic persistence in backyard poultry farms, led to calls for a "systems approach" to the pandemic prevention (Bogich et al., 2012a), and a cross-sectorial "One Health" collaboration of animal health, public health, and environmental agencies (FAO et al., 2008; Karesh, 2009; Zinsstag et al., 2011). International development agencies, which had been trending towards specialized programs to target specific infectious diseases, are now actively involved in this systems approach to pandemic prevention. This involves funding for crucial infrastructure investments required for pandemic prevention, and a specific focus on collaborative One Health programs (Bogich et al., 2012a). With most EID events occurring in regions that are under-resourced in public health capacities, disease-based programs for AIDS, malaria, TB, and polio do not address the underlying flaws in public health systems that predispose locations to outbreaks of emerging infectious diseases (Standley and Bogich, 2013).

Standley and Bogich (2013) propose an "ecohealth" approach, addressing destructive land use change and biodiversity loss in places like China, Brazil, and India. This approach defines how we can deal with pandemics as distinct

from dealing with hurricanes or earthquakes: by identifying and mitigating the underlying causes, particularly anthropogenic activities that promote pathogen spillover, amplification, and spread. Strategies include programs that educate and promote alternatives to high pandemic risk behavior like the trading, butchering, and consumption of wild animals, or the comingling of livestock and wildlife on farms. They also include more fundamental approaches that address large-scale anthropogenic changes. For example, 43 percent of past EID events are attributable to land use change and agricultural changes, including extractive industries (timber/logging, oil and gas, mining, and plantations). The economic impact of EIDs from land use change is estimated to be $10–40 billion over the next 10 years, which could be considered a potential liability to extractive industries. Industrialized mining and plantation operations in EID hotspot countries are likely to be on the front line of disease outbreaks, and are often under pressure to improve their environmental impacts. Programs that better quantify the risk of novel pathogens to these industries, and the economic damages they might entail, may become valuable in mitigating their impact on global health, conservation, and the environment (Murray and Daszak, 2013).

The two-fold approach of treating emerging pandemics as targets for international development programs and as byproducts of economic activity is relatively new and suggests that long-term solutions to their emergence can be found. A future without pandemics may be possible, but only with the very best interdisciplinary science, ambitious approaches to risk prediction, and bold strategies taken by industry and development agencies to ensure against them.

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A8

MISCONCEPTIONS AND EMERGING PATHOGENS: WHAT CAN MATHEMATICAL MODELS TELL US?

Andrew ***Dobson***[25]

The last 25 years have seen a renaissance in the use of mathematical models in epidemiology; much of this is largely due to the influence of Anderson and May and their colleagues (Anderson and May, 1992; Grenfell and Dobson, 1994, 1995). The transformation came about as the models they developed were based upon empirical assumptions. This allowed the whole discipline to move from an overt fascination with mathematical elegance, to embrace data and become the pragmatic powerhouse that is at the center of quantitative insight to any modern epidemiological problem. At first glance, this creates problems for the use of these models in studies of emerging diseases, as almost by definition, there will be no data prior to emergence. Nonetheless, all of the recent major studies of disease emergence have quickly led to the almost obligatory use of mathematical models in infectious disease biology. A nice index of this was the chance remark by the editor of one major journal during a recent influenza outbreak, "Half the world is worried about this new pathogen—while we're facing an epidemic of submitted papers, all claiming to have produced the definitive predictive model for it!"

In this short overview, I will take a brief personal and idiosyncratic review of the key ways in which mathematical models have been used, misused, or could potentially be used to provide insights into the dynamics of emerging pathogens. I will offer no specific recommendations or recipes for the "best way" to use models to understand pathogen emergence. This is partly because different model structures will provide different insights to different pathogens; moreover, each new emergence usually leads to the development of new mathematical tricks, techniques, and approaches that

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provide powerful new tools for the current crisis and often retrospective insights into older emergences.

Dynamics of Initial Cross-Over

A huge number of pathogens are circulating in all free-living species of animals and plants. One of the most profound testimonies to the shortsightedness of scientific exploration is that we know neither how many other species share the planet with us, nor how many are pathogens or parasites of the more apparent and better classified free-living species (Dobson et al., 2008). The most conservative estimate is that 50 percent of species are parasitic, but it could be significantly higher, potentially larger than 90 percent. Although a huge number of pathogens could potentially colonize humans (or domestic livestock and crops), only a relatively small proportion seem to have done so. Although searching for "the next pandemic virus" has achieved the momentum of a well-oiled government job-creation scheme (a curious European phenomenon that may be unfamiliar to USA readers!), I suspect that a large proportion of pathogens that might jump the species barrier to humans may already have attempted this leap and have failed the test. The simple logic here is humans have explored most of the terrestrial parts of the planet and exposed themselves to a multitude of insect bites, scratches by plants, and samplings of local cuisine; this suggests there are very few pathogens that one of us has not yet been exposed to. Yet it would be foolish to be apathetic. A pathogen that failed to establish in the past might get a second chance in the future if the host it contacts has different susceptibility and moves further or contacts more people while infectious. Conservatively, there are likely to be a couple hundred other pathogens out there that could create a new pandemic, but our attempts to locate them on virological fishing expeditions do a poor job of differentiating between exotic minnows and efficient pike. So my principle focus here will be to assemble the known structures of a mathematical framework that needs to be applied if we are to quantify zoonotic disease emergence of a pathogen and our immediate response to it.

A recent review explains the mathematical logic of epidemic dynamics at the human–animal interface (Lloyd-Smith et al., 2009). The classification of epidemic potential is based on the relative magnitude of R_0, the basic reproductive number of the pathogen, or more formally the number of secondary cases that an initial infected individual creates in a wholly susceptible population, before "case zero" either recovers or succumbs to infection. Lloyd-Smith et al. base their classification on an earlier review by Wolfe et al. (2007) that classified pathogens along a five-point spectrum with those that are exclusive to wildlife as type I, while those that are exclusive to humans as type V. Most zoonotic pathogens can be arranged along the spectrum from II to IV based upon their affinity for sustained transmission in the novel human hosts and the associated pathology. Type II pathogens are those that can cause primary infections in humans, but humans

are unable to transmit the pathogen on to other humans; classic examples would be *Brucella abortus* and West Nile virus. Type III pathogens occur when the primary infections are able to infect a number of secondary hosts, but these stuttering chains of transmission quickly fade out. Classic examples here would be Nipah and Hendra virus that are endemic in Pteropid fruit bats, and humans either acquire infection either directly or indirectly from livestock (pigs and horse,s respectively) (Plowright et al., 2011; Pulliam et al., 2011). The most worrying type of zoonotic disease is that in type IV, where the primary infection can give rise to self-sustaining chains of infection. Classic examples here are plague (*Yersinia pestis*) and pandemic influenza. Lloyd-Smith et al. (2009) point out that each level of classification corresponds to a different range of values of R_0; thus type IV (and V) will have $R_0 > 1$, type III will have $R_0 < 1$, and type II, $R_0 = 0$. All of this has made estimation of R_0 a central part of any emerging disease outbreak.

Before briefly considering ways in which R_0 might be measured, it is worth noting that the vast majority of pathogens will be type I. There will then be a smaller number of type II, even less of type III, and so on. This does suggest a future and potentially more focused line of inquiry for virus hunters. Is there any underlying taxonomic signal in the R_0 values for zoonotic pathogens? Are there some families of viruses with high proportions of type III and type IV zoonotic pathogens, and are the relative proportions of these different types of pathogen similar or very different in different taxa of viruses, bacteria, fungi, and so on? Putting together a database to address these questions might well provide a more quantitative framework of where to look for potential future pandemic pathogens. It should also provide important background information on how hosts infected with similar pathogens have been diagnosed and treated. All of this assumes a significant degree of phylogenetic inertia in the ways in which the pathology of taxonomically similar pathogens are expressed.

R_0 or Not?

Most mathematical models for emergent disease start with the development of an expression for R_0, the basic reproductive number of the disease. It played a central role in the development of the initial response to the SARS epidemic (Dye and Gay, 2003; Lipsitch et al., 2003; McLean et al., 2005). There is a significant volume of mathematical literature on R_0 and many examples of the use of this concept (Diekmann and Heesterbeek, 2000; Diekmann et al., 1990). Most mathematical epidemiologists were delighted that R_0 played a central role in the movie *Pandemic*, and it was a testimony to the elegance of the concept that it resonated well with audiences.

There are two approaches to estimating R_0: one is classified by the publication feeding frenzy that follows the appearance of data describing the course of an epidemic outbreak; a range of increasingly sophisticated statistical methods are used here, and they increasingly prove central to guiding the public health

response. The second approach involves deriving algebraic expressions for R_0 in the absence of any epidemiological data. These "mathods" are potentially highly informative for identifying the weakest links in the transmission cycle and then determining methods of control that can break these weak links in the chain of transmission.

The simple threshold condition ($R_0 > 1$) is useful for defining the absolute conditions for whether a pathogen will establish, while also pointing towards the level of control needed to contain an outbreak. Nonetheless, there are some important clarifications about the magnitude of R_0 that strongly determine what happens once an outbreak begins to take off. The first of these insights deals with the relationship between the magnitude of R_0 and persistence time of the epidemic. If R_0 is significantly larger than 1, anywhere above 4, and host population is relatively restricted, then the epidemic may rise quickly, but will concomitantly run out of new susceptible host, and the epidemic will quickly burn itself out as chains of transmission are broken. This consistently happens with measles in small towns and villages (Keeling and Grenfell, 1997) and with Ebola and Nipah virus outbreaks. In contrast, when R_0 is a little bit larger than unity, but less than 2, then outbreaks can persist for longer. An interesting example of this is illustrated in theoretical work recreating distemper outbreaks in different carnivore species in Serengeti National Park (Craft et al., 2008). Species such as jackals with large populations exhibit sharp epidemics of short durations; in contrast, outbreaks persist for much longer in hosts with lower abundance, particularly if they are split into relatively isolated social groups (such as lions). The pathogen then causes an outbreak in each social group, but then more slowly jumps between social groups, or between species, and despite having a lower R_0, persists for much longer. The first (and most eloquent) demonstration of this is found in the work of Swinton and colleagues on the outbreaks of distemper in seal population in the North Sea (Swinton, 1998; Swinton et al., 1998). Theoretical models for persistence sharply illustrated that persistence time increases hugely as populations are subdivided into social groups whose rate of contact is always lower than rates of contact within group (Figure A8-1). This effectively lowers R_0 for populations of identical size, but hugely increases pathogen persistence.

Anderson and May proposed that this sort of mechanism was likely central to the initial emergence of HIV with the virus entering the human population in small, weakly coupled villages in Africa, none of which could support a sustained outbreak, but each of which was weakly coupled to an unexposed village that could keep the chain of infection intact (Anderson and May, 1986). Eventually the pathogen was passed into hosts who had contact with much larger and more actively interacting community, and the epidemic was detected in the United States and other Western countries. The epidemic of AIDs that emerged in the 1980s in major Western cities contrasts sharply with the previous half century of HIV in rural Africa, where dynamics were most likely characterized by low

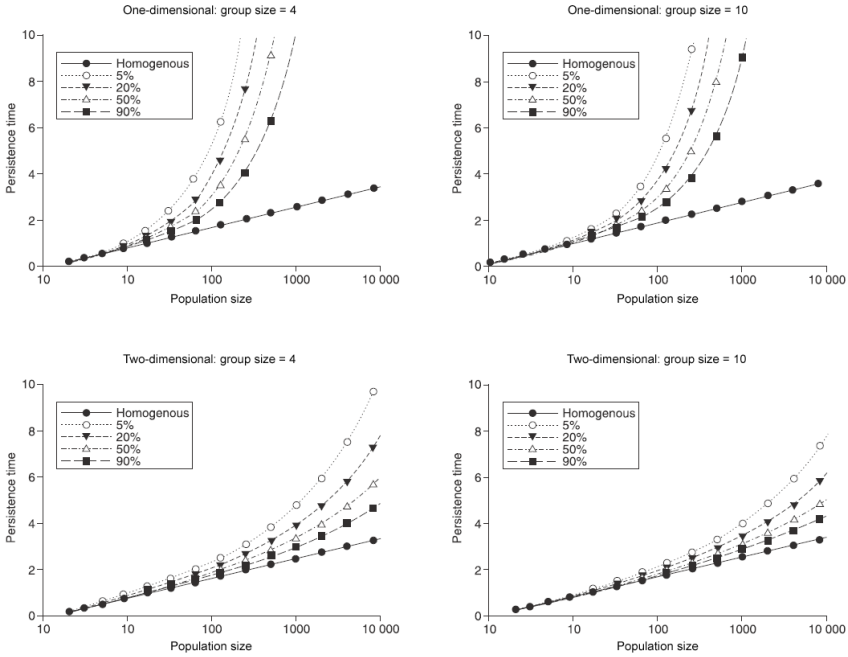

FIGURE A8-1 The expected persistence time of a pathogen that infects its hosts for 2 weeks and is infectious for the second of those weeks in populations of different sizes. The four different graphs compare populations that are divided into social groups of different sizes (left GS = 4; right GS = 10); the different lines compare persistence in a well-mixed population with no groups with ones where the rate of between-group contacts is 5 percent, 20 percent, 50 percent, and 90 percent of the rate of within-group contacts. The upper two graphs are for groups arranged in a linear sequence (along a coastline) and that only contact the groups on either side of them; in the bottom two figures the groups tessellate a plane, so each group is in contact with at least four other groups
SOURCES: McCallum and Dobson, 2006; Swinton, 1998. Reprinted with permission of Cambridge University Press.

R_0 slowly moving the pathogen through a sequence of weakly connected and relatively isolated villages somewhere in the forests of central Africa.

A related effect that operates in a similar fashion has been proposed by Pulliam and colleagues (Pulliam et al., 2007, 2011). They observe that many immunity-inducing pathogens may facilitate emergence by initially creating an outbreak that creates an intermediate level of herd immunity in the novel host population that reduces the pool of susceptible hosts to a level where a second crossing over of the pathogen from the reservoir creates an outbreak with an R_0 closer to unity, and thus one that will persist for longer and be more able to spread

to the new population. They suggest this was a dominant factor in the emergence of Nipah virus in Malaysia and show that many other pathogens have epidemic demography that would also allow them to establish in this fashion (Pulliam et al., 2007). When they plot the transmission and virulence parameters of a number of pathogens into a graph that determines emergence potential they find that many emergent pathogens have these characteristics (Figure A8-2).

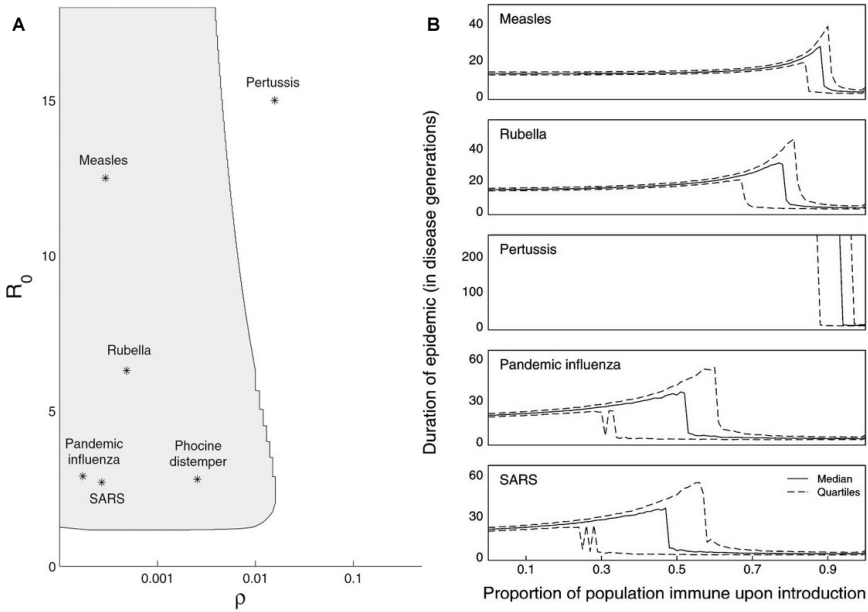

FIGURE A8-2 (A) Deterministic prediction of the parameter ranges where epidemic enhancement may be observed. The range of parameter values (grey) for a population size of N = 50,000 and the initial condition $(S_0, I_0) = (N - 1, 1)$ which demonstrate the behavior of an initial epidemic which dies out (there exists $t > 0$ such that $I_t < 1$) followed by persistence upon reintroduction ($I^* > 1$), depending on the level of population turnover between pathogen extinction and reintroduction. R_0 is the basic reproductive number of the pathogen in a naïve host population; ρ is the duration of infectiousness relative to the average duration of immunity. Stars represent parameter values taken from the literature for a variety of common and emerging infectious diseases. Note that the x-axis is shown on a log scale. (B) Enhancement of epidemic duration for diseases in human populations. Epidemic duration in a population of N = 50,000 individuals for a variety of human pathogens as a function of population immunity at introduction. Solid lines show the median duration in disease generations for 1,000 simulation runs at each level of initial population immunity; dashed lines show quartiles. Each pathogen shows some level of enhancement of epidemic duration with increased immunity except pertussis. Enhancement of epidemic size is not observed for these pathogens for N = 50,000.
SOURCE: Pulliam et al., 2007.

Incubation and Infectious Period

Two parameters of any model for R_0 are central to our ability to control the initial emergence of a novel pathogen. Ironically we tend to worry more about the transmissibility of the pathogen, which is always the hardest thing to estimate, than we do about these other two equally vital parameters: incubation and infectious period. Key insights into the importance of these parameters come from work comparing SARS, influenza, and HIV (Fraser et al., 2004). This work shows that although R_0 is fundamental in determining the level of intervention, even pathogens with low R_0 can cause huge epidemics if they have a long silent incubation period during which transmission occurs without any apparent symptoms. The classic example of this is HIV, which has caused the largest epidemic in human history since the plague epidemics of thirteenth-century Europe. This contrasts sharply with SARS where symptoms of infection appear almost simultaneously to ability to infectiousness; this made it relatively easy to contain SARs through a combination of isolation of infectious individuals and contact tracing (Figure A8-3).

This problem with long "silent" incubation periods is particularly worrying from the current vogue for virus hunting. I think that if the approaches currently used to detect emerging pathogens were retrospectively applied to the HIV virus, they would dismiss it as a mild and innocuous pathogen of limited concern. This is primarily because the incubation period of the virus is as long as the life expectancy of most primate species used in laboratory research (Anderson, 1991). If injected into humans, we would only see an initial rise in virus abundance that was quickly knocked back by the host's immune system. Although an astute clinician might detect the virus's rapid mutation rate, I suspect that the absence of any symptoms in the first 5 to 10 years postinfection would lead to the virus being dismissed as a hazard. From a simple mathematical perspective this makes me much more concerned about viruses with long silent incubation periods (and the opportunities to infect thousands of people) than it does about highly virulent viruses whose violent symptoms make for powerful movies, but also for ready detection, isolation, and the development of a rapid response.

There Be Dragons!

Maps are powerful tools that have multiple uses in biology and epidemiology. For example, they have been widely used in conservation biology to identify areas of unusually high biological diversity in areas with relatively low land values, or to identify areas with unusually high extinction rates (Bibby et al., 1992; Conroy and Noon, 1996; Dobson et al., 1997). Conservation biology is essentially a complementary discipline to infectious disease biology; one discipline seeks to drive organisms to extinction, the other hopes to bring back rare species from the brink. Both disciplines have benefitted from the huge rise of geographical information systems (GIS) that allows maps to be readily created from detailed

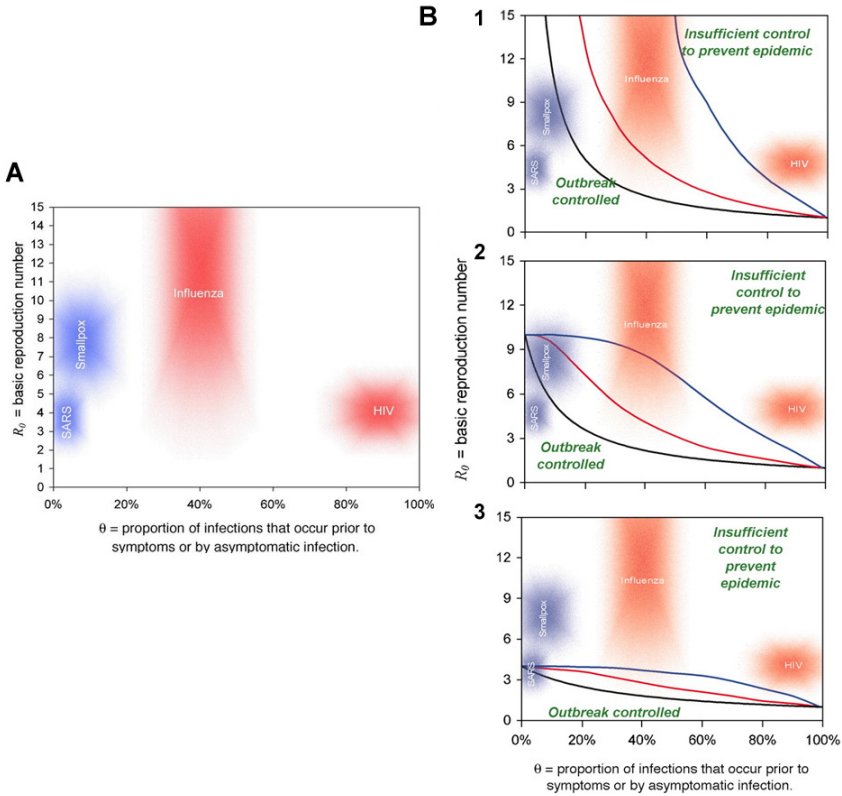

FIGURE A8-3 (A) Parameter estimates. Plausible ranges for the key parameters R_0 and θ for four viral infections of public concern are shown as shaded regions. The size of the shaded area reflects the uncertainties in the parameter estimates. The areas are color-coded to match the assumed variance values for β(τ) and S(τ) of Fig. 1 in Fraser et al. (2004) appropriate for each disease, for reasons that are apparent in Fig. 3 in Fraser et al. (2004). (B) Criteria for outbreak control. Each curve represents a different scenario, consisting of a combination of interventions and a choice of parameters. For each scenario, if a given infectious agent is below the R_0–θ curve, the outbreak is always controlled eventually. Above the curve, additional control measures (e.g., movement restrictions) would be required to control spread. Black lines correspond to isolating symptomatic individuals only. Colored lines correspond to the addition of immediate tracing and quarantining of all contacts of isolated symptomatic individuals. The black (isolation only) line is independent of distributional assumptions made (low or high variance), whereas the colored (isolation + contact tracing) lines match the variance assumptions made in Fig. 1 in Fraser et al. (2004) (red = high variance; blue = low variance). The efficacy of isolation of symptomatic individuals is 100% in Panel B-1, 90% in Panel B-2, and 75% in Panel B-3. Contact tracing and isolation is always assumed 100% effective in the scenarios in which it is implemented (colored lines). Curves are calculated using a mathematical model of outbreak spread incorporating quarantining and contact tracing.
SOURCE: Fraser et al., 2004.

geographical data and more sparse biological and epidemiological surveys. Maps also have a very distinguished history of use in epidemiology. This stretches from John Snow's original map identifying the Broad Street pump as the most likely source of cholera in London, through the path-breaking work of Cliff, Haggett, and Ord (Cliff and Haggett, 1988; Cliff and Ord, 1981): their studies of the history of measles in Iceland, combined with the work of Bartlett (1957, 1960, 1966), paved the way for our current deep understanding of the dynamics of SIR pathogens (Anderson and May, 1983, 1985, 1990; Bjornstad et al., 2002; Ferrari et al., 2008; Grenfell and Anderson, 1985; Grenfell et al., 2001).

The great power of maps is that politicians and government decision makers have an instinctive understanding of maps (they use them to plan their vacations and political or military campaigns); in contrast, they seem much more wary of mathematical models, or even graphs (although they have teams of policy makers that happily abuse these models to plan economies and election campaigns!). The central problem with maps is apparent in some of the oldest maps; when there was limited or no information for an underexplored region there was a tendency to assume "There be dragons." This creates a historical precedent to use maps to identify the location of unknown scary monsters such as emerging pathogens or endangered species that have not been seen for some time. More disconcertingly, it means that we tend to forget that the data that underlie maps need to be verified and tested against an epidemiological model that provides some mechanism to explain the observed geographical patterns of incidence. Sometimes this is done (see Cliff and Haggett, 1988; Cliff and Ord, 1981). All too frequently the map is presented as a predictive tool, when all it is really presenting is a rather undigested mass of data detectable in the literature. When these maps are used as a predictive tool, many quantitative disease modelers become nervous. These fears could be allayed by some relatively simple mathematical or statistical tests of the map's utility. The simplest approach to seeing if a map of emerging disease hot spots has any predictive value would be to take the first half of the historical data used to make the map and see if it has any predictive "skill" in reproducing the latter half of the observed data (an approach widely used by climatologists). I suspect that these approaches would exhibit high skill in predicting the locations of large urban areas with major medical facilities that consistently detect new antibiotic resistant strains of bacteria. The approach will be less powerful at detecting areas for new unknown (viral) diseases (which may or not emerge), as this will reflect where people have decided to work on a hunch that this will be a hot spot, or because it was one in the past. I was very amused when a colleague told me that he had received funding for his emerging disease work because a hot spots map had identified his site as a likely hot spot. This was because he was one of the few people to have published a previous epidemiological survey from within this broad geographical location! Most quantitative ecologists working on emerging pathogens are exceptionally skeptical about maps produced that purport to predict hot spots of disease

emergence. This skepticism is well justified by the very limited ability of these maps to predict anything other than antibiotic-resistant strains of pathogens that tend to emerge in around Western cities where drugs are widely used and there are well-funded medical schools focused on detecting these strains. This form of prediction is essentially a self-fulfilling fantasy!

A Role for Climate?

There is increasing interest in the role that climate change will play in the emergence of new pathogens. At the risk of being hypocritical, I am going to use a couple of maps to shape the discussion about how climate change will interact with other aspects of global change to affect pathogens. Here it is important to explicitly acknowledge that climate change is only one component of global change. While all sane scientists not in the deep pockets of oil industry now acknowledge that anthropologically driven climate change is a real effect that is increasingly influencing the Earth's climate, predicting how this will influence patterns of infectious disease dynamics and outbreaks will not be straightforward (Rodó et al., 2013), not least the influence of climate change may be masked by other aspects of global change, particularly in the parts of the world where most people are going to be living over the next 100 years.

The work of Jetz et al. (2007) on how geographic distributions of all the world's bird species are likely to change over the next 100 years is instructive here. Jetz et al. (2007) base their analysis on the Millennium Ecosystem Assessments of land use change under four different scenarios. The work is based on detailed forecasts for climate, land use change, human population growth, and agricultural expansion over the next 100 years (Alcamo et al., 2005; Reid et al., 2005). These scenarios were then applied to the current distribution data for each of the world's bird species. Birds were chosen as we have better data for birds than for any other taxa. The impact of land use change was applied to the geographical range of each species, and this was used to quantify the proportional loss of habitat for all bird species under complementary drivers of anthropological land use change (agriculture and urbanization) and climate change. Figures A8-4 and A8-5 present map projections and latitudinal cross sections that result from these analyses. The results generalize for other taxa and so provide important implications for pathogens, as well as for their nonhuman reservoir species. The figure illustrates that although climate change will dominate the future of polar regions, the impacts of land use change will hugely mask any climate change signature in the tropics and temperate regions. As the vast majority of birds (and mammals, plants, insects, etc.) live in the tropics, then it is going to be very hard to detect a climate change signal when we try and predict any aspect of the future of these systems.

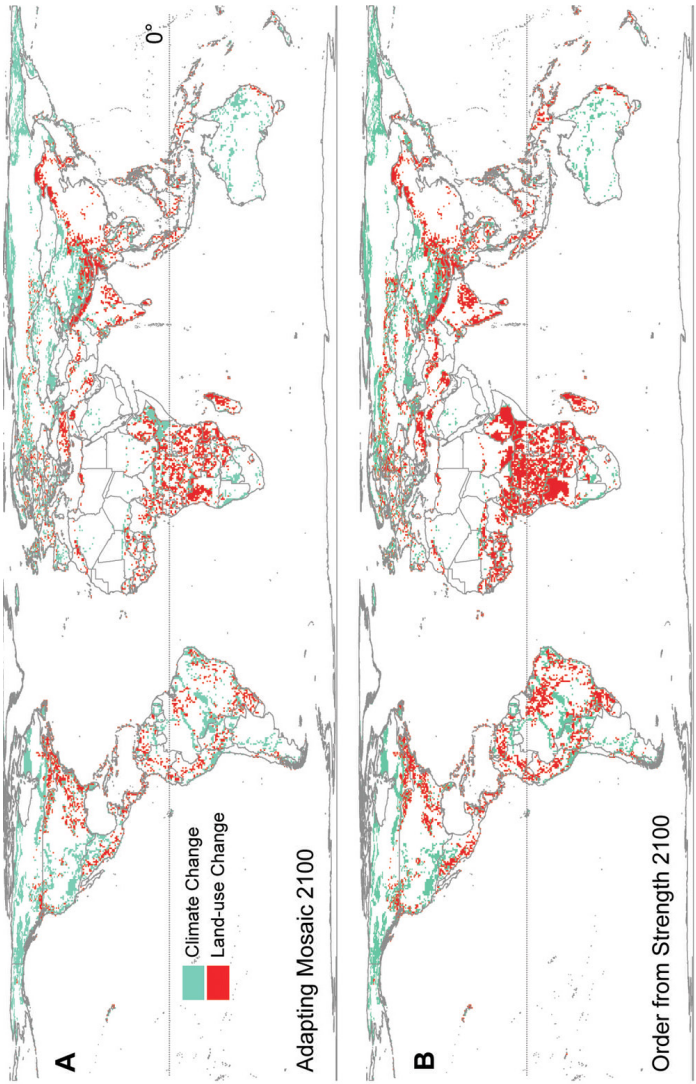

FIGURE A8-4 Geographic patterns and projected impact of environmental change. (A, B) Patterns of change in land cover due to land use and climate change by 2100. This represents the summed, current-day occurrence of qualifying species across a 0.5° grid. Patterns are given for the environmentally proactive "Adapting Mosaic" scenario, and the environmentally reactive "Order from Strength" scenario. Maps are in equal-area cylindrical projection.
SOURCE: Jetz et al., 2007.

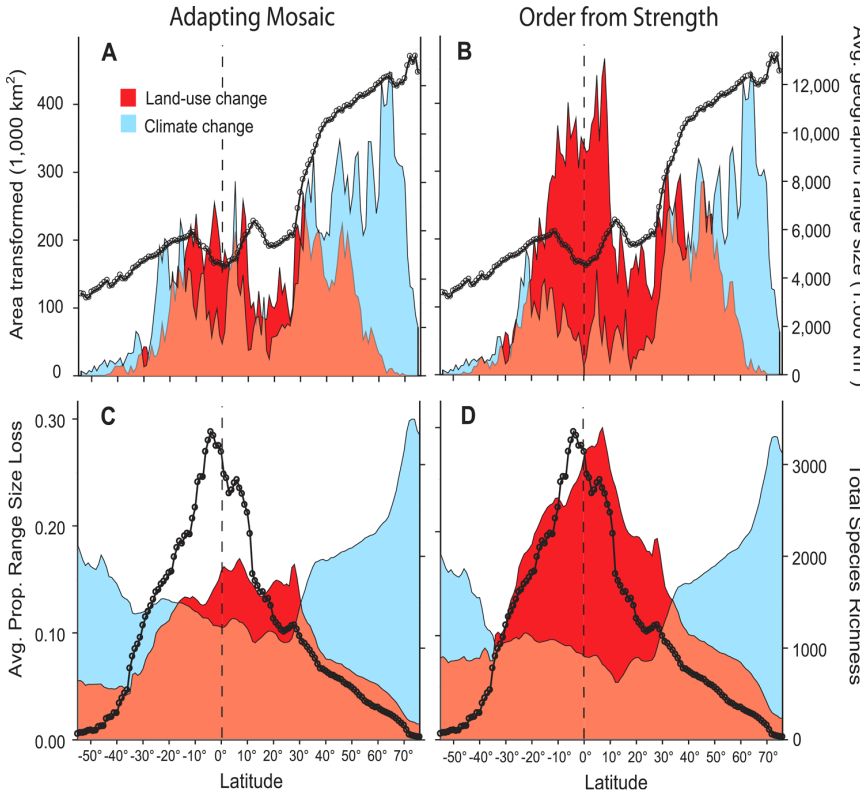

FIGURE A8-5 Environmental change, avian biogeography, and loss in range size. Projected latitudinal pattern in type of global environmental change, geographic range size, species richness, and the resulting loss in geographic range size (8,750 bird species, 1° bands of latitude). Climate (cyan, on top and semitransparent) and land use (red) changes between now and 2100 are evaluated for two scenarios: on the left, "Adapting Mosaic" (A, C), and on the right, "Order from Strength" (B, D). Top (A, B): Total area transformed (area plot, lighter color indicates overlap) and average (± SE) current geographic range size of species per latitudinal band (point and line plot); Bottom (C, D): Average proportional loss of range size (area plot, lighter color indicating overlap) and total number of bird species whose range currently overlaps at each latitudinal band (point and line plot). Whereas climate change leads to a significant net change of habitat in the polar and temperate regions, the small numbers of bird species that live there on average have very large geographic ranges. Thus, proportional contractions in range size there are much smaller than for the vast majority of bird species that live in the tropics and experience significant reductions in their smaller range sizes due to land use change. The outcome is many species with significant range reduction in the tropics and subtropics, because of the coincidence of habitat conversion with areas of high species richness. This is particularly the case in the environmentally reactive "Order from Strength" scenario, where large areas of land are converted to agriculture.
SOURCE: Jetz et al., 2007.

There are three insights that I want to make from these figures:

1. This does not mean that climate change is not important; it means we need to understand how climate interacts with other aspects of global change.
2. In particular, if we want to understand how climate change will affect disease dynamics then we should expand studies of disease dynamics in the Arctic as these systems have a much stronger climate signal and many less confounding effects. Work undertaken here is already providing important insights that will eventually help interpret what will eventually happen in the temperate and tropical regions.
3. Our biggest worry about emerging pathogens in the tropics will come from land use change modifying the natural habitats of wild reservoir species living in these regions and the increasingly large human population that interact with them.

R_0, Biodiversity, and Dilution Effects

The principle scientific justification for virus hunting in the tropics is that these regions contain the highest levels of biological diversity and hence more species should equate with more undiscovered pathogens. This in turn has led to some dubious estimates of the number of undiscovered viral species that assume all host species harbor the same number of pathogen species (Anthony et al., 2013). The logic of this approach assumes some of the methodology (and none of the rigor) of previous attempts to estimate global insect diversity by taking the numbers of insects associated with a small number of host trees and multiplying these numbers up by the known number of tree species (Erwin, 1982; Gaston, 1991, 1994; Hodkinson, 1992). Future attempts to estimate viral diversity would benefit hugely from the adoption of the methodology employed in these earlier entomological studies. In particular it should also be realized that host population size, density, and spatial distribution will all play a crucial role in determining the diversity of microbial pathogens harbored by any host species, and it is highly likely that rare species will host lower pathogen diversity than more common species.

Rare hosts and hosts of low abundance create significant challenges for pathogens who adapt to these constraints by either reducing their virulence, so as to reduce the chance the hosts die between encounters, or increase their efficiency of transmission to ensure it occurs on the rare occasions that hosts encounter each other. These constraints mean the pathogens of rare species with low abundance are most likely to be STDs; there is little chance for anything else to be transmitted or maintained in the host population (Altizer et al., 2003; Lockhart et al., 1996). Common hosts are likely to harbor a greater diversity of pathogens, particularly if they live in large social groups (Ryan et al., 2013). All of which

suggests that virus hunters who head for the tropics to look for undiscovered viruses in rare species are significantly, scientifically deluded.

An alternative perspective on biodiversity considers the role it may play in buffering pathogen emergence and reducing the potential for the emergence of novel pathogens. Disease ecologists call these phenomena "the dilution effect" (Dobson et al., 2006; Hudson et al., 1995; Keesing et al., 2006; Schmidt and Ostfeld, 2001), and there is an intense debate about the role they play in buffering disease outbreaks (Lafferty and Wood, 2013; Ostfeld and Keesing, 2013; Randolph et al., 2012). Dilution effects can only occur when a pathogen uses multiple species of hosts. When one or more of these host species is able to withstand infection with the pathogen, but fails to transmit it efficiently to other hosts, it effectively creates a dilution of transmission rates and slows the rate of epidemic spread. Dilution effects are likely to be most efficient for vector-borne diseases than for directly transmitted pathogens (although evidence does suggest they are important for directly transmitted pathogens with frequency-dependent transmission such as Hanta virus). Dilution effects are also likely to be stronger for mosquito-borne pathogens than for tick-borne pathogens, as the abundance of the vectors is independent of host abundance for mosquitoes, but not for ticks (Dobson, 2009). Ironically, the best studied example of the dilution effect comes from work on tick-transmitted Lyme disease (LoGuidice et al., 2003; Ostfeld and Keesing, 2000; Ostfeld and LoGiudice, 2003).

From the perspective of pathogen emergence, we simply do not know whether these effects are strong enough to buffer rates of disease emergence. These is some correlative evidence that supports the case that they might be operating (Bonds et al., 2012; Ezenwa et al., 2006; Roche et al., 2012), and if this is the case then it presents a powerful argument for finding ways to conserve species diversity as agriculture and land use intensifies.

Subsequent Evolution

The emerging pathogens that cause me to lose most sleep are those caused by the evolution of resistance to the drugs and antibiotics we have used over the last 50 years (Cohen, 1992; Palumbi, 2001). These are pathogens that we know have caused significant mortality to humans and domestic livestock in the past. We know they have no difficulty establishing and multiplying in their host populations. People now in their mid-50s have benefited from their absence for most of their lives; yet, it is likely that at least half of us will acquire them late in life (probably in a hospital or while travelling on public transport), and they will be our terminal interaction with a pathogen.

The mathematics of drug resistance has been studied from a variety of perspectives. One of the earliest and simplest insights comes from May and Dobson who show simply that the rate at which drug (or pesticide/insecticide) resistance evolves is mainly determined by the log of the basic reproductive rate of the organism evolving resistance (May and Dobson, 1986). This explains very simply

why mosquitoes and bacteria quickly evolve resistance; in contrast, birds of prey were unlikely to ever evolve resistance to egg-shell thinning: if it takes a hundred generations to evolve resistance, then what takes months for bacteria requires centuries for a bird of prey.

There is really only one pathogen that has emerged recently where no attempt has been made to eradicate the pathogen and its evolution has been studied beyond the first few generations of cases. Work on *Mycoplasma gallisepticum* (MG) in the North American house finch provides a number of important insights that are likely to generalize to other emergent pathogens should they escape detection and control at the initial stages of emergence. MG emerged from domestic fowl into wild finches in the fall of 1993. House finches were the most conspicuous hosts as their pathology of MG is characterized by pronounced swelling of the eyes, which reduces their ability to locate food and likely increases their susceptibility to predation (Dhondt et al., 1998; Dobson, 2013). Through a large Citizen Science network established by the Laboratory of Ornithology in Cornell, the spread and impact of the disease has been monitored for the last 20 years (Hosseini et al., 2006). The pathogen has now spread across the entire United States infecting house finches both in their introduced range (eastern United States) and in their native range (western United States) as well as up to 30 different species of birds. The eastern population has declined by around 60 percent (around half a billion birds), less significant declines are observed in the west (Dhondt et al., 2006; Hochachka and Dhondt, 2000). Detailed laboratory, field, and genetic studies illustrate that the pathogen has evolved continuously since emerging, and this evolution has both increased and decreased virulence depending on the condition determining selection. This evolution can happen quite quickly and is reversible (Dhondt et al., 2005; Hawley et al., 2010, 2013). There is essentially no difference in the behavior of identical strains of the pathogen in inbred eastern birds and outbred, more genetically diverse western birds; essentially, the hosts show no real evidence for genetic resistance to the pathogen. This is not surprising as their age-structured population has only been exposed to less than 10 generations of selection; the pathogen has likely had several thousand generations of selection in this time. All of which should give pause for thought to those who think or preach that we can readily breed or otherwise genetically modify hosts for disease resistance. Even for small rapidly breeding hosts like passerine birds, the asymmetry in host and pathogen demographic rates will always allow the pathogen to evolve at rates that make the hosts genetic response essentially inert. The situation is even more asymmetrical when we consider humans and emerging viruses.

Conclusions

There is increasing evidence that pathogens play a significant role in determining the economic well-being of most of the world's nations (Bonds et al., 2012); this occurs through their direct effects on the size and efficiency of the labor force. The traditional economic argument that the wealth of nations is

determined solely by governance is now seen as a deeply flawed and biased argument (Acemoglu et al., 2000, 2003; McArthur and Sachs, 2001). Although the economic impact of recent disease outbreaks is frequently cited as a central reason to increase funding for research on emerging pathogens, I suspect that the continued impact of older diseases such as malaria and the neglected tropical diseases has a larger annual effect on the global economy than any of the recent emerging disease threats. Ultimately we need more funds to study the dynamics of both emerging and endemic pathogens and their hosts. Disease is as important as governance in driving national economies—biodiversity may play a role in buffering pathogens.

Pathogens are a large component of natural ecosystems—perhaps as much as 90 percent of biodiversity is parasitic on free-living species. Pathogens emerge when we disturb natural ecosystems—but, we have as much chance of a new pathogen emerging in our own back yards as we have of something else emerging from the tropics. We need to think more deeply about the population dynamics of pathogen emergence, and step back a little from the romance of fishing for tropical viruses with microchips. If we ask the simple question "Would the tropical virus hunters have identified HIV?" I suspect the long incubation period with no initial pathology would have led them to dismiss it as inert and innocuous and to miss it entirely.

Ultimately pathogens emerge and cause problems for humans, domestic livestock, and other wildlife species because we have disturbed their natural habitat in ways that modifies their transmission rates. This suggest that developing a better mathematical understanding of the dynamics of food webs and the role that parasites play in these large complex nonlinear systems will provide alternative insights into the way in which pathogens emerge (Dobson et al., 2009; Hudson et al., 2006; Lafferty et al., 2008). Similar mathematical models will also be needed to understand how immune systems function and how the brain communicates with the nervous and endocrine systems. These mathematical understandings of the function of complex systems are easily as important to the future of human health as is the current focus on genomic understanding. Indeed, in the absence of the understanding about how the parts coded for by genes interact together, we are simply dealing with the "natural history" of these systems at a heroically tiny, but essentially disconnected, biological scale.

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ENVIRONMENTAL CHANGE AND INFECTIOUS DISEASE: HOW NEW ROADS AFFECT THE TRANSMISSION OF DIARRHEAL PATHOGENS IN RURAL ECUADOR[26]

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Abstract

Environmental change plays a large role in the emergence of infectious disease. The construction of a new road in a previously roadless area of northern coastal Ecuador provides a valuable natural experiment to examine how changes in the social and natural environment, mediated by road construction, affect the epidemiology of diarrheal diseases. Twenty-one villages were randomly selected to capture the full distribution of village population size and distance from a main road (remoteness), and these were compared with the major population center of the region, Borbón, that lies on the road. Estimates of enteric pathogen infection rates were obtained from case-control studies at the village level. Higher rates of infection were found in nonremote vs. remote villages [pathogenic *Escherichia coli*: odds ratio (OR) = 8.4, confidence interval (CI) 1.6, 43.5; rotavirus: OR = 4.0, CI 1.3, 12.1; and *Giardia*: OR = 1.9, CI 1.3, 2.7]. Higher rates of all-cause diarrhea were found in Borbón compared with the 21 villages (RR = 2.0, CI 1.5, 2.8), as well as when comparing nonremote and remote villages (OR = 2.7, CI 1.5,

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Abbreviations:

CI: confidence interval; OR: odds ratio.

4.8). Social network data collected in parallel offered a causal link between remoteness and disease. The significant and consistent trends across viral, bacterial, and protozoan pathogens suggest the importance of considering a broad range of pathogens with differing epidemiological patterns when assessing the environmental impact of new roads. This study provides insight into the initial health impacts that roads have on communities and into the social and environmental processes that create these impacts.

The more public health scientists learn about infectious disease processes, the more they can implicate environmental changes in the recent emergence or reemergence of infectious diseases (Colwell et al., 1998; Morse, 1995; Patz et al., 2000). Given the increasing number of emerging pathogens recently identified, there is an urgent need to understand how environmental change influences disease burden. Such changes are potentially more visible in places where they have been caused by human activity, such as construction of dams, pipelines, and roads. Anthropogenic environmental changes that cause populations to move and settle in new ways can provide the opportunity to observe the relationship between environmental change and disease transmission. Where such environmental changes are unevenly distributed across a region, thereby producing the conditions of a natural experiment, these relationships can be observed easily and systematically. The construction of a new road in a previously roadless area in northern coastal Ecuador provides just such a natural experiment to examine how changes in the social and natural environment, mediated by road construction, affect the epidemiology of diarrheal diseases.

Various studies have examined the impact of road construction on disease incidence (Birley, 1995). For example, the building of the TransAmazon Highway was associated with an increase in malaria (Ault, 1989; Coimbra, 1988). These increases in incidence were attributed to the presence of water pools created by road construction practices. More recently, a study in the Peruvian Amazon indicated that mosquito biting rates are significantly higher in areas that have undergone deforestation and development associated with road development (Vittor et al., 2006). Analogously, a study in India measured a higher prevalence of dengue vectors along major highways than elsewhere (Dutta et al., 1998). Studies in Uganda suggest that the main road linking Kenya to Kampala has higher proportions of HIV-positive women working in bars and HIV-positive truck drivers than does the surrounding area (Carswell, 1987). In general, transportation changes mobility and circulation of humans, which can affect the incidence of sexually transmitted diseases (Panos Institute, 1988), as well as health-care-seeking behavior (Airey, 1991, 1992). As opposed to sexually transmitted diseases, fecal–oral pathogens can survive outside of the human host and therefore will behave differently under environmental changes. Some studies have suggested that remote villages separated by large distances are less able to sustain transmission of certain fecal–oral pathogens, such as amoebas and rotavirus (Black, 1975; Gilman et al., 1976;

Gunnlaugsson et al., 1989). The impact that environmental changes from road construction have on these diarrheal diseases remains largely unexplored and unknown, despite the fact that diarrheal diseases remain a major cause of mortality among infants and children under 5 years of age (WHO/UNICEF, 2004).

In 1996 the Ecuadorian government began a road construction project to link the southern Colombian border with the Ecuadorian coast. A two-lane asphalt highway was completed in 2001, spanning 100 km across the southern end of the Chocó rainforest near the Pacific Ocean. Secondary roads continue to be built, linking additional villages to the paved road (Figure A9-1). These roads provide a faster and cheaper mode of transportation compared with rivers. The extent to which roads influence communities should be measured by their proximity in time and distance to a given village (e.g., remoteness) and not merely by their presence or absence.

To examine the impact of remoteness on diarrheal disease we implemented a hierarchical design that collects data by village to obtain information about the region, and by individual to obtain information about potential confounding factors that may bias the analysis. Roads influence disease transmission through a variety of mechanisms. For example, road proximity can increase in- and outmigration rates causing multiple demographic changes in the age, racial, and socioeconomic profile. These rapid and complex changes can reduce social connectedness within a community, which may in turn reduce a community's ability to maintain good sanitation and hygiene conditions. Road proximity can also affect short-term travel patterns, thereby increasing the potential for the introduction of new pathogen strains into communities.

In addition to diarrheal symptoms, three specific marker pathogens (*Escherichia coli*, rotavirus, and *Giardia*) were followed, each with a distinct epidemiology. Both pathogenic *E. coli* and rotavirus are responsible for a large proportion of diarrhea mortality and severe morbidity throughout the developing world, whereas *Giardia*, also a major cause of diarrhea, is more pervasive, resulting in higher infection rates (Blaser et al., 2002). Taken together, these three pathogens represent the primary pathways (food, water, and person-to-person) for transmission of diarrhea.

Results

Table A9-1 presents community characteristics, with two methods for characterizing location: remoteness of a community relative to the town Borbón, and river basin in which a community resides. The least remote community has a remoteness value of 0.012, and the most remote village has a remoteness value of 0.198. Close villages were defined as those with a remoteness value of < 0.03; medium villages were defined as those with a remoteness value between 0.03 and 0.13; and remote villages were defined as those with a remoteness value $>$ 0.13. These classifications are also represented in the regional map (Figure A9-1).

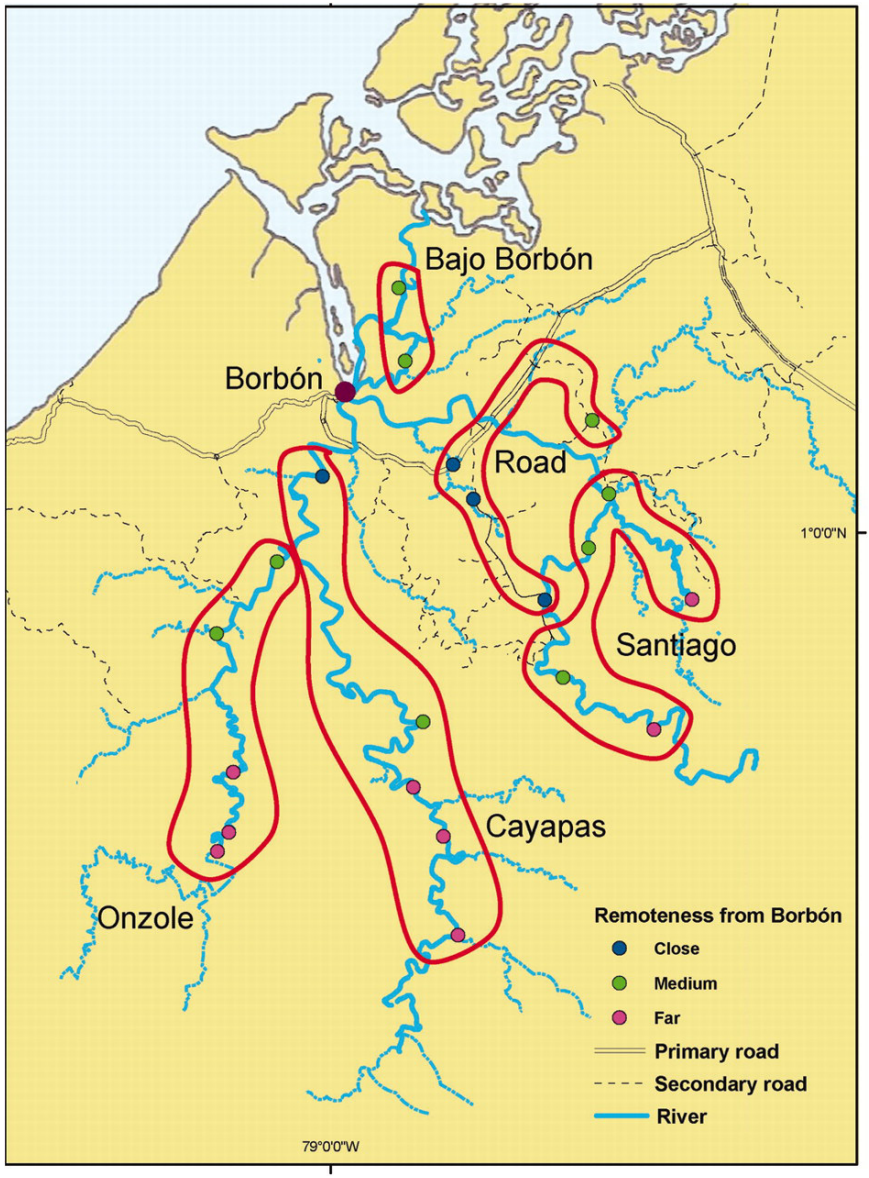

FIGURE A9-1 Map of study region. The 21 villages are categorized by river basin (Santiago, Cayapas, Onzole, Bajo Borbón, and road) and by remoteness (close, medium, and far).

TABLE A9-1 Community Characteristics

Village	Population size	Remoteness metric	Remoteness category	River basin
1	284	0.012	Close	Road
2	731	0.015	Close	Road
3	78	0.022	Close	Cayapas
4	482	0.027	Close	Road
5	156	0.040	Medium	Santiago
6	55	0.040	Medium	Bajo Borbón
7	138	0.040	Medium	Bajo Borbón
8	72	0.049	Medium	Road
9	90	0.049	Medium	Santiago
10	60	0.061	Medium	Onzole
11	86	0.080	Medium	Onzole
12	110	0.113	Medium	Cayapas
13	135	0.122	Medium	Santiago
14	83	0.140	Far	Onzole
15	300	0.152	Far	Santiago
16	228	0.155	Far	Santiago
17	79	0.158	Far	Cayapas
18	268	0.165	Far	Cayapas
19	28	0.173	Far	Onzole
20	443	0.190	Far	Onzole
21	130	0.198	Far	Cayapas
Borbón	864	0		

Remoteness is a measure of the time and cost of travel to Borbón. Roads provide cheaper and faster access to Borbón, and therefore remoteness is a measure of the proximity to the road. Note that the population of Borbón is the sample size enrolled in the study, rather than the size of the entire population (≈ 5,000).

Village population size ranged from 28 to 731, and the random sample of 200 houses in Borbón resulted in 864 individuals, or ≈20% of the population.

A total of 298 cases of diarrhea were identified in the communities during the three case-control cycles, and 44 cases were identified in Borbón during the one case-control cycle (Table A9-2). In addition, a total of 845 and 125 controls were sampled from the communities and Borbón, respectively. Crude prevalence estimates are shown in Table A9-3 for diarrhea and infection by both case status and remoteness category. The crude prevalence estimates for diarrhea [RR = 2.0, 95% confidence interval (CI) 1.5, 2.8] and pathogenic *E. coli* (RR = 16.0, 95% CI 13.2, 19.2) were significantly higher in Borbón compared with those in other communities (Table A9-4). These large differences between infection prevalence in Borbón vs. the community are seen in both cases and controls (Table A9-3). We found no evidence that crude prevalence estimates for rotavirus and *Giardia* varied between Borbón and the other 21 communities.

TABLE A9-2 Number of Cases and Controls by Remoteness

Remoteness category	No. of villages	Population	No. of collection days	No. of cases	No. of controls
Remote	8	1,669	45	112	317
Medium	9	895	45	91	248
Close	4	1,592	45	95	280
Community*	21	4,156	45	298	845
Borbón	1	867	15	44	125

For communities other than Borbón, figures are the sum from three 15-day case-control studies across all 21 study villages between August 2003 and February 2006. Borbón figures are from one 15-day case-control study in July 2005.

*Total from all 21 villages (sum of remote, medium and close villages).

Adjusting for age of individuals, community population size, and sanitation level, the prevalence of infection was significantly higher in villages closer to or along a road compared with those communities far from the road for pathogenic *E. coli* [odds ratio (OR) = 3.9, 95% CI 1.1, 13.6], rotavirus (OR = 4.1, 95% CI 2.0, 8.4), and *Giardia* (OR = 1.6, 95% CI 1.0, 2.4); the same was true for all-cause diarrhea (OR = 1.8, 95% CI 1.2, 2.6) (Table A9-5). Precipitation was not included in the final model because its P value was > 0.2. These overall infection trends were largely driven by the controls, as evident from the crude prevalence estimates in Table A9-3 that are stratified by case status. Although the crude diarrhea prevalence values show no trend as a function of remoteness, the adjusted risk estimates comparing both remote and medium as well as remote and close were significant, after adjusting for the population size and sanitation level of each community (Table A9-5).

To test for a trend, remoteness was modeled as a continuous variable. The relative risk of infection associated with a decrease in remoteness from the farthest to the closest village was significant for all infections: pathogenic *E. coli* (OR = 8.4, 95% CI 1.6, 43.5), rotavirus (OR = 4.0, 95% CI 1.3, 12.1), and *Giardia* (OR = 1.9, 95% CI 1.3, 2.7). For all-cause diarrhea the relative risk was also significant (OR = 2.7, 95% CI 1.5, 4.8) (Table A9-5).

Discussion

We observed strong trends in infection rates and all-cause diarrhea in villages across a gradient of remoteness for our marker pathogens even after adjusting for population size, sanitation, and precipitation. This result suggests that villages farther from the road have lower infection rates than villages closer to the road. This relationship between infection and road proximity is also seen in Borbón, the only community directly connected to both the primary road and all of the major rivers that serve the region. We observed significantly higher rates of *E.*

TABLE A9-3 Crude Infection Prevalence by Case Status and Remoteness (prevalence per 100 persons)

Remoteness category	Diarrhea prevalence, cases/100	Overall infection prevalence, infections/100			Asymptomatic infection prevalence, infections/100			Symptomatic infection prevalence, infections/100		
		E. coli	Rotavirus	*Giardia*	*E. coli*	Rotavirus	*Giardia*	*E. coli*	Rotavirus	*Giardia*
Remote	2.6	1.0	2.7	16.7	0.6	2.2	15.8	0.4	0.6	0.9
Medium	4.6	3.1	3.6	16.6	2.3	2.7	15.2	0.5	0.9	1.5
Close	2.2	3.9	6.7	23.2	3.0	6.2	22.4	0.1	0.5	0.8
Community	2.8	2.4	4.5	19.4	1.9	4	18.4	0.3	0.6	0.9
Borbón	5.6	22.5	3.6	19.5	20.7	2.3	17.6	1.7	1.2	1.9

For communities other than Borbón estimates are based on the average of three 15-day case-control studies across all 21-study villages. Borbón estimates are based on one 15-day case-control study. Overall infection prevalence is based on a weighted average of infection in cases and controls. Prevalence estimates are based on a 15-day period prevalence.

TABLE A9-4 Comparison of Infection Prevalence in Communities vs. Borbón

	Community, cases/100	Borbón, cases/100	Relative risk (95% CI)
E. coli	1.6	22.5	16.0 (13.2, 19.2)
Rotavirus	4.5	3.6	0.8 (0.6, 1.2)
Giardia	19.4	19.5	1.0 (0.9, 1.2)
Diarrhea	2.8	5.6	2.0 (1.5, 2.8)

For communities other than Borbón estimates are based on the average of three 15-day case-control studies across all 21 study villages. Borbón estimates are based on one 15-day case-control study. Pathogen prevalence is based on infection (a weighted average of cases and controls). Relative risk is the prevalence risk ratio (the risk of illness or infection in Borbón relative to the communities).

coli and all-cause diarrhea in Borbón than in the other 21 study communities. These health differences have policy significance given that both pathogenic *E. coli* and rotavirus are major causes of mortality and severe morbidity in children.

These data were collected across three river basins during three visits to each town over 2 years, minimizing the chance that unmeasured localized events either temporally or spatially confounded the risk estimates. We found no statistical relationship between diarrhea or infection rates and time period or river basin. Any unmeasured confounding would have had to continue over the 2-year study period or had to occur across the three river basins.

Explaining the causes of the trends discussed here requires understanding the ecological and social impacts of roads. One common purpose (and consequence) of a new road is increased logging. Deforestation causes major changes in watershed characteristics and local climate, both of which can affect the transmission of enteric pathogens (Curriero et al., 2001). Perhaps more important than ecological processes, social processes facilitated by roads such as migration, creation of new communities, and increased density of existing communities can affect pathogen transmission. Changes in community social structures often create or are accompanied by inadequate infrastructure, which affects hygiene and sanitation levels, and in turn the likelihood of transmission of enteric pathogens. Roads

TABLE A9-5 Infection as a Function of Remoteness

OR (95% CI)

	E. coli	Rotavirus	*Giardia*	Diarrhea
Remote	1.00	1.00	1.00	1.00
Medium	3.0 (0.8, 11.9)	1.3 (0.5, 3.2)	1.2 (0.7, 2.0)	1.8 (1.1, 3.0)
Close	3.9 (1.1, 13.6)	4.1 (2.0, 8.4)	1.6 (1.0, 2.4)	1.8 (1.2, 2.6)
Continuous	8.4 (1.6, 43.5)	4.0 (1.3, 12.1)	1.9 (1.3, 2.7)	2.7 (1.5, 4.8)

OR of infection/disease for individuals in communities that are classified as close or medium from Borbón as compared with those communities that are classified as far (remote). The continuous measure is the OR comparing the farthest with the closest using a continuous measure of remoteness. Estimates were adjusted for age of individual, population size of village, and community-level sanitation.

can also increase flows of consumer goods such as processed food, material goods, and medicines and may also provide communities with increased access to health care, health facilities, and health information.

By determining the transmission potential of the causal factors associated with new roads, we can better interpret the observed trends in infection rates across our study region. The propensity of a pathogen to persist within a community is characterized by the reproductive number R_o, defined as the average number of infections caused by an infectious individual in a completely susceptible population (Anderson and May, 1991). For directly transmitted diseases, R_o is a function of (*i*) contact rate among others within or outside the community, (*ii*) infectivity (the probability of infection given a contact), and (*iii*) duration of the infectious period. For enteric pathogens that can persist in the environment, R_o is also a function of a pathogen's viability outside the human host and its ability to move to a new susceptible one. The consistent and strong trends observed in these data across viral, bacterial, and protozoan pathogens suggest that R_o for many enteric pathogens is lower for remote villages compared with nonremote villages; i.e., these remote communities are less able to sustain transmission of pathogens.

The trends in infection rates that we observed are partially explained by the effect of social connectedness on the risk of transmission of many pathogens. Figure A9-2 shows a causal diagram that illustrates how demographic changes, measured by rates of in- and out-migration for a community, and contact outside of village, measured by short-term travel of people in and out of a community, might increase levels of infection or disease for fecal–oral pathogens. Localized migration facilitated by roads can lead to a community whose residents have few social connections, which is one measure of social capital (Bebbington and Perreault, 1999). Previous studies have shown that communities with more social capital tend to be successful in creating adequate water and sanitation infrastructure because they tend to know one another, are accustomed to working together, and share social norms (Grootaert and van Bastelaer, 2002; Isham and Kahkonen, 1998; Watson et al., 1997). On the other causal pathway, road proximity can increase the contact that individuals within a village have with those outside the village, increasing the rate of introduction of pathogens.

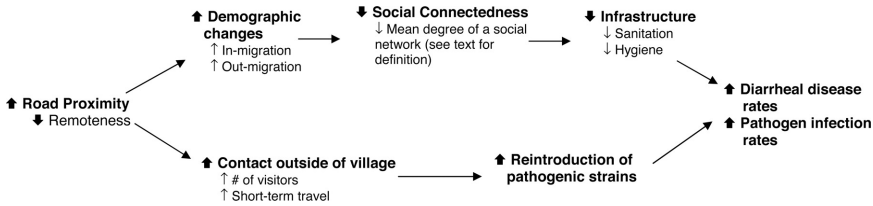

FIGURE A9-2 Causal diagram linking proximity of the road to increases in infection and diarrheal disease.

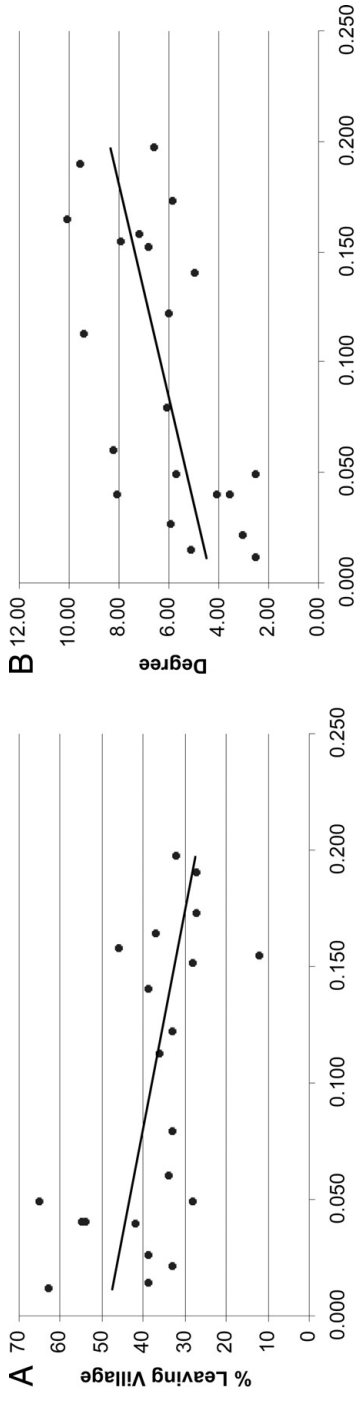

FIGURE A9-3 Relationship between social factors and remoteness. (A) Movement outside of community, measured by the percentage leaving the village during the past week (linear fit $R^2 = 0.25$, $P \leq 0.05$). (B) The social connectedness within a community, as measured by the number of villagers a given individual spent time with during the past week (linear fit $R^2 = 0.50$, $P \leq 0.05$).

Our study villages show some evidence of these hypothesized relationships among demographic characteristics, social connectedness, and movement of people. Village data suggest that connectedness, as measured by the average number of individuals a given person spends time with (social network degree), is positively associated with remoteness (Figure A9-3B). Additionally, villages closer to the road have increased movement of people (Figure A9-3A), which provides opportunities for pathogen incursion. The slope of the line reflects the strength of the relationship: twice as many connections exist in the most remote village compared with the least remote. Likewise, 28% of the remote villagers said they had left the village in the last week, compared with 48% of the least remote villagers.

Pathogen-specific outcomes provide additional insight into the relationship between remoteness and transmission. Observed trends were strongest for *E. coli*, followed by rotavirus and then *Giardia*. This differential can be partially explained by the biological and environmental factors that govern transmission dynamics and level of R_o; e.g., pathogen infectivity, as measured by infectious inoculum, shedding rates, and environmental persistence, as measured by the ability of the pathogen to remain viable in the environment, all directly affect R_o. Infectivity data suggest that *Giardia*, with a low ID_{50} (the inoculum at which 50% of exposed subjects are infected) and long shedding duration, and rotavirus, with a low ID_{50} and high shedding rates, are more infectious (Carter 2005; Regli et al., 1991; Teunis et al., 1986) than diarrhea-causing *E. coli* (Dupont et al., 1971, 1989; Feachem, 1983; Haas et al., 1999; Karch et al., 1995; Teunis et al., 1986). Diarrheagenic *E. coli* species tend to persist in the environment for shorter periods of time than either *Giardia* or rotavirus (Carter, 2005; deRegnier et al., 1989; Enriquez et al., 1995; Estes, 1991; McFeters et al, 1974; Raphael et al., 1985).

The above observations on both infectivity and environmental persistence suggest that *Giardia* is able to maintain transmission within the more remote villages despite limited outside social contact and higher levels of social connectedness. Likewise, *E. coli* would be less able to maintain transmission, and rotavirus would lie somewhere in between. The significant difference in *E. coli* infection rates between Borbón and the other communities and the lack of difference in *Giardia* infection rates are consistent with this hypothesis.

The significant and consistent trends across viral, bacterial, and protozoan pathogens suggest the importance of considering a broad range of health outcomes when assessing environmental impact. Each of our marker pathogens has a different epidemiology that is affected by environmental changes in different ways. A stratified analysis that looks across pathogen types, and not just at a broader disease category like diarrhea, allows for a more sensitive measure of change and can elucidate more specific interventions to alleviate these environmental impacts. We propose this design as a general model that can be used to examine anthropogenic environmental determinants of health in other places.

A number of issues require further examination. In this regional analysis we compare remote and nonremote villages at a given point in time. Investigating changes in incidence compared with changes in remoteness over time may provide additional causal information about how road development affects disease, because the time scale of these social changes may take years or decades, and the details are complex and poorly understood. In addition, molecular analysis of pathogens could elucidate transmission patterns across the landscape, and data on human migration patterns might provide information on causal linkages between roads and diarrheal disease. To substantiate the causal diagram shown in Figure A9-2, better measures of social capital and its relation to water and sanitation are needed. Gathering information on other health outcomes such as nutrition and vectorborne and sexually transmitted disease would also provide the opportunity to broaden our examination of causal linkages between road development and disease, because these are likely to vary for different etiologies.

Environmental effects are often both geographically widespread and temporally extended and therefore can be difficult to correlate with disease outcomes. The ability to observe change requires a study design and analysis that involve data collection within a systems-level framework. The natural experiment created by road construction in this region, combined with the regional design, allows these relationships to be studied. When associations between exposure and outcome are placed in the broader context of processes in which they occur (Figure A9-2), one can examine the causal linkages between environmental change and disease at a systems level.

When international agencies like the World Bank make decisions about whether to invest or how best to proceed in large-scale infrastructure projects, their impact assessments have begun to pay attention to variables associated with environmental, social, and health factors (World Bank, 1997). Although the World Bank now includes human health as a component of the environmental impact of road construction (Tsunakawa and Hoban, 1997), few studies of the health effects of roads exist, particularly with respect to infectious disease transmission (see www.who.int/hia/examples/en). This analysis provides insight into the interactions between roads, the social and environmental processes that they affect, and the resulting impacts on the health of human communities. These complex causal pathways suggest that efforts to mitigate the negative effects of roads should consider a larger range of their short- and long-term health implications.

Materials and Methods

Study Population and Selection Process

The study area is located in the northern Ecuadorian province of Esmeraldas in the canton Eloy Alfaro, which comprises ≈150 villages. Villages are located

along three rivers, the Río Cayapas, Río Santiago, and Río Onzole, all draining toward the town Borbón, the main population center of the region. Borbón, with ≈5,000 inhabitants, is distinct from the other communities along the river. It has a higher population density but nonetheless maintains an underdeveloped infrastructure for its size, with untreated sewage, rudimentary solid waste management systems, and minimal water and sanitation services that vary in quality between households. The communities outside Borbón, on the other hand, are smaller in size and density. Their water is primarily obtained from rivers and consumed untreated, although rainwater is used intermittently, and a few communities have wells or receive piped water from surface sources. Sanitation facilities are of varying quality, although they generally would be classified as unimproved by World Health Organization criteria; flush toilets are uncommon. The region is primarily populated by Afro-Ecuadorians, with a smaller proportion represented by Chachis, an indigenous group that mostly resides in more remote villages. There are an increasing number of mestizos (people of mixed origin) moving into villages close to or on the road. More details on the region can be accessed elsewhere (Rival, 2003; Sierra, 1998, 1999; Whitten, 1965, 1974).

The construction of the road from Borbón westward to the coast was completed in 1996. The portion of the road connecting Borbón eastward to the upper reaches of the Andes was completed in 2003. Secondary and tertiary dirt roads off of this two-lane asphalt highway are continually being built, mostly for logging. At the time the data were collected, both the primary and secondary roads reached 15% of the 150 villages in the canton.

All villages in the region were categorized based on their geographic location relative to Borbón. A sample of 21 villages was selected by using block randomization to ensure that villages throughout the study region were represented. At the beginning of the study, four of the 21 study villages were connected to the road. All households within each village were recruited. In Borbón, a random sample of 200 households (of ≈1,000) was selected for inclusion in the study. Consent was obtained at both the village and household level. Institutional review board committees at the University of California (Berkeley), Trinity College, and Universidad San Francisco de Quito approved all protocols.

Study Design

Between July 2003 and May 2005 each enrolled village was visited three times on a rotating basis. Each visit lasted 15 days, during which all cases of diarrhea were identified by visiting each household every morning. For each occurrence of diarrhea two controls were randomly sampled from the same community and one control was sampled from the case household. One 15-day case-control study was conducted in Borbón in July 2005.

Cases were defined as an individual who had three or more loose stools in a 24-h period. Controls were defined as someone with no signs of diarrhea in the past 6 days.

Microbiologic Analyses

Every morning during the 15-day period field staff members visited each household to find cases of diarrhea and collect stool samples from cases and controls. The samples were tested for rotavirus, pathogenic *E. coli*, and *Giardia*. All stools were stored on ice and processed within 48 h. In the field an EIA kit was used to identify rotavirus (RIDA Quick Rotavirus; R-Biopharm, Darmstadt, Germany). An aliquot of stool was preserved in liquid nitrogen and tested for *Giardia* in Quito with an ELISA kit (RIDASCREEN *Giardia*; R-Biopharm). For bacterial analysis, stool was plated directly onto MacConkey and XLD agar. All lactose-negative isolates were analyzed for urease and oxidase, and with API 20 E (bioMèrieux, Marey l'Etoile, France) to speciate the bacterial isolates. Lactose-negative isolates that were identified as either *Shigella* or *E. coli*, along with five randomly chosen lactose-positive isolates, were further analyzed by PCR. Pathotype-specific primers were used to diagnose the following: enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enteroinvasive *E. coli* (EIEC), and *Shigella* spp., as reported previously (Tornieporth et al., 1995). The primers amplified the *bfp* gene of EPEC, the LT and *STa* genes of enterotoxigenic *E. coli*, and the *ipaH* gene of EIEC and *Shigella* spp. The specific procedure is discussed elsewhere (Tornieporth et al., 1995). Both a positive and negative control were used in each gel run. A positive control for each pathotype was provided by Lee Riley (University of California, Berkeley). A K12 *E. coli* strain was used for the negative control. In the following analysis *Shigella* and *E. coli* cases were grouped together.

Demographic and Socioeconomic Survey

To determine individuals' movements and social interactions, we administered demographic and sociometric surveys to all study participants. The surveys included questions regarding travel to and from the community, as well as social contacts outside the individual's household during the previous week. The degree of social connectedness for each individual was defined as the number of names provided to the interviewer in response to the question, "who did you spend time with in your community, other than household members, during the past week?" plus the number of times that individual was nominated by others within the community (Bell, 1999; Scott, 2000). The surveys were developed after extensive anthropological observations to obtain regionally appropriate phrasing of questions. They were translated and back-translated to ensure accuracy. Interviewers

were trained together to ensure uniformity. All data were entered into Access (Microsoft, Redmond, WA). Standard quality control procedures were conducted, including examining the data for logical errors and double entry of 10% of the surveys. The surveys were administered once to each study participant, with an average of 82% coverage per village. To cover all study villages, half of the surveys were administered in the summer of 2003 and half in the summer of 2004.

Statistical Analyses

For each village, travel time and total cost of travel to Borbón were recorded by field staff members. For each village i, rank of remoteness, R_i, was then calculated by summing normalized values of time, T_i, and cost, C_i. Specifically,

$$R_i = \frac{T_i}{\sum_{:}^{21} T_i} + \frac{C_i}{\sum_{:}^{21} C_i}$$

Because the metric is the result of two values standardized to a [0,1] scale, the possible range of R_i is from 0 (the town Borbón itself) to 2 (the theoretical farthest community from Borbón). Villages were classified into three groups based on their remoteness metric: close, medium, and far from Borbón.

Community prevalence of infection for each village was calculated by aggregating data from all three case-control cycles and weighting cases and controls appropriately; i.e., we assumed that all cases were identified during the 15-day surveys and that the controls were a random sample of those without diarrhea. Specifically, the population prevalence of pathogen i in community j was estimated as follows:

$$P_{ij} = \frac{w_{1j}}{w_{1j} + w_{2j}} \frac{I_{cases_{ij}}}{N_{cases_i}} + \frac{w_{2j}}{w_{1j} + w_{2j}} \frac{I_{controls_{ij}}}{N_{controls_i}}$$

where $I\text{cases}_{ij}$ and $I\text{controls}_{ij}$ are the number of individuals in which pathogen i was isolated in the cases and controls, respectively, $N\text{cases}_i$ and $N\text{controls}_i$ are the number of cases and controls, respectively, w_1 = the inverse of the proportion of cases tested for the particular pathogen (this weight is equal to one when diarrhea is the outcome variable), and w_2 = (total population − no. of cases identified)/(no. of controls).

To estimate the change in risk of infection/disease by remoteness we used a logistic regression model, parameterizing remoteness in two different ways: (*i*) as a continuous variable (distance between the closest village, which is adjacent to Borbón, to the farthest among the study villages) and (*ii*) as a pair of

categorical indicator variables ("close" and "medium," with "far" considered baseline). Models included one individual-level variable (age of participant at time of case control visit) as well as the following community-level variables: sanitation level (percentage of individuals who stated that they used improved sanitation, i.e., latrines or septic tanks), population size, and average 30-day rainfall (using data from the 15 days before and 15 days during the case-control study). For all analyses, we derived the statistical inference using robust estimates of the standard errors from a generalized estimating equation approach (Zeger et al., 1988). This approach accounts for residual correlation of the outcomes of individuals within the same villages and provides inference that is not sensitive to model misspecification. The relatively low prevalence of diarrhea in this population permitted us to estimate relative risk with the prevalence odds ratio from our logistic model (Jewell, 2004). All analysis was conducted by using STATA version 8 (Stata, College Station, TX).

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A10

IN-ROADS TO THE SPREAD OF ANTIBIOTIC RESISTANCE: REGIONAL PATTERNS OF MICROBIAL TRANSMISSION IN NORTHERN COASTAL ECUADOR[32]

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Abstract

The evolution of antibiotic resistance (AR) increases treatment cost and probability of failure, threatening human health worldwide. The relative importance of individual antibiotic use, environmental transmission, and rates of introduction of resistant bacteria in explaining community AR patterns is poorly understood. Evaluating their relative importance requires studying a region where they vary. The construction of a new road in a previously roadless area of northern coastal Ecuador provides a valuable natural experiment to study how changes in the social and natural environment affect the epidemiology of resistant *Escherichia coli*. We conducted seven bi-annual 15-day surveys of AR between 2003 and 2008 in 21 villages. Resistance to both ampicillin and sulphamethoxazole was the most frequently observed profile, based on antibiogram tests of seven antibiotics from 2210 samples. The prevalence of enteric bacteria with this resistance pair in the less remote communities was 80 percent higher than in more remote communities (OR = 1.8 [1.3, 2.3]). This pattern could not be explained with data on individual antibiotic use. We used a transmission model to help explain this observed discrepancy. The model analysis suggests that both transmission and the rate of introduction of resistant bacteria into communities may contribute to the observed regional scale AR patterns, and that village-level antibiotic

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use rate determines which of these two factors predominate. While usually conceived as a main effect on individual risk, antibiotic use rate is revealed in this analysis as an effect modifier with regard to community-level risk of resistance.

Introduction

Antibiotic resistance (AR) threatens human health worldwide (Hogberg et al., 2010). As resistant bacteria spread, and failure of antibiotics in the clinical setting increases in frequency, infections require more expensive drugs and are more likely to be associated with serious morbidity and/or mortality (IOM, 2003). The cost of these failures exceeds billions of dollars annually in the United States (Foster, 2010). That the evolution of AR is influenced by individual antibiotic use in human and veterinary medicine is well known (Collignon et al., 2009; Love et al., 2011), and programmes aimed at limiting the spread of resistant bacteria often focus on restricting antibiotic use and/or choosing therapeutic options that minimize selection for resistance (Drusano, 2003). Yet, resistance mechanisms are often complex, suggesting that resistant bacteria are not likely to arise by antibiotic selection pressure over the course of treatment alone, and in many cases, the genes that confer resistance must have been acquired by colonizing bacteria or shared among bacteria on mobile genetic elements (MacLean et al., 2010).

The emphasis on evolution of AR during treatment ignores the role of acquisition of resistant bacteria via other transmission routes, such as environmental pathways and human contact patterns. The relative role of these different factors in determining the prevalence of AR within and across communities has not been studied, however, and in general, little is known about the spread of resistant bacteria in community settings. The relationship between the total antibiotic use and the rate of AR spread among individuals in a population is an important but unresolved question, as is the role of broader ecological processes in spreading resistant bacteria among animals and humans (Smith et al., 2002a, 2006). Studying population-level processes shifts the emphasis from individual use to overall antibiotic use rates and the number of other people who carry resistant bacteria (Bonten et al., 1998). Transmission models are important tools to study such system-level population processes.

Mathematical models of infection transmission have been used throughout the twentieth century to help understand the epidemiology of infectious diseases (Anderson and May, 1991). These theoretical approaches describe the ecological and evolutionary dynamics of host–pathogen interactions that generate disease patterns in space and time (Smith et al., 2002b). Mathematical models have been applied to the emergence and the spread of resistant bacteria, extending simple transmission models to reflect competition, such as simple infections

with colonization inhibition (Bonhoeffer et al., 1997), complex infections with resistance (Austin et al., 1997), or amplification of resistant bacteria owing to overgrowth following antibiotic use (Smith et al., 2002a). In general, these models have focused on hospital settings (Bonten et al., 2001) and quantify the effects of different infection control measures (Bonhoeffer et al., 1997; Bootsma et al., 2006; Lipsitch et al., 2000; Massad et al., 1993). In hospital settings, health care workers are often modelled as vectors that spread resistant organisms among patients (Austin et al., 1999).

Mathematical models can also offer important insights into the mechanisms and extent of the spread of AR in community settings, which are more difficult to study. Recent AR models have focused on movement of patients among hospitals (Austin et al., 1999), long-term care facilities (Smith et al., 2004), and the community (Austin et al., 1997) and the role of antibiotic use in agriculture (Smith et al., 2002a). Emergence of AR can be modelled as an invasive pathogen (Smith et al., 2002b) into the human population (Smith et al., 2002a, 2005) using models that incorporate spatial and social processes (Singer et al., 2006).

Evaluating the relative importance of individual medication use, environmental transmission, and rates of introduction of AR bacteria in explaining community AR patterns requires studying a region where there is variability in all of these factors. The construction of a new road in a previously roadless area of northern coastal Ecuador provides a valuable natural experiment to study how changes in the social and natural environment, mediated by road construction, affect the evolution and the spread of AR enterobacteria. This study area, comprising villages with varying degrees of remoteness relative to the main road (Figure A10-1), offers an ideal location for studying AR at a community scale. Since we postulate that the social and ecological changes that might affect the spread of AR bacteria will unfold over a large time scale, we use remote villages as a proxy for conditions prior to the construction of the road and close villages as a proxy for conditions after. We, therefore, use a cross-sectional design along with statistical models to examine AR as a function of remoteness, and we use mathematical models to explain the relative contributions of: (i) antibiotic use; (ii) transmission of AR bacteria, generally mediated through standard water, sanitation, and hygiene environmental pathways; and (iii) rates of introduction of resistant bacteria, represented in our model as an ingestion factor, in explaining observed patterns of AR in 21 communities. The spread of resistant bacteria is framed here as a spatially inhomogeneous process that affects prevalence. This occurs through both environmental sources and human movement patterns, whose effects are modified by conditions that increase the potential for human-to-human transmission, such as poor sanitation. Based on 5 years of data across 21 communities, we describe regional patterns of AR prevalence and use a transmission model to provide plausible explanations for these observed patterns.

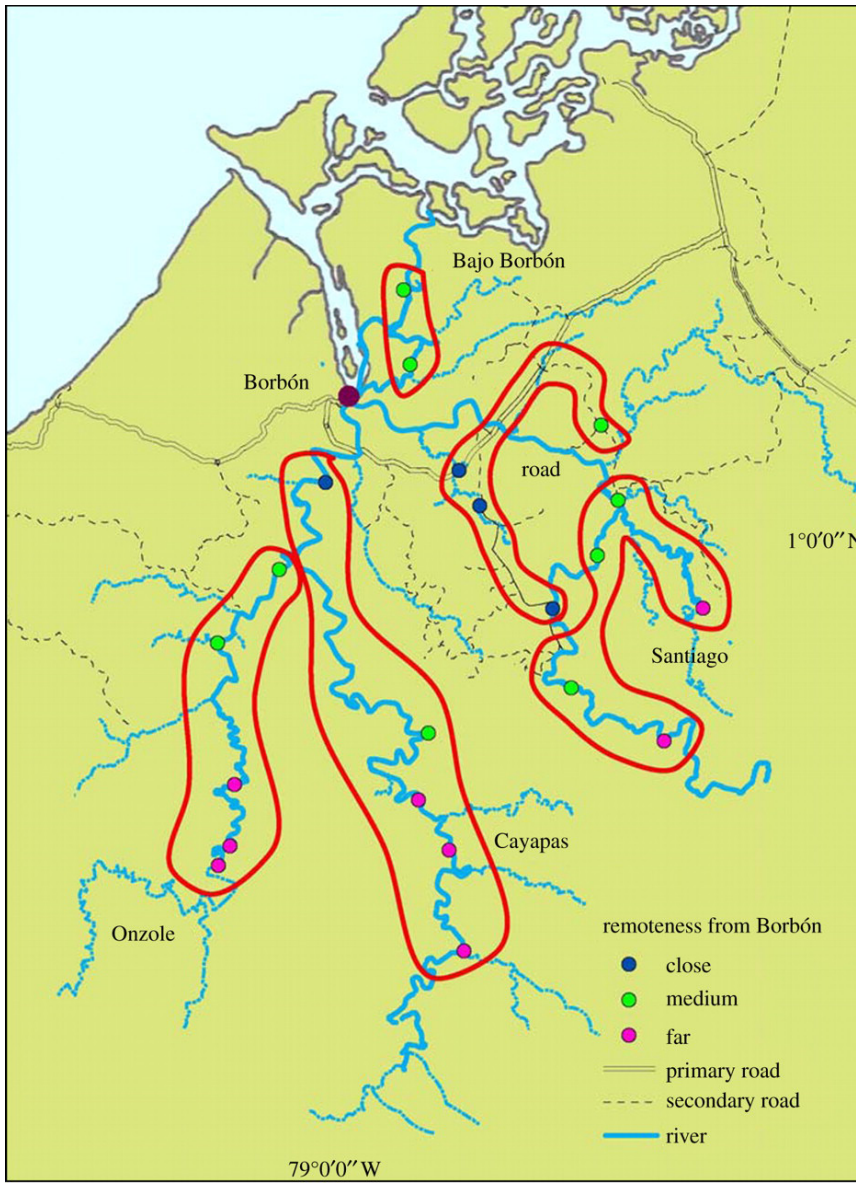

FIGURE A10-1 Map of study region. The 21 villages are categorized by river basin (Santiago, Cayapas, Onzole, Bajo Borbón, and road), and by remoteness (close, medium, and far).

Methods

Study Site

In the northern Ecuadorian province of Esmeraldas, approximately 150 villages (ranging from 20–800 inhabitants) lie along the Cayapas, Santiago and Onzole rivers, which all flow towards Borbón, the main population centre of the region (with 5000 inhabitants). Villagers primarily consume untreated surface source water and sanitation facilities are inadequate. The region, populated primarily by Afro-Ecuadorians (Whitten, 1965), is undergoing intense environmental and social changes owing to the construction of a new highway along the coast, which connects previously remote villages to the outside world. Construction of the road was completed from Borbón westward to the provincial capital of Esmeraldas in 1996 and from the coast eastward to the Andean mountains in 2003. Secondary and tertiary dirt roads off of this two-lane asphalt highway are continually being built, mostly for logging and the area has come to be known as one of the world's top 10 biodiversity hotspots (Myers et al., 2000). At the time these data were collected, 15 per cent of the 150 villages in the region were accessible by road.

All villages in the region were categorized based on their geographical location relative to Borbón. A sample of 21 villages was selected by using block randomization to ensure that villages of varying remoteness and population sizes were represented; four of these were connected to the road when this study began. All households within each village were recruited, except in Borbón, where a random sample of 200 households (from approx. 1000) was selected for inclusion in the study. Consent was obtained at both the village and household level. Institutional review boards at the University of California Berkeley, University of Michigan, Trinity College, and Universidad San Francisco de Quito approved all protocols.

Study Design

Between August 2003 and February 2008, each enrolled village was visited seven times, with each visit lasting 15 days. Villages were visited on a rotating basis, during which time field staff identified all cases of diarrhoea through active surveillance. For each case of diarrhoea (defined using WHO standards as three or more loose stools in a 24 h period), two controls were randomly sampled from the same community, and one control was sampled from the case household. Controls were defined as someone with no signs of diarrhoea in the previous 6 days. Four 15-day case-control visits were conducted in Borbón. Antibiotic usage was measured through a sequential random sample of households where many of the households were measured more than once. A key informant was asked whether any household members had used antibiotics within the last week and, if so, they were asked to name the drug. Responses from the key informant were

converted to the individual level by recording usage for those identified by the survey and imputing a response of "No usage" for the remaining individuals who were known to live in the house from previous demographic surveys.

Classifying Remoteness

For each village, travel time and total cost of travel to Borbón were recorded by field staff members. Specifically, transport time was estimated assuming the use of a motorized canoe or bus, depending on location, and transport cost was determined through inquiries of key informants within each community. For each village, i, rank of remoteness, R_i, was calculated by summing normalized values of time, T_i and cost, C_i. Specifically,

$$R_i = \frac{T_i}{\sum_j^{21} T_j} + \frac{C_i}{\sum_j^{21} C_j}.$$

Since the metric is the result of two values standardized to a [0,1] scale, the possible range of R_i is from 0 (the town Borbón itself) to 2 (the theoretical farthest community from Borbón). Villages were classified into three groups based on their remoteness metric: close, medium, and far from Borbón. The categorical breakpoints were selected by maximizing the differences in the mean remoteness values for each category.

Microbiological Analysis

Stool samples were collected by field staff from cases and controls, stored on ice and processed within 48 h and tested for the presence of *Escherichia coli* and AR. Lactose-positive isolates that were identified as *E. coli* were further analysed for antibiotic susceptibility (to ampicillin (amp), cefotaxime, chloramphenicol, ciprofloxacin, gentamicin, sulphamethoxazole–trimethoprim (sxt) and tetracycline) using the disc-diffusion method following standard methods. To test for the presence of *E. coli*, stool was plated directly onto MacConkey agar; lactose-positive colonies were further cultured in Chromocult agar. The five most prominent lac+ isolates were initially selected and one confirmed *E. coli* isolate was randomly chosen for further AR analysis. All lactose-negative isolates were analysed for urease and oxidase, and with API 20 E (bioMérieux Corp) to speciate the bacterial isolates. Lactose-positive isolates that were identified as *E. coli* were further analysed for antibiotic susceptibility (to amp, cefotaxime, chloramphenicol, ciprofloxacin, gentamicin, sxt and tetracycline) using the disc-diffusion method following standard methods (Bauer et al., 1966; Blake et al., 2003). As sulphamethoxazole and trimethoprim work synergistically, they are commonly

used together, often in the same pill. Therefore, one standard clinical approach is to screen for the combined resistance to both at the same time with discs impregnated with both antibiotics, and the resulting resistance to both antibiotics is then listed as sxt resistance. This was done as part of this study, with the limitation that we do not have information on *E. coli* isolates that were resistant to sulphamethoxazole, but not trimethoprim, or vice versa. These seven antibiotics were chosen to be included in this study because they were reported to be the most commonly used antibiotics in the region both by physicians within our field staff and by other physicians who also work in the study region.

Statistical Analysis

Our statistical analysis consists of the following: (i) calculating prevalence of each AR profile correcting for the unequal sampling probabilities of cases and controls; (ii) estimating the variability of individual-level antibiotic use using random effects models to compare variability over time over space; (iii) estimating the association between AR and remoteness using binary response general estimating equation (GEE) models; (iv) summarizing prevalence of antibiotic use in terms of drugs most frequently used, and in terms of prevalence of use; (v) exploring how antibiotic use rates vary as a function of remoteness to investigate their potential utility in explaining observed AR patterns; and (vi) examining the assumptions associated with aggregating our AR data over time.

Calculating Prevalence

The data used to estimate the distribution of AR was a non-standard case-control design consisting of cases, household controls, and community controls. Since cases are relatively rare, simple estimators of prevalence are potentially biased owing to over-representation of cases. To obtain community prevalence estimates, therefore, required different analytical techniques that use the following weighting procedure. Cases (those presenting with diarrhoea) were given a weight of 1, since all cases in each community were sampled, giving them a sampling probability of 1. Household controls (those sampled within a house with a case and not presenting with diarrhoea) are weighted by the inverse of the proportion of the susceptible population of household controls represented by the control sample. The equivalent weight is also calculated for the community controls (note, this weighting was done by community and collection cycle, and thus the weighted contribution of a community/cycle to the analysis is the same regardless of its total population size, i.e. the communities are the units). Using these weights, we calculate the standard Horvitz–Thompson estimator (Lohr, 1999) of prevalence, which yields unbiased estimators of population means and proportions in unequal probability samples.

Variability of Antibiotic Use

To compare the variability of antibiotic use over time and over space, two random effect models are fit with antibiotic use as the dependent variable. In the first model, the variance of the random offset corresponding to household is estimated; in the second, the variance of the random offset corresponding to time point. Comparison of the size of these variances is then used to give an indication of whether there is more variability between households (spatial) or between time points (temporal). Further details on this analysis are given in the electronic supplementary material.

Association Between Antibiotic Resistance Prevalence and Remoteness

To explore the relationship between amp–sxt resistance prevalence and remoteness, we estimate the odds ratio between the binary indicator of amp–sxt resistance and (i) the binary indicator of medium/close remoteness, using "far" as the reference category, as well as (ii) the binary indicator of residence in Borbón using the other communities as the reference category. To correct for unequal probability sampling, each observation is replicated a number of times equal to its sampling weight. Odds ratios are estimated by fitting a logistic regression model to this expanded dataset. To derive the statistical inference for the relevant measures of association, we relied on the clustered non-parametric bootstrap, specifically re-sampling 21 villages with replacement from the expanded dataset and estimate the odds ratio from this "bootstrap dataset" (Efron and Tibshirani, 1993). This process is repeated 10,000 times to estimate the sampling distribution of the odds ratios, and we use the quantile method to derive the 95% CI. In the far versus medium/close comparisons, only bootstrap datasets that have at least two villages from each remoteness category are included, since the sampling of villages was done to create variability between villages in terms of remoteness. Therefore, datasets with 1 or 0 villages in one or more remoteness categories do not reflect the sampling distribution of interest. Similarly, in the Borbón versus community comparisons, bootstrap datasets that did not include Borbón at least once did not contribute to the reported confidence intervals (CI).

Prevalence of Antibiotic Use

To characterize the per-day prevalence of use, we calculate the proportion of individuals that report having used antibiotics within the last week and scale this quantity by 7, tacitly assuming that individuals only used drugs on 1 day within the last week and it was equally likely to have been any day. Since individuals could have ingested drugs on more than 1 day, our use rate constitutes a lower bound. To look at what drugs are most commonly used, we summarize the relative frequency of drugs used among those that reported use (electronic supplementary material, table S1).

Antibiotic Use and Remoteness

Antibiotic use at a community level is estimated by the sample proportion of respondents who reported using antibiotics. We consider an individual to have used antibiotics if they indicate they have consumed any of: amp, amoxicillin, sulphamethoxazole, trimethiprim, or benzipenicillin. Ordinary least-squares regression was used to look at the relationship between the village-level proportion and remoteness. Although the proportion reporting use is clearly bounded between 0 and 1, the discrepancies from the regression line appeared symmetric (electronic supplementary material, figure S2), making ordinary least squares a tenable choice.

Aggregation of Antibiotic Resistance Data Over Time

To justify that the effect of remoteness on amp–sxt resistance is static, this relationship is assessed at each of the seven time points using a GEE model in the same way as was done in estimating the relationship between remoteness and AR prevalence on the full dataset. For each time point separately, we fit an independence GEE model with remoteness category as the lone predictor and amp–sxt resistance as the response variable. Confidence intervals for the odds ratios comparing "far" with the two other categories were produced using the same non-parametric bootstrap described for the full dataset, and intervals were examined for overlap (electronic supplementary material, figure S1). Greater detail is given in the electronic supplementary material.

Modelling

We use a village-level compartmental transmission model (Smith et al., 2002a) to examine the observed patterns of AR prevalence in our study communities. We chose a compartmental model, which assumes populations are well-mixed, because it provides better explanatory power than more complex model structures for understanding factors that drive transmission. A deterministic model does not allow for the possibility of stochastic die-out, but at the phenotypic level, we do not observe this; i.e. all communities have non-zero prevalence. At the genotypic level, there could be stochastic die-out of specific strains, however, we do not have the genotypic information to illustrate this and therefore did not include this level of resolution in the model. The equation and parameters are shown in Figure A10-2. This model tracks four conditions among humans: (i) not colonized with resistant bacteria (W); (ii) transiently colonized with resistant bacteria, such that the bacteria have a high probability of dying out (X); (iii) colonized with resistant bacteria such that the population is more stable and less likely to die out compared with the exposed state (Y); and (iv) amplified or colonized with resistant bacteria such that bacterial species are present in high numbers and are actively reproducing (Z).

	parameter definitions	values (d^{-1})
λ	per capita rate of exposure to new AR strains (exposure rate)	10^{-3}
α	rate at which populations in exposed people are lost (transient loss rate)	0.1
θ	per capita rate at which exposed people become colonized (colonization rate)	0.001
σ	rate at which regular populations are lost (colonized loss rate)	0.003
γ	rate at which amplified populations are lost (amplified loss rate)	0.007
φ	per capita rate at which amplified populations revert to low-density colonized populations (recolonization rate)	0.003
ρ	per capita rate that humans are prescribed an antibiotic that amplifies the AR bacteria populations (prescription rate)	0.01
η	transmission rate between unexposed and colonized individuals	0.0154/0.0325
β	transmission rate between unexposed and amplified individuals	0.154/0.325

state variables:

W: unexposed
X: exposed (transient infection likely to die out)
Y: colonized (stable infection less likely to die out)
Z: amplified (stable with increasing population size)

model equations:

$$\frac{dX}{dt} = (\lambda + \eta Y + \beta Z)W - (\theta + \alpha + \rho)X$$

$$\frac{dY}{dt} = \theta X + \phi Z - (\rho + \sigma)Y$$

$$\frac{dZ}{dt} = \rho(X + Y) - (\gamma + \phi)Z$$

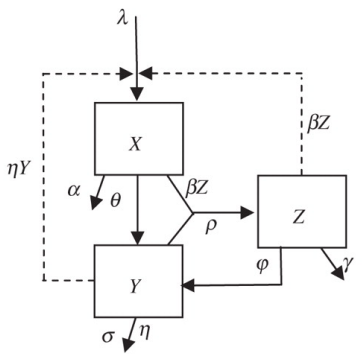

FIGURE A10-2 Deterministic antibiotic resistance model. $W = 1–X–Y–Z$. See Smith et al. (2009a) for details.

The model assumes that human exposure to resistant bacteria comes from either: (i) the spread of these AR bacteria through standard water, sanitation, and hygiene pathways, or (ii) the ingestion of new antibiotic resistant strains that arise from either environmental sources (e.g., food or water) or introduction through movement of people to and from the region. AR spread is modelled as person-to-person transmission. Amplified resistant bacteria (Z) are assumed to transmit at a higher rate, β, than the unamplified or colonized bacteria, which transmit at a rate η. The rate of ingestion is described by the parameter λ. Antibiotic use, at a rate ρ, is assumed to alter the community ecology of the gut, eliminating competition with antibiotic-sensitive bacteria and allowing the population density of resistant bacteria to increase. The remaining five parameters that represent the rates of movements between states are described in Figure A10-2 as well as in Smith et al. (2009a).

Although we observe that cases have higher prevalence of AR than do controls, both cases and controls have higher prevalence of AR in the less remote villages. Thus, in the simulation analysis, we do not make a distinction between cases and controls.

An estimate of the transmission rate was established using *E. coli* prevalence data from our study region. Previous analysis of these data suggests an eightfold difference in *E. coli* prevalence comparing remote versus non-remote villages (Eisenberg et al., 2006). We use the prevalence values from this analysis for these two types of villages in conjunction with a susceptible–infected–susceptible (SIS) model (with disease duration of one week) to estimate β, the rate of transmission from amplified to susceptible individuals. β is estimated to be 0.154 new infections per infectious individual per susceptible individual per day for the most remote village, and 0.325 for the least remote village, a transmission rate ratio of 2.11. To explore the sensitivity of transmission to AR prevalence, we vary this ratio in our simulation analysis from 0.9 to 9 keeping the baseline transmission rate for remote villages at 0.154. The rate of transmission from colonized to susceptible individuals, η, is assumed to be one-tenth the value of β because colonized individuals have smaller populations of AR bacteria in their gut than amplified individuals.

The antibiotic use rate, ρ, is based on survey data collected in each village, and does not vary by remoteness. The antibiotic use data, employed to estimate the antibiotic use rate parameter, ρ, are presented in §3. We specify the range for the antibiotic use rate by extending the 95% CI, resulting in the range ρ: 0.001 to 0.01 antibiotics per person per day.

The per capita rate of human exposure to new strains (introduction rates), λ, is unknown for this region. We use the same per day baseline rate (0.001) reported in Smith et al. (2009a) to represent a remote village. To explore the sensitivity of λ to AR prevalence, we vary the rate of non-remote villages so that the ratio ranges from 1 to 10. The assumption that introduction rates are higher in non-remote villages is consistent with the observation that there is more human

movement to and from outside the region in these non-remote villages (Eisenberg et al., 2006), providing more opportunity to introduce AR bacteria.

To examine the interaction between antibiotic use rates, transmission rate ratios comparing remote and non-remote villages, and introduction rate ratios comparing remote and non-remote villages, we simulate the model for a range of each of these three factors and use contour plots to present their relationship. The outcome measure is the risk ratio comparing a remote to a non-remote village. This risk ratio measure was compared with the empirical results presented in Table A10-2.

Results

Between 2003 and 2008, a total of 2,210 *E. coli* isolates were successfully analysed (518 were cases with diarrhoea and 1,692 were controls without diarrhoea). We stratify our analysis by case/control status since the microbiota of those with diarrhoea is quite different from those without diarrhoea. Using results of screening isolates for sensitivities to seven antibiotics, we observed 39 unique profiles. The nine highest frequency profiles are listed in Table A10-1. The distribution of antibiotic profiles differs between cases and controls with cases having a tendency towards a higher frequency of resistance. Three of the most frequently observed profiles include resistance to amp and sxt. Sulphamethoxazole-resistant genes and trimethoprim-resistant genes are almost always present on the same integrons, while β-lactamase genes encoding resistance to amp can sometimes also be found in the same integron (Novais et al., 2006; Robin et al., 2010) or

TABLE A10-1 Estimated Prevalence, Weighted by the Inverse Sampling Probability, of Antibiotic-Resistant *E. coli* Profiles

	Prevalence (per 100)		
Profile	Total	Cases	Controls
none	67.5	51.5	67.8
amp–sxt–tet	8.0	19.8	7.8
tet	6.9	4.0	7.0
other	3.5	4.7	3.5
amp	3.0	3.5	3.0
sxt–tet	2.9	1.8	2.9
amp–sxt–tet–clo	2.6	4.6	2.6
amp–tet	2.3	3.5	2.3
amp–sxt	2.1	6.3	2.1
sxt	1.0	0.3	1.1

Cases are defined as those with diarrhoea and controls are those without. All profiles with frequencies of less than 1 percent are placed in the "other" category. The antibiotics tested are: ampicillin (amp), tetracycline (tet), sulphamethoxazole–trimethoprim (sxt), chloramphenicol (clo), cefotaxime (ctx), gentamicin (gen) and ciprofloxacin (cip).

outside of the integron, but on the same plasmid (Miriagou et al., 2003; Woodford et al., 2009). In contrast, tetracycline resistance is never found as part of an integron (Partridge et al., 2009). Thus, amp and sxt resistance are more likely to be horizontally and clonally transmitted together. For this reason, and because antibiotics that select for amp–sxt resistance are frequently used in the region (see below), we focus analysis on amp–sxt.

We first report on the relationship between remoteness and amp–sxt resistance, showing that amp–sxt resistance decreases with remoteness. We next present our data on antibiotic use and show that there is no relationship between antibiotic use and remoteness, suggesting that the relationship between AR prevalence and remoteness cannot be explained by differences in use rates alone. We present the results of an infection transmission model that examines the interaction between antibiotic use, transmission of resistant bacteria and introduction of resistant bacteria into villages in determining regional patterns of AR. The model analysis suggests that patterns of transmission as well as patterns of introductions of resistant bacteria into communities contribute to the regional-scale AR patterns we observed, and that antibiotic use rates determine which of these two factors predominate.

Ampicillin–Sulphamethoxazole–Trimethoprim Resistance as a Function of Remoteness

Ampicillin–sulphamethoxazole–trimethoprim (amp–sxt) resistance is significantly associated with lack of remoteness (Table A10-2). This trend is consistent

TABLE A10-2 Prevalence and Odds Ratio of Simultaneous Antibiotic Resistance to amp and sxt Among Participants Living in 21 Villages in Ecuador

	Sulphamethoxazole and Ampicillin Resistance			
Remoteness	Case prevalence (infections per 100)	Control prevalence (infections per 100)	Overall prevalence (infections per 100)	OR (95% CI)
Far	35.2	12.4	12.8	1.0
Medium	32.6	13.4	13.8	1.1 (0.6, 1.8)
Close	43.0	20.1	20.5	1.8 (1.3, 2.3)
Community	37.6	15.6	16.0	1.0
Borbón	46.4	19.4	20.0	1.3 (1.1. 1.6)

Cases are defined as those with diarrhoea and controls are those without. Medium and close categories are compared with the far category. Observations are weighted based on their inverse sampling probability to account for unequal probability sampling.

for both cases and controls. Estimating the community prevalence based on a weighted sum of the case and control observations, there was little difference in villages of far and medium remoteness (OR = 1.1 [0.6, 1.8]) whereas close villages have higher prevalence relative to far villages (OR = 1.8 [1.3, 2.3]). Similarly, there are higher levels of resistance in Borbón, the main population centre of the region, compared with the communities collectively (OR = 1.3 [1.1, 1.6]). Although data were observed at seven different time points, we aggregate the data in this analysis, making an assumption about temporal stability of these relationships. This assumption is supported by data presented in electronic supplementary material, Figure S1, which show that the confidence intervals for the odds ratios stratified by time overlap.

As with any symptom-based definition, there is the possibility of misclassification; however, if we assume that the disease misclassification is non-differential across our exposure (in this case remoteness of our study villages), then misclassification will bias the results towards the null. We would, therefore, expect greater differences among our remoteness categories if we could adjust for this bias.

Antibiotic Use

During the study period, we surveyed 1,875 individuals about their antibiotic use in a population that averaged around 4,000 at any given time. On average, each sampled individual was surveyed 1.3 times over the study period, ranging from one to six times, also resulting in multiple measurements of each household. A random effects analysis of these data supports our sampling strategy for added coverage across households rather than coverage over time (see electronic supplementary material). Among those individuals reporting use, the most frequently named antibiotics were amoxicillin (20% of antibiotics mentioned), amp (13%), sulphamethoxazole/trimethoprim (8%) and ciprofloxacin (8%) (electronic supplementary material, table S1). In the analysis presented in this manuscript, we restrict focus only to drugs that select for amp–sxt resistance. In addition to its constituent drugs, we also include amoxicillin and benzylpenicillin. These are in the family of beta lactams, and therefore their use potentially selects for amp resistance. Over the 5 years of collecting survey data across the region, the average use rate was 0.05 per individual per week. Assuming use is evenly distributed throughout the week, this corresponds to a rate of 0.006 per individual per day, with an associated 95% CI of (0.003, 0.010). This rate per day is used in our subsequent simulation studies. There was no relationship between antibiotic use and remoteness at the community level (see electronic supplementary material, figure S2).

A Transmission Perspective on the Observed Antibiotic Resistance Patterns

We use a transmission model to examine how the interaction among antibiotic use, transmission rates of antibiotic resistant *E. coli*, and introduction rates of antibiotic resistant *E. coli* into villages affect the community-level AR patterns that we observed. As described in the transmission model, the transmission and introduction rates vary by remoteness, whereas antibiotic use does not. Our transmission model analysis suggests that the level of antibiotic use determines which factors explain the risk ratio of AR prevalence when comparing a close village with a far village: the ratio of transmission rates (close versus far) and/or the ratio of introduction rates (close versus far). This result is shown using contour plots of the risk ratio as a function of both the transmission rate and introduction rate ratios for both low and high antibiotic use rates (see electronic supplementary material, figure S3).

To examine the marginal effects of transmission ratio and antibiotic use rate, we integrate out the introduction rate by calculating the geometric mean of the observed risk ratios across all introduction rate values (Figure A10-3). This

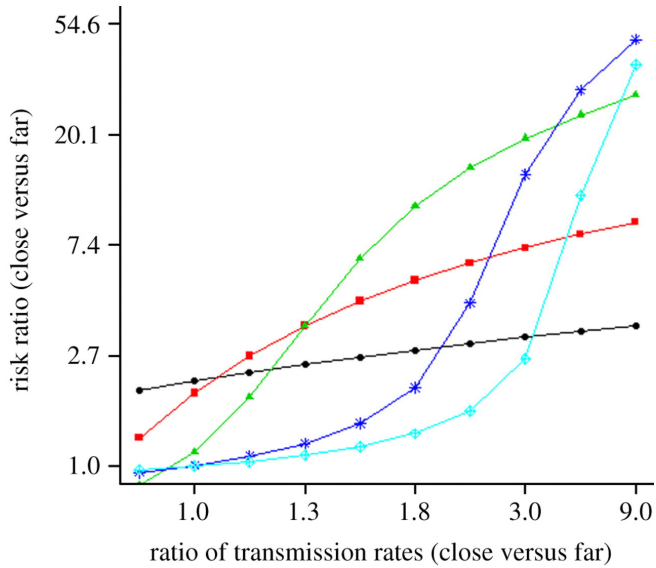

FIGURE A10-3 The risk ratio of AR prevalence comparing a non-remote village (close) with a remote village (far) as a function of the ratio of transmission rates for close versus far villages. Each plot is for a different antibiotic use rate (ρ) ranging from 0.001 to 0.01 antibiotics per person per day. The transmission rate of the remote village is 0.154 (see text for justification). See Figure A10-2 for remaining parameter values. Circles with solid line, $\rho = 0.001$; squares with solid line, $\rho = 0.002$; triangles with solid line, $\rho = 0.003$; asterisks with solid line, $\rho = 0.006$; diamonds with solid line, $\rho = 0.01$.

is virtually identical to risk ratios corresponding to fixing the introduction rate ratio to its midpoint value of two. Figure A10-3, therefore, presents a plot of the effect of the ratio of transmission rates in close versus far communities on the risk ratio for sxt–amp resistance in close versus far communities for various antibiotic use rates to display the interaction between use rate and transmission ratio (Figure A10-3). For extremely low antibiotic use rates (e.g. $\rho = 0.001$ per day), the transmission rate ratio has little effect on the risk ratio; i.e. given little selection pressure on AR in the village, transmission cannot amplify the prevalence levels. Under this scenario, the prevalence differences among villages can be attributable to differences in the introduction rates of resistant bacteria. The transition from no relationship to a very strong relationship between the transmission ratio and risk ratio can be seen as ρ increases. As this happens, the transmission rate ratio becomes the predominant determinant of the risk ratio; i.e. antibiotic use selects for AR and resistant bacteria spread throughout the villages via transmission pathways. It appears that in our study region, AR prevalence is most sensitive to changes in the transmission rate ratio. This conclusion is based on our site-specific estimates of: (i) ρ (0.003 to 0.01); (ii) the ratio of the transmission rate, β, comparing close versus far villages (2.11); and (iii) the risk ratio of AR prevalence (1.8 [1.3, 2.3]).

Discussion

Roads have important impacts on social and ecological processes that in turn have impacts on health (Birley et al., 1998). The relationship between roads and disease has been examined for a variety of infectious diseases including HIV, malaria, dengue, and diarrhoeal disease (Carswell, 1987; Dutta et al., 1998; Eisenberg et al., 2006; Vittor et al., 2006). Here, we provide data from a 5-year regional-scale observational study showing that roads can also impact the spread of resistant bacteria. Focusing on *E. coli* resistance to amp–sxt, the most common pairing of antibiotics observed, we found a higher prevalence of antibiotic-resistant bacteria in villages along the road compared with more remote villages. These results are consistent with those of other researchers, who have found higher levels of AR organisms in sites with greater anthropogenic influence (Bartoloni et al., 2009; Pallecchi et al., 2008; Pei et al., 2006; Walson et al., 2001).

However, we found no relationship between antibiotic use and remoteness, which probably relates to the presence of both governmental and nongovernmental organizations that deliver medical care, including antibiotics, throughout the region. Given its homogeneous distribution along the remoteness gradient, we employed a village-level transmission model to better understand how antibiotic use impacts prevalence patterns at a regional scale. Our model analysis suggests that at the regional-scale individual antibiotic use serves to modify the effect of two potentially important processes: the transmission of

E. coli from person to person mediated through environmental pathways, and the introduction of *E. coli* from outside the region owing to the movement patterns of people into and out of the region (Eisenberg et al., 2006). As antibiotic use rates decrease across the region, the differential rate of introduction becomes a more important determinant of our observed prevalence patterns. Transmission becomes an important determinant when antibiotic use increases; i.e. antibiotic use amplifies transmission. Thus, antibiotic use has a regional-scale impact that differs from those impacts that are derived from only considering the individual-level scale.

At the individual scale, experimental evidence suggests that resistant bacteria can be out-competed by their sensitive counterparts (Zeitouni and Kempf, 2011). The implication of this is that once the pressure of antibiotics is removed, the population of resistant bacteria may decrease relatively quickly, making an individual's antibiotic use act primarily as a main effect on his/her probability of colonization with a resistant strain. However, at the community level, the effect of antibiotic use is more complex. Evidence suggests that the fitness costs of resistance can be very low (Andersson and Levin, 1999; Lenski, 1998; Schrag et al., 1997), and therefore the subsequent slow decline in the prevalence of resistant bacteria once the antibiotic use ceases provides continued opportunity for resistant organisms to spread from host to host, from host to the environment, and from the environment to the host. Therefore, interplay between antibiotic use, disease transmission rate, and rate of introduction from the environment must be considered when characterizing drivers of population-level prevalence of resistant bacteria.

Our analysis suggests that the antibiotic use rate acts to modify the impact of the transmission rate and outside introduction rate, indicating that the effect of antibiotic use rate on community-level prevalence cannot be thought of in isolation. When antibiotic use is high (e.g. $\rho = 0.01$, antibiotics per person per day), the bacteria resistant to the antibiotic being used is selected for within the individual, thereby making it more likely for a transmission event to involve a resistant organism. Under these conditions, transmission becomes a major driver of AR prevalence, with outside introduction having a comparatively very small effect. When antibiotic use is low (e.g. $\rho = 0.001$, antibiotics per person per day), most transmission events involve sensitive bacteria, rendering the transmission rate impotent as a driver of AR prevalence (Figure A10-3). In this setting, oral exposure, which occurs through ingestion of bacteria into the gastrointestinal tract, is the primary driver of prevalence; this exposure comes from a variety of sources including introduction from outside the region. Many studies have demonstrated that AR can spread between individuals sharing the same home (Miller et al., 1996), day care centre (Fornasini et al., 1992; Reves et al., 1990), or even community (Mlander et al., 2000). For enteric organisms both transmission and outside introduction occurs through water, sanitation, hygiene, and food

pathways—modes of spread especially strong in agricultural settings (Marshal et al., 1990) and developing countries (Calva and Bojalil, 1996). The transmission of bacteria can occur through these pathways in developed countries as well, albeit at lower rates.

Typical models of AR are set in controlled environments such as hospitals, and focus on the competitive advantage given to resistant bacteria through antibiotic use. In such models, invasion of resistant bacteria from the outside is ignored, potentially because the focus of hospital settings is on the large amounts of antibiotic use and how they are optimally prescribed (e.g., Bonhoeffer et al., 1997). On the other hand, in a community setting, the invasion and the spread of resistant bacteria are an important determinant of prevalence. The inclusion of the rate of introduction of antibiotics and its interaction with transmission and antibiotic use, therefore, is a central piece of our analysis.

The complete understanding of the dynamics of AR spread in the context of social and ecological changes can only be obtained through a systematic and ecological perspective as presented in this study. Our data and analysis support the proposal that understanding the mechanisms of the evolution and the spread of resistant bacteria require a consideration of the ecological dynamics that shape microbial population structure (Singer et al., 2006). These dynamics are mediated through factors that determine selection pressures, routes of transmission and the invasion of resistant bacteria (Singer et al., 2006), which may overwhelm the direct effects of individual antibiotic use in determining the emergence and dissemination of AR across communities or regions. In our study region, the major driver of selection pressure and routes of transmission appears to be a new network of roads, which have strong influence on the social and ecological environment and in turn on the health of communities (Airey, 1992; Coimbra, 1988; Dutta et al., 1998; Vittor et al., 2006). Roads may affect the evolution and the spread of resistant bacteria by influencing the use of antibiotics in the human population, changing hygiene and sanitation, and introducing resistant bacteria when people travel or migrate into a region.

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SOCIAL CONNECTEDNESS CAN INHIBIT DISEASE TRANSMISSION: SOCIAL ORGANIZATION, COHESION, VILLAGE CONTEXT, AND INFECTION RISK IN RURAL ECUADOR[40]

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Abstract

Social networks are typically seen as conduits for the spread of disease and disease risk factors. However, social relationships also reduce the incidence of chronic disease and potentially infectious diseases. Seldom are these opposing effects considered simultaneously. We have shown how and why diarrheal disease spreads more slowly to and in rural Ecuadorian villages that are more remote from the area's population center. Reduced contact with outside individuals partially accounts for remote villages' relatively lower prevalence of diarrheal disease. But equally or more important is the greater density of social ties between individuals in remote communities, which facilitates the spread of individual and collective practices that reduce the transmission of diarrheal disease.

Introduction

Studies of the transmission of infectious diseases (Jolly et al., 2001; Klovdahl et al., 2001) often use social networks as maps of direct contact that facilitate person-to-person transmission of pathogens. From this perspective, relationships are increasingly associated with greater individual-level risk (Newman, 2002). The social cohesion and organization embodied in networks is, however, also critical to the functioning of communities (Hunt and Hunt, 1976; Pahl-Wostl

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et al., 2007; Wallace, 1988), but researchers typically neglect the influence of these factors on community-level infectious disease risk.

Social relationships have long been employed as contacts in transmission models (Aparicio and Pascual, 2007; Bansal et al., 2008; Klovdahl et al., 2001; Meyers et al., 2003) and as protective factors for chronic disease (Berkman and Glass, 2000; House et al., 1988). However, outside the literature on sexually transmitted diseases (Cohen et al., 2007; Holtgrave and Crosby, 2003) there are few examples of the protective role of social relationships in the epidemiology of infectious diseases (Cohen et al., 2003). Yet individuals in strongly connected, socially cohesive communities are more likely to perceive economic and social interests as shared. Consequently, they may be more motivated and better organized to pursue collective goals such as building and maintaining effective water and sanitary infrastructure (Entwisle et al., 2007).

This means that understanding infectious disease risk at the community level requires understanding not only how certain social networks may spread disease but also how other social networks may influence the infrastructure and behavior that can prevent population-level exposure. We examined 2 types of social networks from the same set of villages to test the hypothesis that increased social network connectedness predicts diminished risk of diarrheal illness, using a sample of 18 villages in rural, northern coastal Ecuador. Figure A11-1 illustrates our conceptual model.

We sought to measure specific risk and protective effects of social relationships via survey and social network analysis methods. In the first part of the analysis, we examined the association of village social networks and different routes of exposure to self-reported illness. In the remainder of the analysis, we attempted to explain these associations in terms of factors that affect village social networks (e.g., remoteness) and the mechanisms by which increased social cohesion is linked to diminished illness risk (e.g., improved water sanitation, education).

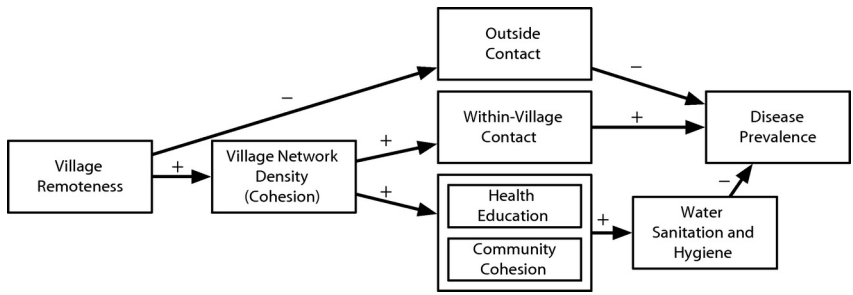

FIGURE A11-1 Postulated conceptual model: Effects of social relationships on disease outcomes, Esmeraldas, Ecuador, 2007.
NOTE: Solid arrows illustrate the hypothesized pathway by which remoteness impacts risk of infection. Arrows are marked by + or – to indicate the directionality of the relationship.

A road was recently built that connects some of these villages to the nearest large town, which has about 5000 inhabitants. Consequently, these villages now vary in their remoteness, measured by distance and time of travel to this trading center. Our previous analysis suggested that increasing remoteness is associated with increasing average degree in village social networks and that increasing average degree is associated with decreased prevalence of diarrheal disease (Trostle et al., 2008). Additionally, the connectivity of villages to communities in and outside the study region decreases with remoteness (Eisenberg et al., 2006). Consequently, less remote villages have more transient inhabitants and are more socially fragmented and therefore may be less able to build and maintain the water and sanitation infrastructure and promote hygiene practices than are more remote villages. We explicitly tested the relationships among these components, as described in Figure A11-1.

We defined a contact network as a network comprising relationships that are likely to facilitate transmission of pathogens, that is, a structure of connections through which an individual, denoted "ego," may infect or be infected by his or her network neighbors, denoted "alters." This network contains all the pathways an infection may follow through the community via direct human contact. In contrast to contact networks, we defined links in sociality networks as connections between people that represent specific types of social engagement. Connections in sociality networks can correspond to casual acquaintance, close friendship and trust, or economic exchange. The presence or absence of these relationships affects infection risk because they often determine whether communities have effective sanitary infrastructure and health services. In this way, more network connections (e.g., friends) may indicate protective social support, instead of increasing exposure, as in a contact-only network (Christley et al., 2005).

Community Social Structure and Risk

Understanding how sociality networks influence infection risk in these villages required us to answer the question of how social organization and action can inhibit or enhance pathogen transmission via the environment. Figure A11-1 illustrates the mechanism by which we posit that this occurs. Poor quality sanitary infrastructure is a leading cause of infection by enteric pathogens such as cholera (Checkley et al., 2004; Rego et al., 2005; Tumwine et al., 2002), and such infrastructure is usually a public good that requires ongoing funding and management by the community. Transmission of many enteric pathogens is often conceptualized as person-to-environment-to-person, with water acting as the environmental reservoir (Koelle and Pascual, 2004). Greater community cohesion may facilitate better overall water quality through the support of community education programs that impart knowledge of household sanitary practices, such as water filtration, and social organization that produces infrastructural improvements,

such as sewage treatment. Alternatively, improved water quality or sanitation may result from the establishment of social norms and the reinforcement of those norms. If this is true, we would expect to find that the average number of social network connections in a village and risk of infection by enteric pathogens are inversely related.

For example, if ego has many relationships (i.e., has high degree) in her or his village sociality network and belongs to a community organization focused on improving local water quality, it may help reduce the entire village's exposure to pathogens. Although these social relationships can also be transmission pathways, the salutary effects of ego's social engagement may preempt transmission via those connections by reducing village-wide exposure to enteric pathogens in the first place.

Measuring Effects of Sociality and Contact Networks on Risk

We analyzed our illness data with respect to 2 networks. The first network comprised individuals, excluding ego's household members, with whom ego reported having spent time in the previous week. This is called the "passing time network." We used this inclusive definition of contact because a wide range of casual and close contacts can transmit gastrointestinal pathogens (Anderson and May, 1992). In addition to being conceptualized as a contact network, the passing time network may represent sociality in a village. This definition of a sociality relationship highlights many connections between people in the community, without capturing fine-grained social structures. If a widespread, but not necessarily strong, level of attachment to the community is sufficient to stimulate social organization and diffuse information that can reduce infection risk, we would expect that greater average degree in the passing time network would predict diminished risk.

An alternate approach is to constrain membership in the sociality network to relationships corresponding to the question "Outside of members of your household, with whom can you talk about important matters?" This is the second network we used in our analysis, which we call the "important matters network." This network typically contains fewer individuals than does the passing time network, but it may better expose the essential structure of the community. If attachment to the community stronger than that implied by the passing time network is necessary to reduce illness risk, relationships in the important matters network should be better predictors of risk than should those in the passing time network. By comparing results from both networks, we were better able to understand how the nature of relationships in the sociality network affected risk.

Our analysis of sociality conceptualizes risk in terms of the network's village-level features and ego's position in this village-wide network. By contrast, the analysis of contact focuses on ego's risk of infection by ill individuals in his or her household and contact network. This approach, therefore, allowed us

to examine the separate effects of the contact and sociological aspects of social relationships on disease outcomes.

Methods

We collected our data in 18 villages in the northern coastal Ecuadorian province of Esmeraldas. These villages are situated along 3 rivers: Cayapas, Santiago, and Ónzole, all of which drain toward Borbón, which is the major population center of the region. In 1996, a new paved road was built westward from Borbón to the coast, and in 2001 a road connecting Borbón to the Andes was completed. A network of smaller roads linking villages to the main road is under continual construction. These villages vary by remoteness, a function of time and cost of travel to Borbón (for a map of the study region, see Eisenberg et al., 2006). Remoteness influences social relationships and network structure, migration into and out of the region, and other factors that affect both social network characteristics and exposure to infectious diseases.

Outcome Measure: Recent Infectious Illness

Our outcome measure is ego's self-reported diarrheal disease or fever in the week before the survey. Diarrheal illness is defined as having 3 or more liquid stools in 1 day (WHO, 1988). Our initial analyses performed with each outcome in a separate model yielded broadly similar risk factors, so we combined these 2 categories of illness into a single binary response variable. The outcome variable was "1" if the individual had experienced either diarrhea or fever, indicating the individual had recently experienced illness that was likely of infectious origin.

Measuring Community Cohesion and Household Attachment

We took several approaches to measuring social cohesion and organization, utilizing data on the structure of community social networks, education, and participation in community organizations.

We measured the average number of relationships in the sociality network for individuals aged 13 years and older. As the number of connections per person grows, the cohesion of the community is expected to grow as well (Bates et al., 2007; Trostle et al., 2008). Unless otherwise noted, we measured this quantity in 1-unit increments.

Because the effects of social connectedness in villages affect household hygiene and water quality, we expected to see the salutary effects of cohesion at the household level. Because of this, we measured the effect of sociality (passing time or important matters) network degree on risk using the sociality degree of the most connected individual in ego's household, which we defined as ego's household degree. We standardized each village's distribution of household

degree to have mean zero and unit variance, and we have presented household degree in SD units from village mean household degree. This allowed us to measure the effect of ego's household social connectedness relative to the average household in her or his village. We performed data processing with Python 2.7 and social network analysis using *igraph* 0.5.4 for Python (http://igraph.sf.net).

Other Covariates

Village remoteness is a composite of time and cost of travel to Borbón, the commercial center in the region. We normalized this scale so that the closest village had a remoteness value of zero and the most remote village had remoteness equal to 1. For additional information on the construction of this scale, see Eisenberg et al., 2006. Contact network exposure is the number of alters in an ego's contact (passing time) network that reported symptoms in the previous week. Household exposure is the number of individuals in an ego's household reporting symptoms in the previous week.

We also included several measures of village and household sanitation and hygiene: (1) observed hygiene is the average of 23 indicators of household cleanliness across all households in the village, (2) improved sanitation is the proportion of households in the village with a septic tank or a latrine, (3) improved water source measures the proportion of households using piped water or collected rainwater, and (4) water treatment measures the proportion of households in the community reporting that they used some kind of water treatment. For values of these measures by village, see Table C (available as a supplement to the online version of this article at http://www.ajph.org).

In addition to these factors, we accounted for individual and village demographics, contact with individuals outside the village, household wealth, and education. For information on the calculation of these covariates, see the supplementary materials (available as a supplement to the online version of this article at http://www.ajph.org).

Modeling Risk for Individuals Nested in Communities

Because we conceptualized individual outcomes as being influenced by potentially unobserved village-level factors, we expected that responses in a village would be correlated. We dealt with this correlation in all regression models by using mixed-effects logistic regression models with village-level random intercepts and estimates of individual-level fixed effects for all covariates over all villages (Laird and Ware, 1982; Stiratelli et al., 1984). We fitted all mixed-effects logistic regression models to data using the *lme4* package in R 2.15 (http://lme4.r-forge.r-project.org).

Indirect Effects of Village-Level Characteristics on Individual Risk

Village remoteness and sociality networks do not directly affect disease but instead act through (or are mediated by) more immediate factors (e.g., sanitation), as illustrated by Figure A11-1. Because quantifying such indirect effects through the difference of regression coefficients (Baron and Kenny, 1986) is not readily extended to binary response variables, we used an alternate approach. We estimated the indirect effect as the difference between the total association of remoteness with illness and the residual direct association of remoteness and illness, adjusted for the proximal variable. These are quantified by the ratios of the expected probability of illness for individuals in far versus near villages, with and without the mediator in the model.

We assessed statistical significance of this effect using a nonparametric bootstrap; we set the threshold for statistical significance at $P < .05$. Positive values of indirect effect indicate mediation and can be interpreted as the change in the risk ratio comparing far and near villages when the mediator is taken into account. We repeated this analysis to estimate the mediation of average village-level degree. For a detailed discussion of this analysis, see the supplementary materials (available as a supplement to the online version of this article at http://www.ajph.org).

Results

Our data set consisted of 3413 cases obtained in a census with a greater than 95% response rate in the 18 villages in our analysis. To facilitate comparisons between different models using the Akaike information criterion, we included in our analysis only the 2912 (85%) individuals with complete observations for all social network, illness, and sanitation variables. Village-level descriptive statistics for remoteness, illness, water sanitation, water quality, and household hygiene appear in Table A11-1, with villages listed in order of increasing remoteness. Descriptive characteristics of the important matters and passing time networks for each village include average degree and the global clustering coefficient (Table A, available as a supplement to the online version of this article at http://www.ajph.org).

Additional village-level descriptive statistics on organization membership, education, and wealth are available in Table B (available as a supplement to the online version of this article at http://www.ajph.org).

We used logistic regression models to examine the effects of exposures (contact outside villages, in households, and in social networks), household and village-level social network characteristics (degree), village-wide socioeconomic status (wealth, education), and social capital (membership in community organizations) on illness (whether a person had fever or diarrhea; Table A11-2). Model 1 (Akaike information criterion = 2110) shows risk associated with routes of exposure, adjusted for age and village size. This model shows that (1) a 10% increase in the proportion of households with visitors from outside the community in the

TABLE A11-1 Descriptive Characteristics of Villages: Effects of Social Relationships on Disease Outcomes, Esmeraldas, Ecuador, 2007

	Remoteness		Sample size	Fever or diarrheal disease	Households w/water treatment	Households w/improved sanitation	Households w/improved water source	Observed household hygiene index
Village	Continuous	Category	N	Cases/100	%	%	%	Mean
1	0.06	Close	158	15	25	43	43	0.64
2	0.07	Close	642	16	74	33	49	0.70
3	0.13	Close	407	13	18	55	59	0.69
4	0.20	Medium	110	11	14	61	7	0.69
5	0.20	Medium	41	14	0	64	15	0.63
6	0.20	Medium	30	23	93	11	2	0.53
7	0.25	Medium	49	8	33	100	0	0.79
8	0.25	Medium	37	30	72	55	100	0.51
9	0.31	Medium	101	12	0	15	0	0.45
10	0.40	Medium	64	15	0	26	100	0.68
11	0.57	Medium	89	18	23	50	77	0.71
12	0.62	Medium	119	19	19	7	19	0.31
13	0.71	Far	62	10	13	52	48	0.38
14	0.78	Far	185	8	33	55	55	0.71
15	0.80	Far	71	0	15	86	99	0.74
16	0.83	Far	285	8	0	41	82	0.73
17	0.96	Far	324	6	13	56	64	0.73
18	1.00	Far	138	14	5	50	28	0.68
Total	—	—	2912	12.3	30.0	45.4	52.4	0.66

TABLE A11-2 Multivariate Models for Risk of Disease in Previous Week: Effects of Social Relationships on Disease Outcomes, Esmeraldas, Ecuador, 2007

Sociality Network Type	Model 1, None, OR (95% CI)	Model 2 Passing Time, OR (95% CI)	Model 3, Important Matters, OR (95% CI)
Demographics			
Age, decades	0.90*** (0.84, 0.96)	0.90*** (0.84, 0.96)	0.90*** (0.85, 0.96)
Village size	1.11*** (1.03, 1.19)	1.05* (0.99, 1.10)	1.04* (0.99, 1.10)
Ownership of material goods by household	0.86 (0.35, 2.12)	0.90 (0.37, 2.20)	0.86 (0.36, 2.09)
Outside contact, %			
Households with outside visitor	1.12* (1.00, 1.25)	1.10 (0.99, 1.22)	1.08 (0.97, 1.21)
Households with outside trip	1.03 (0.91, 1.16)	1.03 (0.92, 1.15)	0.96 (0.86, 1.08)
Food-sharing exposure	0.84 (0.45, 1.56)	0.84 (0.45, 1.55)	0.89 (0.48, 1.66)
In-household exposure			
No. infected in household	1.59*** (1.41, 1.79)	1.55*** (1.37, 1.74)	1.54*** (1.36, 1.73)
Mean-centered household size	0.86*** (0.81, 0.90)	0.86*** (0.82, 0.91)	0.87*** (0.82, 0.92)
Contact network exposure			
No. infected alters in passing time network	0.91 (0.74, 1.11)	0.97 (0.80, 1.19)	0.95 (0.78, 1.16)
Sociality network			
Household degree		0.64 (0.37, 1.10)	0.59** (0.40, 0.85)
Average degree		0.89** (0.81, 0.98)	0.83** (0.72, 0.95)
Average degree × household degree		1.06 (0.96, 1.17)	1.17** (1.04, 1.32)
Graph clustering		1.18 (0.94, 1.48)	1.12 (0.89, 1.42)
Goodness of fit			
Log-likelihood	−1045	−1038	−1037
Akaike information criterion	2110	2107	2103

NOTE: CI = confidence interval; OR = odds ratio.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .005$.

week before the survey predicted an increased risk of illness (odds ratio [OR] = 1.11; 95% confidence interval [CI] = 1.00, 1.25), (2) a 1-person increase in the number of ill individuals in ego's household predicted increased risk of illness (OR = 1.59; 95% CI = 1.40, 1.78), and (3) a 1-person increase in the size of ego's household was associated with diminished risk (OR = 0.86; 95% CI = 0.81, 0.91). Model 1 also shows no significant change in risk associated with a 1-individual increase in the number of ill alters in ego's community contact network (OR = 0.91; 95% CI = 0.74, 1.11).

For both networks, a 1-unit increase in average village-level degree, adjusted for household and village-level network characteristics, was associated with diminished risk when household degree was fixed at its village mean (passing time: OR = 0.89; 95% CI = 0.81, 0.98; important matters: OR = 0.83; 95% CI = 0.72, 0.95). This translated into an adjusted reduction in risk of 45% or 48% between the least connected and most connected villages for the important matters and passing time networks, respectively. This protective effect remained unchanged in the absence of controls for the number of ill contacts in the community.

The statistically significant interaction in model 3 between village average and household important matters degree (OR = 1.17; 95% CI = 1.02, 1.34) suggests that the protective effect of village-level average degree applied to households with degree less than 0.6 SD above the village mean. Above this level, the associations become nonsignificant, and our data cannot resolve the relationship. This indicates that in villages with high average degree, individuals were always protected regardless of the degree of their household. But in villages where average degree was lower, household degree became protective. This relationship is analogous to herd immunity obtained through high vaccine coverage. (For further discussion of this interaction see the supplement to the online version of this article at http://www.ajph.org.)

As with average degree, residence in the most versus the least remote village in our sample was associated with a large decrease in ego's unadjusted risk of infectious illness (OR = 0.49; 95% CI = 0.29, 0.84). As shown in Table A11-3, this effect can be explained by 4 statistically significant village-level mediators ($P \leq .05$): the percentage of households with an outside visitor in the previous week (indirect effect = 0.058; $P = .013$), improved sanitation (indirect effect = 0.040; $P = .011$), improved water treatment (indirect effect = 0.072; $P = .035$), and ego's household size (indirect effect = 0.014; $P = .007$). We also included average degree in the passing time network (indirect effect = 0.045; $P = .051$) as a mediator, as it has a strong theoretical link with remoteness and was close to our cutoff for statistical significance.

To assess whether these 5 variables could fully explain the association between remoteness and illness, we fit a logistic regression model predicting ego's illness as a function of remoteness, household size, village average passing time degree, and improved sanitation and water treatment. In this model, the relationship between remoteness and illness was no longer significant, and the point

TABLE A11-3 Indirect Effects of Remoteness and Village-Level Average Degree on Risk of Illness: Effects of Social Relationships on Disease Outcomes, Esmeraldas, Ecuador, 2007

Pathogen Exposure	Remoteness, Indirect Effect (95% CI)	Average Passing Time Degree, Indirect Effect (95% CI)	Average Important Matters Degree, Indirect Effect (95% CI)
Outside contact, %			
Households with outside visitor	0.058** (0.008, 0.099)		
Households with outside trip	0.002 (–0.081, 0.121)		
In-household exposure, mean-centered household size	0.014** (0.004, 0.041)		
Wealth, ownership of material goods by household	0.006 (–0.015, 0.019)	0.031*** (0.005, 0.067)	0.010** (0.001, 0.032)
Sociality network			
Average degree, important matters	0.078 (–0.067, 0.352)		
Average degree, passing time	0.045* (–0.011, 0.184)		
Mean village years of education	–0.019 (–0.087, 0.050)	0.017** (0.000, 0.042)	0.020 (–0.041, 0.115)
Participation in community organizations			
Mean no. of organization memberships in village	–0.041 (–0.136, 0.026)	–0.039 (–0.039, 0.151)	–0.028 (–0.116, 0.093)
Max no. of organization memberships in household	0.000 (–0.003, 0.011)	0.002 (0.006, 0.012)	0.005 (–0.016, 0.016)
Water quality and sanitation			
Observed hygiene index	0.006 (–0.010, 0.019)	0.072*** (0.020, 0.142)	0.095 (–0.079, 0.377)
Community improved sanitation	0.040* (0.006, 0.094)	0.146*** (0.058, 0.443)	0.133** (0.033, 0.310)
Community water treatment	0.072* (–0.008, 0.203)	0.168** (0.029, 0.362)	0.004 (–0.009, 0.037)
Community water source	–0.019 (–0.076, 0.031)	–0.007 (–0.025, 0.010)	0.007 (–0.043, 0.076)

NOTE: CI = confidence interval. Positive values indicate mediation. Relative strengths of mediation may be interpreted in terms of differences between values of indirect effect for different mediators of the same distal variable, e.g., remoteness.

*$P \leq .05$; **$P \leq .01$; ***$P \leq .005$. P values reflect proportion of bootstrapped values of indirect effect.

estimate was closer to the null (OR = 0.75; 95% CI = 0.37, 1.53), suggesting that these variables explain much of the variability in risk associated with remoteness and are likely important mediators linking remoteness to illness.

The analysis of indirect effects thus far suggests that remoteness influences risk through village networks and more proximal water and sanitation factors. Further analysis showed that village-level social networks may also exert influence on risk through a number of mechanisms. Improved community sanitation was the strongest mediator of the effect of both average important matters and passing time degree (important matters: indirect effect = 0.133; $P = .003$; passing time: indirect effect = 0.146; $P \leq .001$), whereas community water treatment (indirect effect = 0.168; $P = .006$) is the strongest mediator of passing time degree. Observed hygiene (indirect effect = 0.072; $P = .002$) and average village education (indirect effect = 0.017; $P = .027$) also mediated passing time degree. Additionally, household ownership mediated the relationship between both important matters and passing time degree and risk (important matters: indirect effect = 0.010; $P = .015$; passing time: indirect effect = 0.031; $P = .009$).

After adjusting for these mediator variables, we found that the effect of living in the village with the highest versus lowest average passing time degree (OR = 0.83; 95% CI = 0.35, 1.98) was nonsignificant and slightly closer to the null, whereas the relationship between average important matters degree (OR = 0.47; 95% CI = 0.26, 0.87) and illness was essentially unchanged. This finding suggests that the relationship between degree in the passing time network and risk can be largely explained by community sanitation, community water, observed hygiene, and household ownership. The relationship between degree and illness in the important matters network was not explained by these variables: our measures of nonnetwork protective factors may not be sensitive to all the pathways by which important matters network degree was associated with decreased risk.

Discussion

Highly connected social networks are usually represented as efficient transmission systems (Newman, 2002). By contrast, we have shown how greater connectivity at the village level may inhibit the prevalence of self-reported diarrheal disease and fever. When controlling for sources of exposure to illness, our analysis shows that increasing village-wide average degree is associated with decreasing risk for all households in the passing time network and for households of average degree or above in all village important matters networks.

Our analysis also connects social network, water sanitation, and hygiene factors to the social and environmental context in which the village is situated, that is, its remoteness. The processes of environmental change reflected by a village's remoteness occur over a long time. As a result, analyzing a cross-sectional slice of a group of villages in the same region that are at different stages of social and

environmental transformation provides insight into the effects of these long-term processes.

We postulated that remoteness would affect risk through contact networks and village cohesion (Eisenberg et al., 2006). To test this, we analyzed the protective effects of local social networks as indirect effects of remoteness. Results from this analysis agree with that theory, showing that more remote villages experience decreased risk not only because of a lower rate of contact with individuals from outside but also because the average individual in them has more relationships in the village passing time network and lives in a larger household than does a comparable person in a less remote village. Further mediation analysis suggests that villages with high average degree experience decreased risk of illness through improved water quality and sanitation.

The finding that individuals in larger households experienced decreased risk may be explained by the fact that increasing household size explains some of the protective effects of remoteness. Larger households may indicate more traditional, cohesive communities. This would be consistent with our finding that the protective effect of remoteness manifested at least partly through increased social cohesion.

The finding that household wealth explains some of the relationship between average degree and risk for both the important matters and passing time networks highlights the potential for social capital and household ownership to be mutually reinforcing. However, household ownership was not an independent predictor of risk of illness when we adjusted for village-level attributes associated with remoteness, and the size of this mediation effect relative to measures of water sanitation quality was small, indicating that these effects do not confound the relationship between social cohesion and risk.

Our conceptual model (Figure A11-1) posited that village remoteness was related to reduced risk through increasing village social organization and cohesion. We postulated that strong social organization supports infrastructure and behavior that decrease disease prevalence. Because we conceptualized sanitation and hygiene as village-level constructs, the relatively small number of villages in our sample made it difficult to directly test the hypothesis that water sanitation and hygiene are outcomes of village-level social cohesion. However, ethnographic observations and interviews in these villages have shown how these effects might be produced. For example, we have observed that remote villages tend to have higher and more frequent participation in meetings designed to disseminate health information, whereas factionalism in villages along the road reduces the likelihood that all community members will participate in the same meeting.

Although we have identified 7 factors mediating distal risk factors and disease, additional mechanisms clearly relate remoteness to risk. However, we have demonstrated that relationships in social networks can protect against waterborne disease and that there are important mechanisms by which these relationships

may decrease risk; the scope of this analysis was not to rule out all alternative mechanisms linking remoteness to risk.

In addition to the protective effects of social organization we have outlined, we found that migration between villages, measured by the proportion of households with a visitor from outside the village in the previous week, predicts increased risk of infection. This confirms previous findings from these villages (Eisenberg et al., 2006).

Networks of social relationships can reduce the individual-level risk of illness from infectious diseases by mitigating population-level exposures, thereby preempting person-to-person transmission over these networks. These results expand on the theory that social connectedness and support are important predictors of chronic illness and mortality (House, 2002; Klinenberg, 2002) as well as risk of tuberculosis and HIV infection (Wallace and Wallace, 1998). Infectious disease epidemiologists and social scientists should incorporate these insights into mechanistic models that can explain outbreak and epidemic time series in terms of both the contact and sociality functions of networks. Such models can provide a more nuanced analysis of the relative contributions of social organization and contact to the risk of infectious diseases.

Contributors

J. L. Zelner and J. N. S. Eisenberg designed the study, analyzed the data, and interpreted the results. J. Trostle designed the study and interpreted the results. J. E. Goldstick contributed analytic tools and analyzed the data. W. Cevallos performed field research. All authors contributed to the writing of the article.

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Human Participant Protection

Institutional review boards at the University of California Berkeley, University of Michigan, Trinity College, and Universidad San Francisco de Quito approved all protocols.

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A12

CLIMATE, WIND STORMS, AND THE RISK OF VALLEY FEVER (COCCIDIOIDOMYCOSIS)

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Introduction

Valley fever (coccidioidomycosis) is a Western Hemisphere disease, having been found in several South American, Central American, and North American countries (Laniado-Laborin, 2007). For the most part, the areas endemic for *Coccidioides* spp. are rural areas of low population densities. However in the United States there are exceptions such as Bakersfield in Kern County, California

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(population nearly one million), and populations surrounding Phoenix in Maricopa County and Tucson in Pima County of Arizona whose combined populations are approximately five million. The total number of infections reported from endemic states (Arizona, California, Nevada, New Mexico, and Utah) in 2011 were 10-fold greater than in 1998 (CDC, 2013). That the case rates for these populations have also increased eight-fold indicates that the rise is not simply due to population growth. In this report, we review some of the factors that are responsible for these changes with particular attention to how weather patterns may influence infection rates.

The Problem of Valley Fever

Coccidioidomycosis is a systemic fungal infection caused by *Coccidioides* spp. Spores (arthroconidia) of the fungus that develop in the soil of endemic regions are aerosolized by wind or mechanical disturbance of endemic soil. Inhalation of an arthroconidium into the lungs of a human or another mammal can initiate a respiratory infection. It is estimated that 150,000 such infections annually occur in U.S. residents. The consequences of infection range from no apparent illness in 60 percent of infections, to a self-limited community-acquired pneumonia in another 35 percent. The remaining 5 percent result in a variety of progressive, even life-threatening, complications, either in the lungs or outside of the chest if the fungus travels through the bloodstream to other organs such as the brain, bones, and skin (Figure A12-1). Since two-thirds of all U.S. infections occur in Arizona, the Arizona Department of Health Services (ADHS) has been investigating the overall impact of this problem to the state. A questionnaire survey of newly diagnosed patients with valley fever in 2007 (Tsang et al., 2010) demonstrated the severe consequences associated with infection:

- Illness lasted an average of 6 months.
- 75 percent of employed persons stopped working, half missing 2 or more weeks.
- 40 percent were hospitalized.

In a more recent report, hospital costs alone in 2012 amounted to over $100 million.[53] This, taken with outpatient care costs and lost productivity, suggests that the economic impact of valley fever on Arizona is easily several hundred million dollars annually. In California for 2000 through 2011, hospital costs were greater than $2 billion (Sondermeyer et al., 2013).

[53] See http://azdhs.gov/phs/oids/epi/disease/valley-fever/documents/reports/valley-fever-2012.pdf (accessed December 2, 2013).

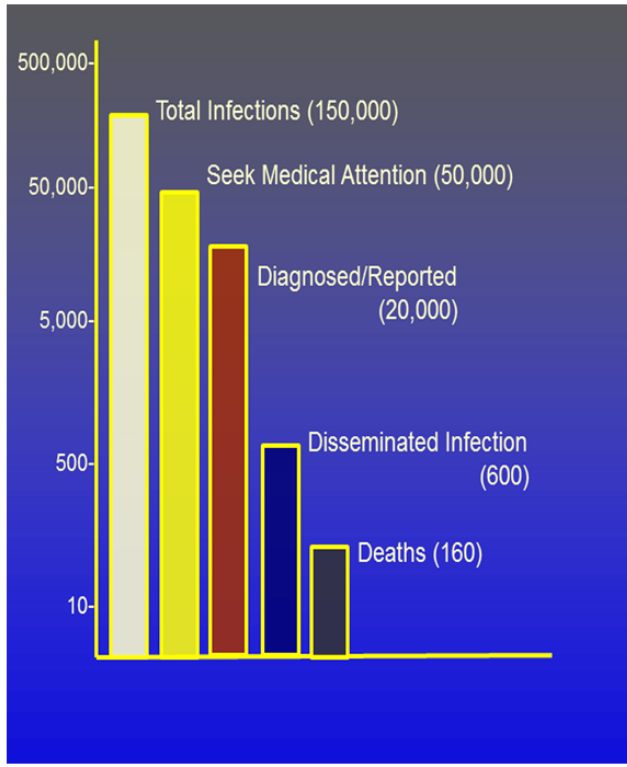

FIGURE A12-1 Coccidioidomycosis. Estimated numbers of total annual U.S. infections with *Coccidioides* spp. and resulting clinical consequences.
SOURCE: Courtesy of Galgiani, 2013.

How Passive Surveillance May Affect Reported Numbers of Valley Fever Infection

There is no question that the nationally reported annual number of patients with coccidioidomycosis has progressively increased since the 1990s. This has been noted in several reports in recent years (CDC, 1996, 2003; Chen et al., 2011; Hector et al., 2011; Leake et al., 2000; Park et al., 2005; Sunenshine et al., 2007; Tsang et al., 2010), but the most recent Centers for Disease Control and Prevention report (CDC, 2013) gives this trend much needed visibility in both the medical community and the general media, which reported on this story nationally. Headlines such as "Valley Fever Cases Skyrocket" and "Valley Fever Cases Are at Their Highest Numbers in Nearly Two Decades" dotted news stories for more than a week following the CDC report. There have been 111,717 cases of coccidioidomycosis reported to the CDC from 1998 through 2011. Arizona

was responsible for 66 percent of these infections and California for 31 percent. Nearly all of the remaining infections were reported from New Mexico, Utah, and Nevada. The annual number of valley fever cases in Arizona and California are shown in Figure A12-2. Case rates reported by the CDC are prevalence estimates based on the general population and not the susceptible population as are disease incidence rates. Care needs to be used when comparing reported case rates between different parts of the country since they do not take into account the proportion of previously infected (now immune) individuals (Tabor and O'Rourke, 2010).

Notably absent from these numbers is representation from Texas, well known to be endemic along its western border (Edwards and Palmer, 1957). There are no reports of coccidioidomycosis from Texas because it is not a reportable disease in that state, underscoring one of the limitations of the National Notifiable Disease Surveillance System (NNDSS): state reporting to NNDSS is voluntary. In addition to missing information from Texas, underreporting by some or many of the nonendemic states is likely as well.

Beyond state reporting decisions, several other surveillance factors need to be met for a patient's infection to be incorporated into the overall case tally. First, only persons sick enough to seek medical care will be included. Second, a clinician needs to consider the diagnosis and order the necessary tests. Third, the tests need to have sufficient sensitivity and specificity to enable the correct diagnosis.

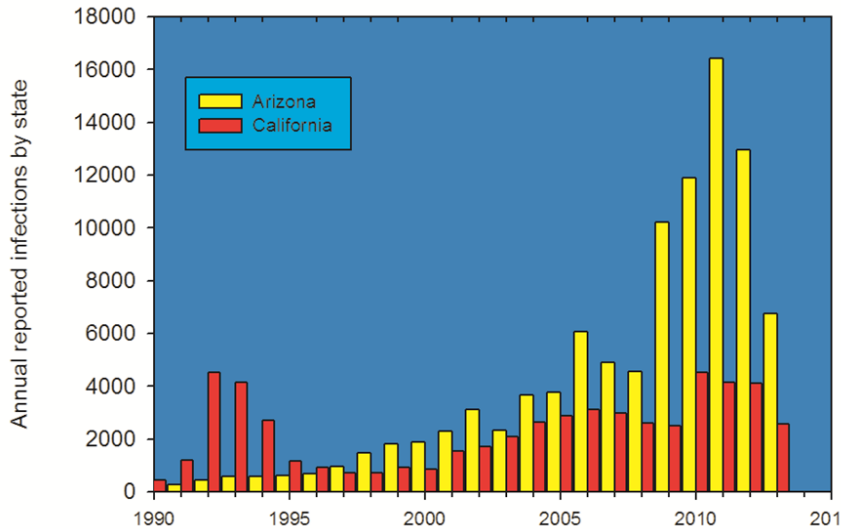

FIGURE A12-2 Annual coccidioidomycosis. Numbers of cases of coccidioidomycosis reported to the CDC by Arizona and California from 1990 through 2013.
SOURCE: Courtesy of Galgiani, 2013.

Fourth, once diagnosed, the infection must be reported to public health authorities. How completely the second, third, and fourth of these steps is conducted has a direct effect on the resulting estimates of disease activity.

Physician awareness of valley fever is variable even within the endemic regions. For example, in a survey by the ADHS, Arizona clinicians were asked about their knowledge, attitudes, and practice with respect to valley fever (Chen et al., 2011). Only 12 percent of respondents indicated they had learned medicine in Arizona schools and 47 percent had no clinical training in Arizona prior to starting practice here. Moreover, 40 percent lacked confidence in diagnosing a coccidioidal infection. In another study of two physician group practices, only 2–13 percent of patients with community-acquired pneumonia were evaluated for *Coccidioides* infection (Chang et al., 2008). These relatively recent studies strongly suggest that the actual number of patients seeking care for valley fever infections is greatly underreported. Moreover, if clinicians improve their capacity for detecting new coccidioidal infections, their changed practices have the potential of significantly increasing the number of reported cases.

Although available serologic tests are effective in diagnosing patients with widespread and long-standing infection, false negatives are common among newly infected patients with disease limited to the lungs. In one study, standard serologic testing missed such infections in about half of first sera tested (Wieden et al., 1996). Improving the sensitivity of clinical testing is under active investigation, and progress in this area could significantly change the number of reported cases. For example, in 2009 a major clinical laboratory in Arizona began using a more sensitive test as indicative of infection. As a result the number of reported cases to the state nearly doubled (Hector et al., 2011).

A puzzling observation in the 2013 CDC report is the disproportionate increase in reported coccidioidomycosis among females in Arizona. The percentage of females with coccidioidomycosis before 2009 was 44 percent, but since 2009 this has risen to 55 percent. One possible explanation for this shift comes from a pair of studies conducted by the University of Arizona Campus Health (Lundergan et al., 1985; Stern and Galgiani, 2010). In their 1985 report, women comprised 44 percent of valley fever cases, but in 2010, females comprised 56 percent of infected scholarship athletes. Between these two studies, screening serologic tests for coccidioidomycosis at Campus Health changed from the less sensitive standard coccidioidal serology (immunodiffusion tests) to the more sensitive enzyme-linked immunoassays (EIAs) (Wieden et al., 1996). This was the same change that was made in 2009 by the major Arizona clinical laboratory mentioned above. Women at the University of Arizona, on average, were found to have lower complement fixation titers (Lundergan et al., 1985), raising the plausible possibility that the increased statewide percentage of females with valley fever could be due to the increased sensitivity of EIAs to lower levels of anticoccidioidal antibodies in women. Certainly further studies are needed to clarify these findings.

Reporting newly diagnosed patients with coccidioidomycosis may not always be complete. For example, although clinicians are required to report new coccidioidomycosis, it may be difficult because of busy schedules. In contrast, if reporting is asked of the clinical laboratory that identifies the positive test, the likelihood of reporting is much greater. In Arizona, the reporting responsibilities were shifted in 1997 to include laboratory reporting, and it is possible that some of the increase in the ensuing years was due to that change.

Relationship Between Weather Patterns and Valley Fever Infections in Arizona

Despite several surveillance considerations just described, none adequately account for the episodic increases seen in California in 1993 and 1994 or in Arizona in 2011 (Figure A12-2). Weather factors such as wind, precipitation, and heat may provide an explanation. The 37 percent increase in Arizona cases in 2011 highlights the interaction of valley fever and weather with the co-occurrence of several spectacular dust storms, known as haboobs. These haboobs were so severe and so directly affecting the urban Phoenix area that time-lapse video footage featured prominently on national evening news programs.[54] As early as 1940, Smith described the relationship between seasonal weather patterns and valley fever incidence: the lowest incidence occurs during the wet seasons; incidence increases with the onset of the dry weather of spring and early summer; the peak season follows the hot summer and increased winds of fall. Smith (1940) also described human activity (harvesting) as an exposure risk. It bears noting, however, that the strength of the association varies across populations and time periods.

Wind is an important factor to generate aerosols of *Coccidioides* spores. For example, in December 1977, a major Santa Anna wind swept across the Central Valley of California, resulting in cases of valley fever in distant, nonendemic areas such as the San Francisco Bay Area (Flynn et al., 1979). In Kern County there were 120 excess cases in the following 3 months (Pappagianis and Einstein, 1978). That was with a Kern County population of approximately 400,000 of which three quarters were likely immune because of prior infection and therefore not susceptible to new infection. In contrast, the Phoenix area population downwind to the July 2011 haboobs was 10 times larger, and three-quarters were likely to be susceptible because of the large in-migration population. Simple extrapolation using these figures results in a prediction of an excess 3,600 infections in the months following July. However, this prediction was not borne out. As shown in Figure A12-3, the week-to-week numbers of reported valley fever cases for the three major urban areas within the endemic region (Maricopa, Pima, and Pinal Counties) were strikingly stable with no apparent increase in cases in the months following the first major July storm.

[54] See http://www.cbsnews.com/2100-201_162-20094755.html (accessed December 2, 2013).

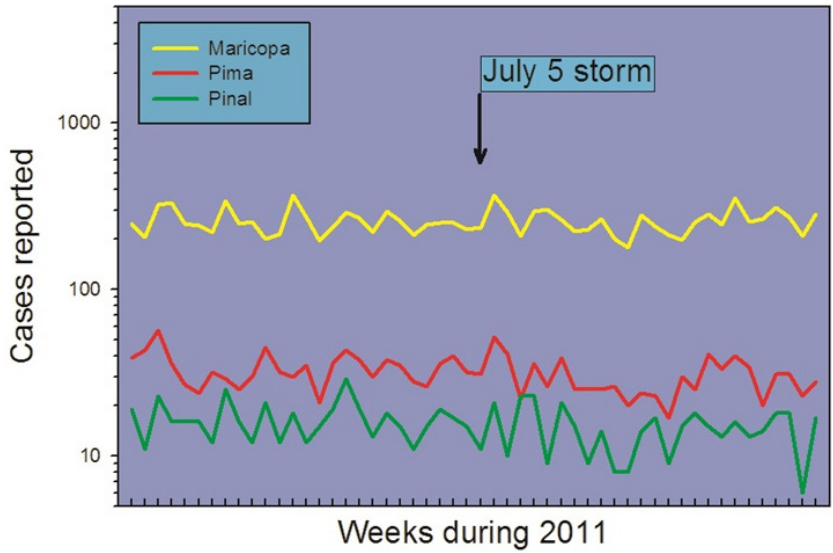

FIGURE A12-3 Dust storms have little effect on Arizona case rates. Weekly reported cases of coccidioidomycosis in selected Arizona counties for 2011.
SOURCE: Courtesy of Galgiani, 2013.

There are at least three possible explanations for how these 2011 observations in the Phoenix area could be so different from what was observed in California in the 1977 storm. First, the California storm occurred in the winter, a time when infections are minimal in Kern County. Therefore, with very low background numbers of cases, the excess cases were very apparent. In contrast, the Phoenix storms occurred when many cases normally are reported. Thus, it is possible that there in fact were excess cases that could not be detected by the passive surveillance that is in place. Second, summer haboobs, although exceptionally spectacular, usually last only a matter of hours. It very well may be that these very short-term peak concentrations and exposures of coccidioidal spores in the air cannot be detected from case reporting due to the attenuating effects of variable disease onset and reporting time. The spores, being 3–5 microns in size, may require only slight turbulence to be lifted from the soil surface into the air. Figure A12-4 is a hypothetical representation of such a situation to illustrate that if spores are being picked up on a regular basis the overall area under the curve for spore density might only slightly be increased from exceptional but brief dust storms. Third, haboobs in the Phoenix area are generally associated with summer thunderstorms, but in different locales across central and southern Arizona they may possess different amounts and types of dust. Much of the dust in and around Phoenix may come from disturbed agricultural and urban land—neither

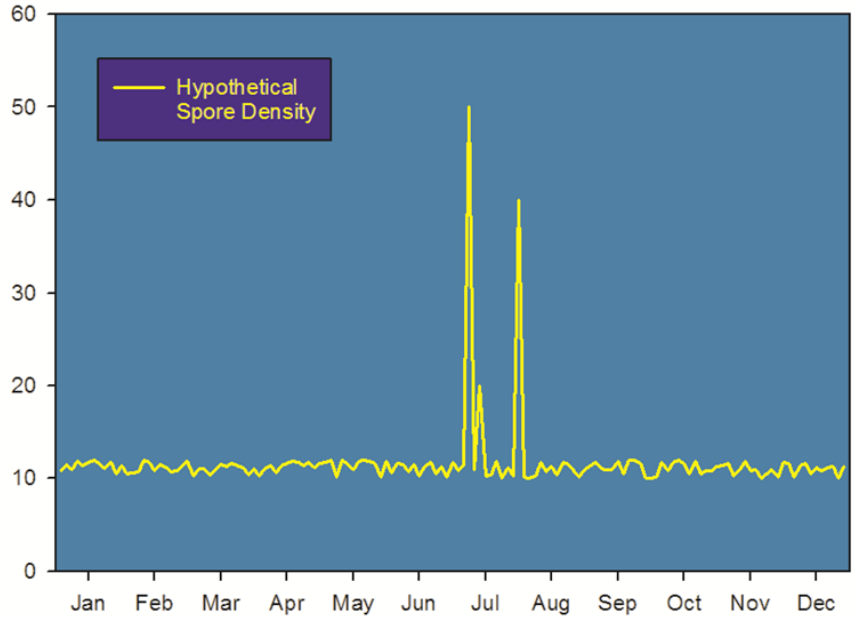

FIGURE A12-4 How dust storm contribution on spore density could be minimal. Hypothetical contribution of episodic wind storms to ambient atmospheric spore density if only small breezes are sufficient to produce an aerosol.
SOURCE: Courtesy of Galgiani, 2013.

of which represents the natural desert soils that *Coccidioides* spp. are thought to favor. Thus the path that these storms cover may largely determine the exposure risk they pose to downwind populations.

Although it is difficult to show a causal relationship between wind storms and the 2011 increase in valley fever cases, a recently developed model shows a strong relationship at seasonal time scales between precipitation patterns and the year-to-year changes in valley fever cases in Arizona. In particular, winter precipitation promotes fungal growth in the soil (Hugenholtz, 1957), and increased precipitation during this period seems to be related to increased incidence of valley fever the following summer and fall (Comrie, 2005; Kolivras and Comrie, 2003; Smith et al., 1946; Tamerius and Comrie, 2011). High summer precipitation, conversely, has a negative effect on incidence, perhaps by reducing the chances of aerosolized spores (Kolivras and Comrie, 2003). Tamerius and Comrie (2011) used data from 1995 through 2006 for rainfall and cases in the Arizona counties of Maricopa and Pima to develop a precipitation-driven model of valley fever cases. They reasoned that the overall trend evident in Figure A12-2 of increasing cases over that period was not climate related and removed the trend to reduce biasing any association between weather and reported cases. Using

an autocorrelation statistical procedure, they were then able to define a primary coccidioidal exposure season of August through March. By examining rainfall patterns before and during these exposure seasons, these authors identified two countervailing relationships. First, the magnitude of rainfall during the winter was positively correlated with the number of reported infections the following season. Second, higher rain amounts during an exposure season resulted in fewer reported infections. Combining these two relationships in a single model during the training period resulted in a correlation coefficient of 0.83 for Maricopa data and 0.73 for Pima County. In preparation for this workshop, this model was updated to the present period for Maricopa County. The model was also used to estimate disease activity backward to 1950 (hindcasting) using historical precipitation data. With the hindcasting, there are no surveillance data available for the majority of this period to validate the accuracy of the results.

Updating the model for Maricopa County The model was updated to investigate the predictive power of winter precipitation and valley fever exposure using current data (1995–2013). The greatest challenge with these data was the aforementioned changes in case definition, reporting, and testing around 2009 that led to a doubling of cases: from under 5,000 to over 10,000 (Nguyen et al., 2013). As in the original publication, the case data were adjusted to estimate exposure dates rather than date of diagnosis or report. Monthly reported incidence (number of cases per 100,000) for each was calculated by dividing the number of cases in Maricopa County by the U.S. Census Bureau estimated annual population for the county. As previously, the data were detrended for the period January 1995–February 2009 by removing the best-fit linear regression (i.e., modeling the residuals). To adjust for the change in the case definition and reporting, the median incidence was subtracted out for the period from March 2009–March 2013. While this standardizes the two distinct periods, the variance for the latter period (2009–2013) is greater and creates difficulty when comparing incidence across study periods. Finally, seasonal incidence was calculated by summing across months during the exposure season (August–March).

Monthly precipitation totals for the grid points in which the Maricopa National Weather Service Station locations fall were acquired from the Oregon State PRISM (Parameter-elevation Regressions on Independent Slopes Model) climate mapping system (http://prism.oregonstate.edu/index.phtml, last accessed December 2, 2013) and averaged for use in the model. The previously identified regression coefficients were applied on the data to estimate the number of exposures per month for the primary exposure season (August–March). There is concordance between the predictions from the model and the observed reported cases for the exposure seasons (Figure A12-5). The model fits relatively well, though it errs in 1998, 2008, 2009, and 2010 (i.e., predicts high when the exposures are low or vice versa). Note that the means of the detrended (observed) time series and the modeled time series have been standardized (forced to equal) for comparison.

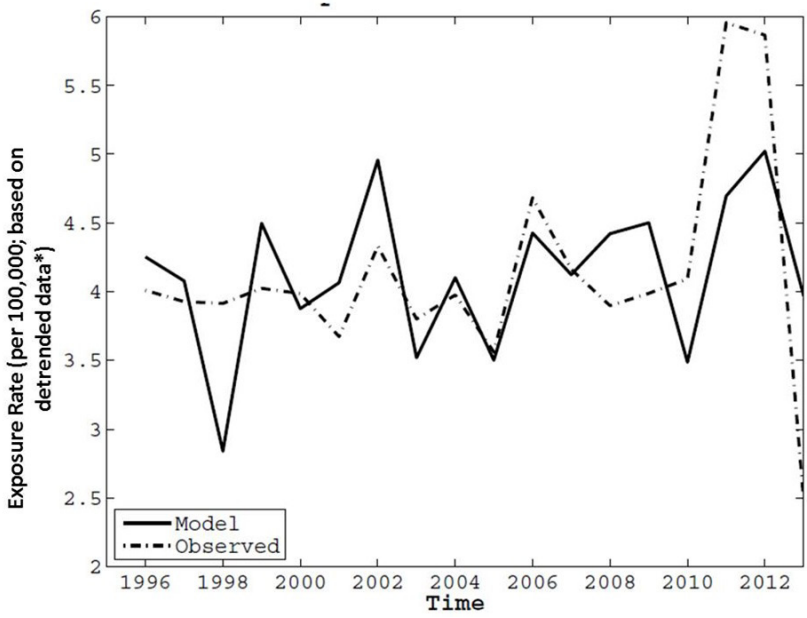

FIGURE A12-5 Model results (1996–2013). Comparison of modeled versus the predicted exposure rates based on October–December precipitation prior to the exposure season and concurrent exposure season (August to March) precipitation. The solid line indicates the model exposure rate and the dashed line the observed rate.

* Tamerius and Comrie, 2010.

SOURCE: Courtesy of James Tamerius.

Hindcasting (1950 through 2013) To estimate the number of cases back in time, we also applied the model to a precipitation time series beginning in 1950 using the same PRISM-based precipitation data for one location, Maricopa County (downloaded from http://www.cefa.dri.edu/Westmap). The model was applied in order to estimate the number of cases that might have been expected in the past. The outcome of this model is the estimated exposure rate for the primary exposure period (August–March) per 100,000.

Average case numbers predicted by the model for the periods 1950–1979 and 1908–2009 are shown in Figure A12-6. The dashed line indicates the time period for which data were available and upon which the original model was built (Tamerius and Comrie, 2011), and the solid line indicates the predictions. Unlike observed temperature increases, the Southwest has not experienced shifting trends in precipitation for the past 110 years (Hoerling et al., 2013). Our precipitation-based model similarly does not appear to indicate any significant change in the predicted seasonal exposure.

Finally, in addition to wind and precipitation, heat and human behavior also play a role the incidence of valley fever. Evidence suggests temperature has a

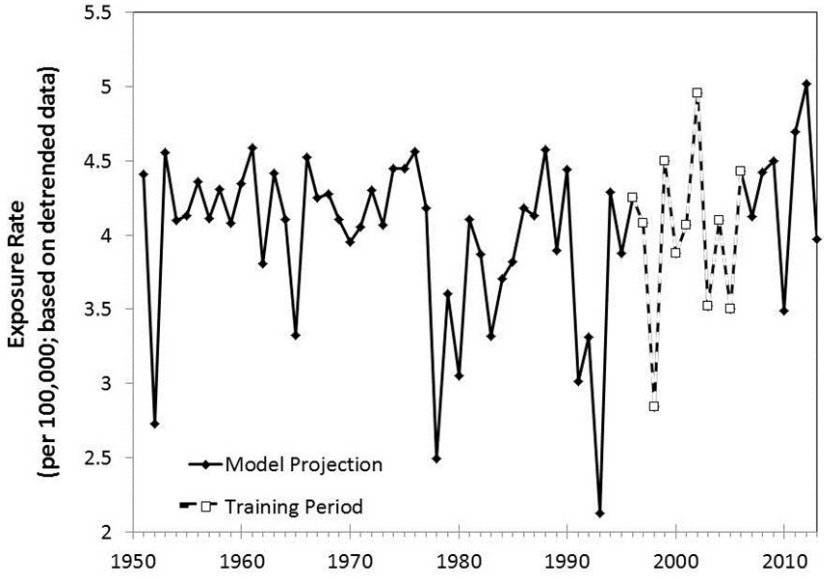

FIGURE A12-6 Hindcasting estimates (1950–2013). Modeled coccidioidal exposure in Maricopa County during August–March for the years 1950 through 2012. The model training period, 1995–2006, is shown as a dashed line while the prediction is a solid line. SOURCE: Courtesy of Andrew Comrie.

role in regulating competition between fungal species. Laboratory experiments showed *Coccidioides* spp. are well adapted to the arid environment, tolerating extreme heat and a wide range of humidity levels (Friedman et al., 1956). High heat and sun is proposed to have a sterilizing effect on soils that may provide a competitive advantage for *Coccidioides* spp. over other soil fungi (Duran et al., 1973; Hugenholtz, 1957; Maddy, 1965). Heat is also thought to facilitate the aerosolization of spores by drying soils. All of these external forces acting upon the fungus are further affected by host behavior. Human or other animal activity such as digging, excavating, and other soil disrupting activities may result in cases outside the climate-driven seasonality (Converse and Reed, 1966; Maddy, 1965). This is further supported by work in Kern County, California, where weather has only a weak association with incidence—the authors attribute human behavior to the observed disease trends in their area (Talamantes et al., 2007; Zender and Talamantes, 2006).

Future Approaches to Better Understand the Effects of Environmental Change on Risk of Coccidioidomycosis

Current knowledge of *Coccidioides* ecology is based mostly on pre-1970 studies and, more recently, inferred from reported human cases that are aggregated

at the county level (Baptista-Rosas et al., 2007; Comrie, 2005; Tamerius and Comrie, 2011). Spatial and temporal precision is low when relying on reported case data, whereas the alternative of analyzing environmental samples collected precisely is expensive and problematic. Indeed, our accumulated understanding about the environmental biology and ecology of *Coccidioides* spp. is largely incomplete, due to specific challenges in identifying the fungus in its natural state. Improvements in PCR detection and direct plating isolation methods for environmental samples are needed in order to replace the standard method of induced infections in laboratory mice (Barker et al., 2012). Here we briefly summarize the literature and identify a pathway to completing this ecological puzzle.

Geographic distribution Much groundwork for identifying environmental correlates of *Coccidioides* spp. habitat was performed in the 1940s and 1950s. Researchers like Maddy (1958) showed an association between valley fever incidence and the lower Sonoran life zone, though subsequent research expanded the endemic zone more broadly. Epidemiological evidence led researchers to believe exposure was inhalational, often windborne (Emmons, 1942a; Smith et al., 1946), despite difficulty recovering *Coccidioides* spp. from the air (Ajello et al., 1965; Anderson, 1958; Converse and Reed, 1966). Weather was also found to play a role in identifying endemic regions that shared a characteristic wet period followed by a dry period with blowing winds (Hugenholtz, 1957; Maddy, 1958; Smith et al., 1946). The association with precipitation patterns has been borne out in modern times as well (Kolivras and Comrie, 2003; Park et al., 2005; Stacy et al., 2012; Tamerius and Comrie, 2011; Zender and Talamantes, 2006).

Rodents and microhabitat Ideas regarding the role of animals in the evolution of *Coccidioides* spp. has been inconsistent. Some researchers have concluded that infected animals, like humans, are accidental hosts to the fungus (Cummins et al., 1929; Pulford and Larson, 1929), while others have proposed a role for the animal carcass as a medium for fungal growth within the soil (Emmons, 1942b; Emmons and Ashburn, 1942). While the mechanism is unknown, there is significant evidence that rodents play a prominent role in the saprophytic phase of this fungus. For example, although the fungus is notoriously difficult to recover from soil (Greene et al., 2000), soil samples collected near animal burrows are often positive for the fungus (Barker et al., 2012; Eulalio et al., 2001; Maddy, 1959, 1965).

Challenges and Future Work

While considerable strides were made in those early years of research on valley fever, Ajello (1967) concluded that "the ecology of these fungi, i.e., the study of their relationship to their environment, is rather superficial and scanty." This sentiment holds today: "ecology of the pathogen, *Coccidioides*, remains obscure" (Barker et al., 2012). Recent outbreaks of coccidioidomycosis in eastern

Washington and northern Utah (Mardo et al., 2002; Marsden-Haug et al., 2013), far outside of known endemic areas, illustrate our poor understanding of these fungi's ecologies. The outbreaks could be due to soil disturbances in isolated patches of *Coccidioides* spp. or due to range expansion. Genetic analyses have shown that valley fever is caused by *C. immitis* in central/southern California and a genetically related, but distinct *C. posadasii* in southern Arizona, Texas, and Mexico (Barker et al., 2007; Fisher et al., 2002). Consideration of differences among these two fungal species will likely help further elucidate distinctions and nuances in the range and habitat of these fungi. However, the difficulty in locating areas of infected soil—which, as noted, may be related to burrowing animals, soil salinity (Ajello, 1967; Friedman et al., 1956), soil type (Maddy, 1958), and vegetation (Egeberg, 1953; Swatek, 1970)—continues to stymie accurate exposure tracking. From a public health standpoint, it is this latter aspect—more narrowly defining exposure risk—that will be critical in reducing the impact of this disease.

Currently, soil samples must be collected in the field, transported to the laboratory, and mouse models exposed to the potentially contaminated soil (Barker et al., 2012; Levine and Winn, 1964; Maddy, 1965) in order to identify *Coccidioides* spp. This is a labor- and cost-intensive method for identifying possible sources and does not lend itself well to large-scale risk mapping. Sorely needed is a means to quickly and accurately identify the microhabitat wherein this fungus thrives.

Conclusions

In this paper, we discuss trends in occurrence of valley fever in the United States. Of note are the challenges this disease presents to prevention efforts: reporting issues, changes in diagnostics and detection, changes in surveillance, and limited tools for assessing risk. We provide an updated version of a precipitation-driven model that fits well for Maricopa County, Arizona. We end with a discussion of the ecology of this disease of the American Southwest and the challenges facing improvements to disease control.

The increase in the number of reported cases and interest following these reports have generated a justifiable spotlight on this disease. As physicians' awareness of the disease increases, there will likely be an increase in testing for valley fever. Accordingly, reported incidence of this disease will likely increase. While improving our capacity to describe the burden of this disease, these increases will be a result of enhanced case identification rather than changes in susceptibility or exposure. In all likelihood, individual patient outcomes will be improved by accurate and earlier diagnosis; however, these changes will not translate into valley fever prevention.

Currently, a serious impediment to prevention is a lack of knowledge about the ecological processes that modulate the presence of *Coccidioides* spp. in the environment. Ecological research is needed that examines the relationships

between the occurrence of *Coccidioides* spp. and soil moisture, soil temperature, and rodent populations. Defining the habitat of this pathogen (identifying specific soils, areas, regions) would enable the identification of risk related to specific human activities or periods of time; possibilities for developing treatment of landscapes to reduce fungal proliferation; and early warning for protection against aerosols (e.g., knowing that sufficient strength winds are blowing across known endemic soils). Until a means to detect the pathogen in the soil is discovered, we are left with broad and sometimes conflicting studies on the risk of acquiring valley fever from the environment.

Also needed is the exploration into the etiological relationships for spore exposure. Not all dust contains viable spores. Many validated models exist for predicting dispersal and exposure of airborne particulates, but not for predicting when and where viable *Coccidioides* spp. spores are entrained into the air from the soil surface. Likely predictors for airborne dispersal and exposure are soil surface temperature, soil surface moisture, vegetative cover, and UV exposure from the sun. Once these ecological and etiological questions can be answered then actionable occupational and land use practices can be identified for disease prevention.

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A13

ZOONOTIC DISEASE RISKS ASSOCIATED WITH TRADE AND MOVEMENT OF ANIMALS

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Globalization of the market for live animals and animal products—combined with human behaviors and preferences for the exotic—are ever-growing risk factors for the translocation of zoonotic diseases to the United States from parts of the world where they are endemic or exist in a reservoir state. Why is there global trade in animals? Animals and animal products are transported across borders for many reasons. They are used for exhibitions at zoos; scientific education, research, and conservation programs; food and nonedible products; for the pet trade; and in the case of companion animals, tourism and immigration. The United States is one of the world's largest consumers of imported wildlife and wildlife products. A recent analysis showed that during 1999–2010, over 80 million vertebrate species were imported to the United States, including 2 million mammalian species; of these, 46 percent were rodent species (Romagosa, 2010; CDC, unpublished data).

In the United States, there is a network of federal, state, and local agency regulations in place to prevent the transmission of diseases carried by animals that could be harmful to humans, other animals, or the environment. There are five U.S. federal agencies whose authorities pertain to movement of live animals: the

[55] Division of Global Migration and Quarantine, U.S. Centers for Disease Control and Prevention.
[56] LandCow Consulting.
[57] Division of Foodborne, Waterborne, and Environmental Diseases, U.S. Centers for Disease Control and Prevention.

U.S. Department of Health and Human Services Centers for Disease Control and Prevention (HHS/CDC), U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA-APHIS), U.S. Fish and Wildlife Service (USFWS), the U.S. Department of Homeland Security (DHS), and the U.S. Food and Drug Administration (FDA). Section 361 of the Public Health Service Act[58] (42 U.S.C. 264) gives the Secretary of Health and Human Services the authority to make and enforce regulations to prevent the introduction into, and the spread of communicable diseases within, the United States. The secretary has delegated the responsibility to oversee the importation of animals, animal products, and other potentially infectious items to CDC. Because of the known human health risks associated with certain animal species, HHS/CDC has promulgated regulations that specifically restrict the importation of animals and animal products such as nonhuman primates (NHPs), dogs and cats, small turtles (those with a shell length of less than 4 inches), African rodents, and goat skin drums from Haiti. Additionally, the importation of animals and animal products of civets (family Viverridae) as well as infectious biological agents, infectious substances, and animal vectors of human disease (such as bats) is restricted under HHS/CDC regulations (HHS, 2001).

CDC's Regulations for Dog and Cat Importation

Importation of dogs and cats is restricted by CDC because these domestic animals carry zoonotic diseases (HHS/CDC, 2003a). They are the most common animals kept as pets in the United States; thus, they have very close contact with humans. Dogs and cats are both capable of transmitting rabies, which is a major reason why CDC's dog and cat regulations are in place. In the United States, widespread mandatory vaccination of dogs has eliminated the canine variant of rabies and dramatically reduced the number of human cases (Velasco-Villa et al., 2008). However, the risk of reintroduction of canine rabies virus variants exists via importation of unvaccinated dogs from areas where rabies is enzootic, such as Asia, Africa, the Middle East, and parts of Latin America. Globally, canine variants are responsible for most of the 55,000 human deaths from rabies estimated worldwide each year (HHS, 2001; WHO, 2009).

Since canine variants of rabies remain a very serious health threat in many other countries, preventing the entry of potentially infected dogs into the United States is a critical public health priority. Each year CDC publishes a list of countries that reported no indigenous cases of terrestrial rabies in the previous year; these countries were formerly known as "rabies-free" countries (CDC, 2014a). At

[58] The Public Health Service Act is a U.S. federal law enacted in 1946. The full act is captured under Title 42 of the United States Code "The Public Health and Welfare," Chapter 6A "Public Health Service" under section 361 of the Public Health Service Act (42 U.S.C. 264). The U.S. Secretary of Health and Human Services is authorized to take measures to prevent the entry and spread of communicable diseases from foreign countries into the United States and between states.

present, CDC allows the entry of dogs from rabies-free countries. Unvaccinated dogs may be imported without a requirement for proof of rabies vaccination if they have been located for a minimum of 6 months or more in a rabies-free country.

Unvaccinated dogs from rabies-endemic countries pose a risk to rabies-free countries for reintroduction of terrestrial rabies. This was evidenced by the reintroduction of terrestrial rabies in Greece and Taiwan (Huang et al., 2013; Tsiodras et al., 2013) Unfortunately, since May 2004 there have been at least four documented instances of dogs being imported to the United States from rabies-endemic areas that subsequently were diagnosed with rabies, necessitating extensive public health investigations to identify persons at risk of exposure and in need of postexposure prophylaxis (PEP) (Table A13-1).

HHS/CDC regulations require that dogs entering the United States be vaccinated for rabies or, if they are not vaccinated, that the importer agree to have the dog vaccinated and confined for 30 days after rabies vaccination to allow for acquisition of vaccine-induced immunity (HHS/CDC, 2003a). While HHS/CDC regulations do not currently require that cats be vaccinated against rabies, HHS/CDC does require that they appear to be healthy upon entry into the United States and recommends that all cats receive rabies vaccinations.

HHS/CDC recognizes the importance of updating its importation regulations to reflect the current global epidemiology of rabies, particularly the importance of preventing the reintroduction of the canine rabies variant into the United States. HHS/CDC published an Advance Notice of Proposed Rulemaking in 2007 seeking input from the public on revising its importation regulations, among other issues, and has used the feedback to draft a new proposed importation regulation. HHS/CDC hopes to publish additional revisions in a Notice of Proposed Rulemaking in the coming year that would strengthen protection of public health by addressing some gaps found in the importation of dogs, cats, and other animals.

TABLE A13-1 Importations of Rabid Dogs to the Continental United States, 2004–2008

Month/Year	No. of dogs with rabies/No. of animals in shipment	Territory or country of origin	No. of persons receiving PEP/No. of persons assessed
May 2004[1]	1/6	Puerto Rico	6/11
June 2004[2]	1/1	Thailand	12/40
March 2007[3]	1/2	India	8/20
June 2008[4]	1/24	Iraq	13/38

Based on data from:

[1]Personal communication, Fredric Cantor, Massachusetts Department of Public Health.

[2]Personal communication, Ben Sun, California Department of Public Health.

[3]Castrodale et al., 2008.

[4]CDC, 2008b.

CDC's Regulations for Turtles: Reemerging Concerns About Salmonella Due to Increased Human Contact with Small Turtles

Although *Salmonella* is prevalent in all reptile populations, to help minimize the risk to the U.S. human population, CDC limits imports of small turtles. Turtles with a shell length of less than 4 inches and viable turtle eggs may not be imported for any commercial purpose (HHS/CDC, 2003c); however, noncommercial imports of up to six turtles with shells less than 4 inches long or viable eggs are permitted. Seven or more small turtles may be imported for science, educational, or exhibition purposes, but the importer is required to obtain a letter of permission from CDC. This rule was implemented in 1975 after it was discovered that small turtles frequently transmitted *Salmonella* to humans, particularly young children for whom the small turtles were very popular as pets. Young children are more susceptible to *Salmonella* infection due to the nature of their interactions with the turtles and lack of hand hygiene.

Also in 1975, the FDA prohibited the sale and interstate distribution of viable turtle eggs and live turtles with a shell less than 4 inches long. FDA restricted the legal sale and distribution of small turtles grown in the United States to the export market only, and required the outside of turtle shipping packages to be labeled conspicuously "for export only." In 1980, the CDC and FDA bans were estimated to prevent 100,000 *Salmonella* infections annually in children younger than 10 years old in the United States (Harris et al., 2010).

The global trade in pet turtles has changed according to consumer preferences, and as a result zoonotic health risks to humans in the United States associated with turtle contact are resurfacing. The United States produced nearly 9 million baby red-eared slider turtles each year from 1997–2003, and 32 million live turtles were farmed and exported from the United States from 2003 to 2005 (National Geographic News, 2009). However, the Chinese turtle industry has been steadily rising, while the supply of U.S.-grown turtles is increasing with no legal outlet. Thus some U.S. suppliers are skirting the FDA regulations that ban the domestic sale of live turtles with a shell less than 4 inches long. They accomplish this by selling turtles in flea markets or from roadside vendors for "educational" purposes, or by selling the terrarium and giving the turtle for "free." These factors, combined with the lack of regulations prohibiting Internet turtle sales, may be contributing to the dramatic increase in turtle ownership over the last 5 years (American Veterinary Medical Association, 2012).

From May 2011 to September 2013, CDC reported 473 human *Salmonella* infections from 41 different U.S. states; 70 percent of ill persons were children 10 years of age or younger; 88 percent of ill persons specifically reported exposure to small turtles (shell length less than 4 inches) (CDC, 2013). In response to this emerging issue, in 2013 CDC warned public health officials globally about the public health risks associated with exportation of animals known to be infected with *Salmonella*.

CDC's Regulations for Nonhuman Primates

NHPs, particularly those recently captured in the wild, may harbor agents in their blood or other body tissues that are infectious to humans. NHPs and NHP products are a potential source of pathogens that can cause severe or fatal disease in humans, including filoviruses, hepatitis A and B viruses, herpes B virus, rabies, tuberculosis, and parasitic infections (NRC, 2003). Cynomolgus, African green, and rhesus monkeys have been associated with outbreaks of hemorrhagic fever viruses such as Ebola and Marburg. Cynomolgus monkeys imported into the United States were previously demonstrated to be infected with Ebola Reston virus (CDC, 1990). Persons working in temporary and long-term animal holding facilities, and individuals involved in transporting animals (e.g., cargo handlers and inspectors) are especially at risk for infection. An epidemiologic link between hepatitis A infections in NHPs, particularly chimpanzees, and their caretakers has been demonstrated (Robertson, 2001). Herpes B virus is a zoonotic agent that naturally infects only macaque monkeys, causing mild illness or no illness, but can cause a fatal encephalomyelitis in humans. Previously reported fatal cases of herpes B virus disease in humans have been caused by animal bites, scratches, or mucous membrane contact with infected materials (Cohen et al., 2002). NHPs, especially macaques, are highly susceptible to tuberculosis; most are imported from areas of the world with a high prevalence of these diseases in humans and animals (CDC, 1993). NHPs might also be a source of flaviviruses (e.g., yellow fever virus), which can be transmitted to humans by mosquitoes that have previously fed on an infected NHP (Mansfield and King, 1998). Transmission of yellow fever from NHPs to humans through vectors has occurred (Richardson, 1987). Imported NHPs have also been known to contract melioidosis, caused by *Burkholderia pseudomallei* (Johnson et al., 2013).

U.S. quarantine requirements for imported NHPs are designed to reduce these infectious disease risks. While NHPs have been regulated by public health authorities since the 1950s, CDC has prohibited the importation of NHPs except for scientific, educational, or exhibition purposes since 1975. Current regulations maintain that imported NHPs and the offspring of NHPs imported after 1975 may not be maintained as pets or as an avocation with occasional display to the general public. Also under current regulations, NHP importers are required to register with CDC, and this registration must be renewed every 2 years. NHPs are required to be held in quarantine for a minimum of 31 days following entry into the United States. CDC's regulations also require registered importers to maintain records on imported NHPs and to immediately report NHP illnesses or deaths that occur during the 31-day quarantine period to CDC. During the quarantine period, all imported NHPs must complete three negative tuberculin skin tests.

Additional requirements for importers of NHPs were developed and implemented in response to specific public health threats. On January 19, 1990, CDC published interim guidelines for handling NHPs during transit and quarantine in response to identification of Ebola virus (Reston strain) in NHPs imported to the

United States from the Philippines (CDC, 1990). In April 1990, there was confirmation of Ebola virus infection but no apparent disease in four NHP caretakers. As a result of these findings, as well as serologic evidence that African green, cynomolgus, and rhesus monkeys potentially pose a threat of human exposure to filoviruses, CDC placed additional restrictions and permit requirements on importers wishing to import these species. In 2013, CDC codified these additional restrictions into comprehensive nonhuman primate regulations found at 42 Code of Federal Regulations (CFR) 71.53 (HHS/CDC, 2013).

CDC's Regulations for Bats

Under 42 CFR 71.54, CDC restricts the importation of infectious biological agents, infectious substances, and animal vectors of human disease. Importers must satisfy several conditions and obtain a CDC import permit before importing any infectious biological agents, infectious substances, or animal vectors of human disease. Because they are viewed as "animal vectors of human disease," all imported bats require an import permit from CDC (HHS/CDC, 2003b). Bat imports additionally require a permit from the U.S. Department of Interior's Fish and Wildlife Service for reasons related to wildlife conservation and prevention of the introduction of invasive wildlife species into the United States. Bats can serve as reservoirs for many zoonotic infectious agents and are prohibited from import for personal use as a pet. Marburg virus is clearly associated with a species of bat called *Rousettus aegyptiacus*, at least in Uganda, and one or more other species are almost surely associated with Ebola virus (Calisher et al., 2006). In addition, bats are known to be the keystone reservoirs for rabies virus, other lyssaviruses related to rabies, and henipaviruses, and were identified as the reservoir for severe acute respiratory syndrome (SARS) coronavirus (Cui et al., 2007).

CDC's Regulations for Rodents: Monkeypox Case Study

The emergence of human monkeypox in the Western Hemisphere in May–June 2003 was a vivid reminder of why importation of wild animals into the United States is a concern from a public health perspective. Monkeypox is a zoonotic disease endemic to Central and West Africa. African rodents are considered to be the natural host of the virus which, in humans, causes a systemic febrile illness and rashes similar to smallpox (CDC, 2004b; Khodakevich et al., 1988). Human infections during the 2003 outbreak were traced back to contact with pet prairie dogs that had contracted monkeypox from diseased African rodents imported for the commercial pet trade (CDC, 2003; Hutson et al., 2007; Reed et al., 2004). The shipment of mammals imported from Ghana contained more than six species and a total of 762 African rodents, some of which were confirmed to be infected with monkeypox virus. The U.S. monkeypox outbreak resulted in 72 human cases, 37 of which were laboratory confirmed (CDC, 2003). Most patients

had direct or close contact with the infected prairie dogs, including 28 children at a day care center and veterinary clinic staff (Reynolds et al., 2007).

On June 11, 2003, CDC and the FDA, pursuant to 42 CFR 70.32(b) and 21 CFR 1240.30, respectively, issued a joint order prohibiting, until further notice, the transportation or offering of transportation in interstate commerce, or the sale, offering for sale, or offering for any other type of commercial or public distribution, including release into the environment of prairie dogs and the six implicated species of African rodents (FDA, 2003; Gerberding and McClellan, 2003). In addition, pursuant to 42 CFR 71.32(b), CDC implemented an immediate embargo on the importation of all rodents (order Rodentia) from Africa. This emergency order was superseded on November 4, 2003, when the two agencies issued an interim final rule creating two complementary regulations restricting both domestic trade and importation, intended to prevent the further introduction, establishment, and spread of the monkeypox virus in the United States. In 2008 the FDA portion restricting interstate movement was lifted because there was no evidence that monkeypox virus was continuing to circulate in the United States. It was agreed that CDC's ban on importation of African rodents was sufficient to protect public health and therefore should remain in place (HHS/CDC, 2003d).

Rodents that originate outside of Africa, from other parts of the world including Asia, Europe, and South America, also constitute a significant public health risk. In addition to harboring poxviruses, rodents are also known to carry hemorrhagic fever viruses, arenaviruses, hantaviruses, rickettsioses, and parasites (Azad, 1990; Eremeeva and Dasch, 2008; Heymann, 2008; Hugh-Jones et al., 1995).

CDC conducted an analysis of the numbers and origins of rodents imported to the United States since CDC's African rodent ban was instituted in 2003. CDC analyzed data from the United States Fish and Wildlife Service's Law Enforcement Management Information System (LEMIS) database, which records the entry of wildlife species to the United States. Since 2003, the CDC ban has effectively limited legal importation of African rodents; the number of rodents from Africa entering the United States decreased by 90 percent. However, the commercial pet market has found a new niche in rodents from other parts of the world, as the number of rodents from Europe, Canada, and South America imported to the United States increased by 300 to 29,800 percent (CDC, unpublished data). These data illustrate the need to reevaluate whether the rodent ban should be expanded to restrict the importation of all rodents to the United States.

CDC's Regulations for Civets: SARS Case Study

In 2003, CDC issued an emergency embargo restricting the importation of civets under 42 CFR 71.32(b). This action was taken because of civets' potential to serve as an amplifying host for transmission of SARS coronavirus to humans.

CDC has interpreted this ban broadly to include all members of the family *Viverridae*. Although bats were ultimately discovered to be the vector of SARS, concerns about the unique susceptibility of members of the family *Viverridae* to SARS coronavirus, and the extremely high viral load that they experience as a result of infection, keeps the embargo in place, with exceptions allowing importation by permit for science, exhibition, or education (CDC, 2004a).

CDC's Regulations on Products from Restricted Animals: Bushmeat

In other parts of the world, especially parts of West Africa, mammalian wildlife species (including rodents, bats, antelope, and NHPs) serve as an important human food source called bushmeat. Bushmeat is highly desired among many African expatriates, and when shipped it is typically not treated (e.g., cooked) to render it noninfectious. Because of concerns about bushmeat's potential to transmit zoonotic diseases, CDC prohibits the importation of mammalian species listed in 42 CFR part 71.

The Bushmeat Crisis Taskforce, an organization that works to prevent the illegal harvesting of meat from wild animals, estimates that approximately 15,000 pounds of meat harvested from African wildlife are illegally imported into the United States each month (Goldman, 2007). Inspection capabilities at U.S. ports of entry are limited, given the scope of trade and travel. For example, in 2012 there were 373,441 nonresident passenger arrivals in the United States from Africa, representing an 86 percent increase in travel since 2004 (International Trade Association, 2012). From September 2005 to December 2010, there were 543 seizures of CDC-prohibited bushmeat at U.S. ports of entry. Nearly 80 percent of bushmeat confiscated by CDC was from West Africa. Half of these confiscations were rodents; included among the confiscations were specimens of NHPs, birds, porcupines, and bats (Bair-Brake et al., 2013).

Many of the animals eaten as bushmeat harbor pathogens that are dangerous to humans, and there are no regulations to ensure that bushmeat is properly decontaminated or otherwise safe for human consumption. Viral pathogens carried by NHPs pose the greatest public health risk. Human immunodeficiency virus infections probably originated from chimpanzee-to-human transmission through hunting and butchering the animals eaten as bushmeat; the virus then adapted to human hosts and was subsequently transmitted from human to human (Hahn et al., 2000). Ebola virus has been detected in chimpanzees in Côte d'Ivoire, and human infections with the virus were found to be associated with contact between chimpanzee hunters and dead chimpanzees (Formenty et al., 1999). Simian immunodeficiency virus was detected in 131 out of 788 (16.6 percent) serum samples from monkeys in Cameroon (Peters et al., 2002), and simian T-lymphotropic virus has been identified in monkeys from Cameroon (Courgnaud et al., 2004). During 2008–2010, a pilot project conducted by CDC and partner organizations

identified simian foamy virus, cytomegalovirus, and lymphocryptovirus in NHP specimens confiscated at U.S. ports of entry. These viruses have been shown to infect humans (Smith et al., 2012a).

Even with regulations in place, inconsistent surveillance and enforcement of penalties at U.S. ports of entry makes bushmeat importation difficult to control; bushmeat continues to be found in mail, checked or hand-carried luggage, and cargo on international flights. CDC, FDA, and other federal agencies are forming a multiagency working group to coordinate efforts to prevent bushmeat importation.

Challenges to Preventing Zoonotic Diseases Associated with Animal Importation and Exportation

As stated earlier, five federal agencies are responsible for regulating live animal movement. A 2010 Government Accountability Office report on live animal importation concluded that agencies needed to work more closely together to reduce the risk of importing zoonotic animal-related diseases (U.S. Government Accountability Office, 2010). Areas of major concern cited by the report's authors included the need to identify and resolve differing program priorities, identify and leverage resources, examine ways to improve data sharing on live animal imports, and assess whether any additional legislative authority was needed to ensure that live animal imports posing a risk of zoonotic and animal diseases do not enter the United States.

There are loopholes in current regulations, and instances where CDC lacks statutory authority to enact certain regulations. For example, CDC's existing regulations allow the importation of dogs too young to be vaccinated for rabies. Furthermore, CDC lacks the statutory authority under the Public Health Service Act to regulate exportation of animals that carry pathogens known to infect humans. Reports of human *Salmonella* infections were traced to frozen mice sold by a U.S. company to a distributor in the United Kingdom, who then sold the mice over the Internet to U.S. and Canadian customers. Possible routes of transmission to humans included handling frozen or thawed mice, handling reptiles infected by consumption of the mice, handling or cleaning the reptile's habitat, or cross-contamination in the kitchen where mice were thawed. The sale of these infected mice resulted in hundreds of human *Salmonella* infections, including at least 34 cases in 17 U.S. states and over 500 cases in the United Kingdom (CDC, 2010; Harker et al., 2011). In addition, there have been recent reports of human *Salmonella* infections abroad associated with contact with small turtles that had been exported from the United States (Angulo et al., 2010).

Fiscal and human resource constraints limit regular inspection and surveillance of shipments, cargo, and luggage and consistent enforcement of CDC regulations at U.S. ports of entry. State and local public health agencies are often asked to help enforce CDC regulations such as dog confinement agreements.

With increasing strain on their budgets, state and local public health officials are less able to comply.

Recommendations

There are multiple regulatory and operational challenges to preventing zoonotic diseases associated with importation of animals, animal products, and other potentially infectious items into the United States. In these instances, updating and strengthening regulations and import restrictions applied to a wider range of species than currently regulated could be the only effective means of preventing the introduction of exotic infections into the United States. CDC is working towards amending its regulations to institute further requirements and restrictions for entry of dogs and other animals of concern into the United States, and it is working on a proposal to limit the list of the rabies-free countries only to those that have no lyssaviruses.

The capacity of U.S. federal agencies that oversee animal importation to identify and track imported animal species and quantify shipments should be enhanced. For example, under the Security and Accountability for Every Port Act of 2006 (SAFE Port Act, Public Law 109-347), federal agencies with regulatory responsibilities related to importation and exportation of goods are required to participate in the International Trade Data System (ITDS). ITDS, working through U.S. Customs and Border Protection's Automated Commercial Environment system, is an electronic information exchange capability, or "single window," through which businesses will transmit data required by participating agencies for the importation or exportation of cargo. ITDS is intended to significantly enhance compliance with federal regulations related to trade, including CDC's animal importation regulations. Once fully implemented in FY2017, ITDS will enable CDC, as well as other agencies with a role in regulating the importation of animals, to receive cargo manifest and other data in advance of arrival at a U.S. port of entry, and benefit from automated targeting algorithms that will target anomalies in inbound animal shipments. ITDS should not only improve compliance with CDC animal importation regulations, but also enable more effective coordination with other federal agencies to address risks posed by imported animals.

The U.S. federal government, as well as state and local agencies, have a major role to play in the promulgation, enforcement, and coordination of policy and regulations. However, prevention of diseases arising from animal importation is also a shared responsibility with animal importers, the pet industry, veterinarians, and other health care providers. When establishing an animal as a new patient, veterinarians should inquire about the animal's origin and its recent history of travel. Veterinarians should also know how to recognize and report foreign animal and zoonotic diseases. Human health care providers should obtain animal contact

history from their patients and be familiar with zoonotic diseases, including those that are not endemic to the United States.

Educational strategies have already been implemented, but they need to be expanded to inform the public about the risks of zoonotic diseases. In 2007, CDC and some of its partners conducted focus group discussions among African expatriates in the United States, many of whom reported consuming bushmeat. A theme that emerged from the discussions included evidence of long-standing cultural practices of hunting and eating bushmeat in their countries of origin, making it difficult for consumers to understand the potential health risks. Focus group participants mentioned that "since U.S. merchants sell bushmeat, it must be legal"; thus there is a lack of understanding among consumers about the illegality of importation (Bair-Brake et al., 2013). This scenario points to the need for further education of consumers and sellers of bushmeat in the United States. Another example is seen through zoonotic transmissions of infectious diseases from pets, such as tularemia, salmonellosis, and lymphocytic choriomeningitis virus infection (CDC, 2004c, 2005, 2008a) and how these incidents have served as opportunities to educate the public about safe handling of animals. Educational materials on the prevention of reptile- and amphibian-associated salmonellosis are available in four languages. Pet retailers have been and can continue to be valuable partners in this effort, and CDC works with this industry in collaboration with the Pet Industry Joint Advisory Council (2014). Multiple guidances published by the American Academy of Pediatrics, CDC, and the National Association of State Public Health Veterinarians (American Academy of Pediatrics, 2012; CDC, 2014b; National Association of State Public Health Veterinarians, 2013; Pickering et al., 2008) also remind the public of the dangers of contact with any wildlife, whether imported or domestic.

This paper has described selected aspects of CDC's animal regulations that exist to prevent the introduction of zoonotic diseases to the United States. Each section illustrated examples where (1) regulations exist, but the fluidity of the pet trade has managed to circumvent them, or there are loopholes in the regulations, or (2) no specific regulation or policy exists, or (3) human behavior and attitudes towards interaction with animals, animal products, and pet ownership preferences pose public health risks. Multiple challenges exist, but educating the public; assessing whether additional authority is needed; strengthening the regulations; instituting stronger surveillance and tracking systems; and recognizing that prevention is a shared responsibility between government, industry, health practitioners, and pet owners are all strategies that can reduce the introduction and spread of zoonotic diseases associated with trade and movement of animals.

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A14

THE GLOBAL DISTRIBUTION AND BURDEN OF DENGUE[59]

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Dengue is a systemic viral infection transmitted between humans by *Aedes* mosquitoes (Simmons et al., 2012). For some patients, dengue is a life-threatening illness (WHO, 2009). There are currently no licensed vaccines or specific therapeutics, and substantial vector control efforts have not stopped its rapid emergence and global spread (Tatem et al., 2006). The contemporary worldwide distribution of the risk of dengue virus infection (Brady et al., 2012) and its public health burden are poorly known (Halstead, 1988; WHO, 2009). Here we undertake an exhaustive assembly of known records of dengue occurrence worldwide, and use a formal modelling framework to map the global distribution of dengue risk. We then pair the resulting risk map with detailed longitudinal information from dengue cohort studies and

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population surfaces to infer the public health burden of dengue in 2010. We predict dengue to be ubiquitous throughout the tropics, with local spatial variations in risk influenced strongly by rainfall, temperature and the degree of urbanization. Using cartographic approaches, we estimate there to be 390 million (95% credible interval 284–528) dengue infections per year, of which 96 million (67–136) manifest apparently (any level of clinical or subclinical severity). This infection total is more than three times the dengue burden estimate of the World Health Organization (2009). Stratification of our estimates by country allows comparison with national dengue reporting, after taking into account the probability of an apparent infection being formally reported. The most notable differences are discussed. These new risk maps and infection estimates provide novel insights into the global, regional and national public health burden imposed by dengue. We anticipate that they will provide a starting point for a wider discussion about the global impact of this disease and will help to guide improvements in disease control strategies using vaccine, drug and vector control methods, and in their economic evaluation.

Dengue is an acute systemic viral disease that has established itself globally in both endemic and epidemic transmission cycles. Dengue virus infection in humans is often inapparent (Endy et al., 2011; Simmons et al., 2012) but can lead to a wide range of clinical manifestations, from mild fever to potentially fatal dengue shock syndrome (WHO, 2009). The lifelong immunity developed after infection with one of the four virus types is type-specific (Simmons et al., 2012), and progression to more serious disease is frequently, but not exclusively, associated with secondary infection by heterologous types (Halstead, 1988; WHO, 2009). No effective antiviral agents yet exist to treat dengue infection and treatment therefore remains supportive (WHO, 2009). Furthermore, no licensed vaccine against dengue infection is available, and the most advanced dengue vaccine candidate did not meet expectations in a recent large trial (Halstead, 2012; Sabchareon et al., 2012). Current efforts to curb dengue transmission focus on the vector, using combinations of chemical and biological targeting of *Aedes* mosquitoes and management of breeding sites (WHO, 2009). These control efforts have failed to stem the increasing incidence of dengue fever epidemics and expansion of the geographical range of endemic transmission (Gubler, 1998). Although the historical expansion of this disease is well documented, the potentially large burden of ill-health attributable to dengue across much of the tropical and subtropical world remains poorly enumerated.

Knowledge of the geographical distribution and burden of dengue is essential for understanding its contribution to global morbidity and mortality burdens, in determining how to allocate optimally the limited resources available for dengue control, and in evaluating the impact of such activities internationally. Additionally, estimates of both apparent and inapparent infection distributions form a key

requirement for assessing clinical surveillance and for scoping reliably future vaccine demand and delivery strategies. Previous maps of dengue risk have used various approaches combining historical occurrence records and expert opinion to demarcate areas at endemic risk (Beatty et al., 2009; Van Kleef et al., 2009; WHO, 2012). More sophisticated risk-mapping techniques have also been implemented (Hales et al., 2002; Rogers et al., 2006), but the empirical evidence base has since been improved, alongside advances in disease modelling approaches. Furthermore, no studies have used a continuous global risk map as the foundation for dengue burden estimation.

The first global estimates of total dengue virus infections were based on an assumed constant annual infection rate among a crude approximation of the population at risk (10% in 1 billion [Halstead, 1988] or 4% in 2 billion [Monath, 1994]), yielding figures of 80–100 million infections per year worldwide in 1988 (Halstead, 1988; Monath, 1994). As more information was collated on the ratio of dengue haemorrhagic fever to dengue fever cases, and the ratio of deaths to dengue haemorrhagic fever cases, the global figure was revised to 50–100 million infections (Rigau-Pérez et al., 1998; Rodhain, 1996), although larger estimates of 100–200 million have also been made (Van Kleef et al., 2009) (Figure A14-1). These estimates were intended solely as approximations but, in the absence of better evidence, the resulting figure of 50–100 million infections per year is widely cited and currently used by the World Health Organization (WHO). As the methods used were informal, these estimates were presented without confidence intervals, and no attempt was made to assess geographical or temporal variation in incidence or the inapparent infection reservoir.

Here we present the outcome of a new project to derive an evidence-based map of dengue risk and estimates of apparent and inapparent infections worldwide on the basis of the global population in 2010. We compiled a database of 8,309 geo-located records of dengue occurrence from a systematic search, resulting from 2,838 published literature sources as well as newer online resources (Freifeld et al., 2008) (see Supplementary Information, section A; the full bibliography (Brady et al., 2012) and occurrence data are available from authors on request). Using these occurrence records we: chose a set of gridded environmental and socioeconomic covariates known, or proposed, to affect dengue transmission (see Supplementary Information, section B); incorporated recent work assessing the strength of evidence on national and subnational-level dengue present/absent status (Brady et al., 2012) (Figure A14-2a); and built a boosted regression tree (BRT) statistical model of dengue risk that addressed the limitations of previous risk maps (see Supplementary Information, section C) to define the probability of occurrence of dengue infection (dengue risk) within each 5 km $\times$ 5 km pixel globally (Figure A14-2b). The model was run 336 times to reflect parameter uncertainty and an ensemble mean map was created (see Supplementary Information, section C). We then combined this ensemble map with detailed longitudinal information on dengue infection incidence from cohort studies and

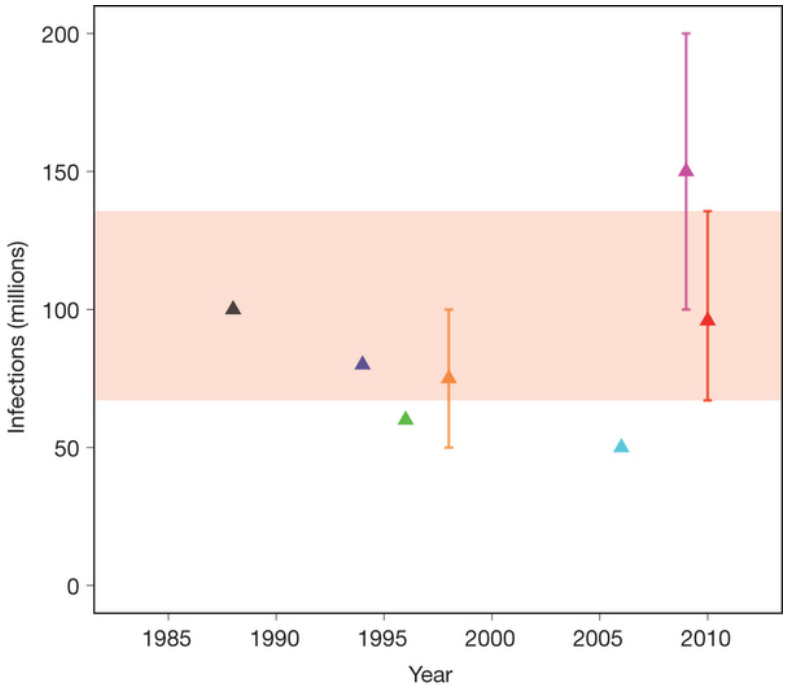

FIGURE A14-1 Global estimates of total dengue infections. Comparison of previous estimates of total global dengue infections in individuals of all ages, 1985–2010. Black triangle (Halstead, 1988); dark blue triangle (Monath, 1998); green triangle (Rodhain, 1996); orange triangle (Rigau-Pérez, 1998); light blue triangle (TDR/WHO, 2006); pink triangle (Beatty et al., 2009); red triangle, apparent infections from this study. Estimates are aligned to the year of estimate and, if not stated, aligned to the publication date. Red shading marks the credible interval of our current estimate, for comparison. Error bars from Beatty et al. (2010) and Rigau-Pérez (1998) replicated the confidence intervals provided in these publications.

built a non-parametric Bayesian hierarchical model to describe the relationship between dengue risk and incidence (see Supplementary Information, section D). Finally, we used the estimated relationship to predict the number of apparent and inapparent dengue infections in 2010 (see Supplementary Information, section E). Our definition of an apparent infection is consistent with that used by the cohort studies: an infection with sufficient severity to modify a person's regular schedule, such as attending school. This definition encompasses any level of severity of the disease, including both clinical and subclinical manifestations.

We predict that dengue transmission is ubiquitous throughout the tropics, with the highest risk zones in the Americas and Asia (Figure A14-2b). Validation

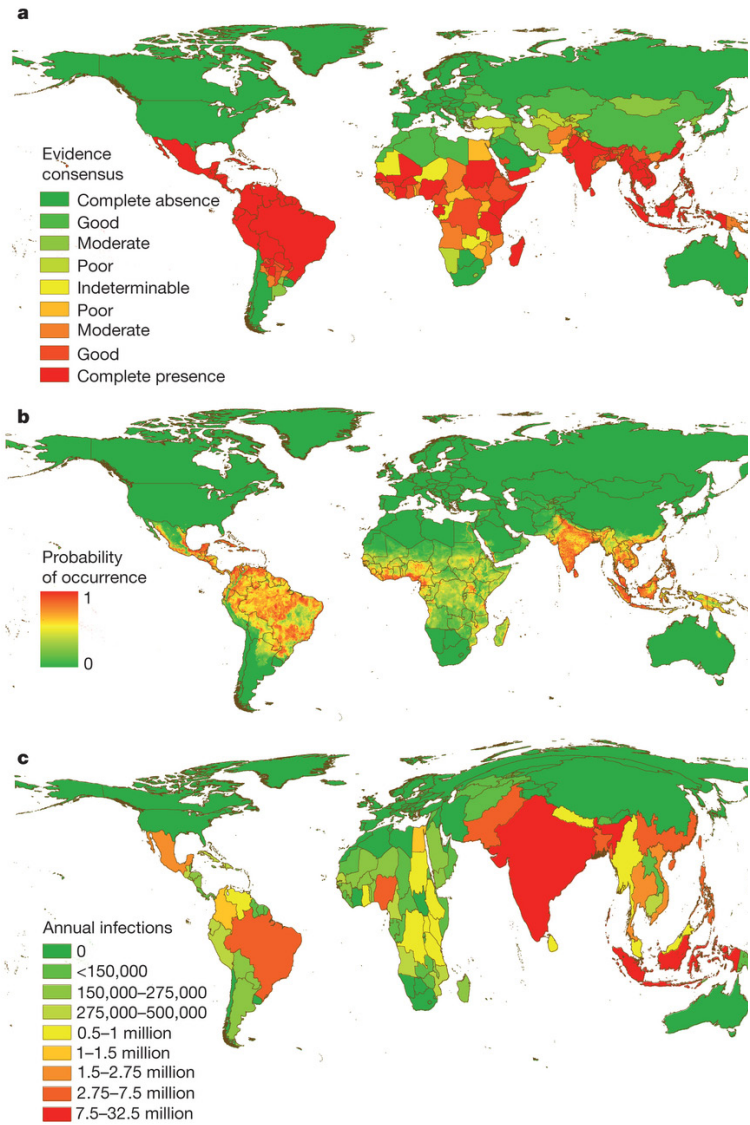

FIGURE A14-2 Global evidence consensus, risk and burden of dengue in 2010. a, National and subnational evidence consensus on complete absence (green) through to complete presence (red) of dengue (Brady et al., 2012). b, Probability of dengue occurrence at 5 km × 5 km spatial resolution of the mean predicted map (area under the receiver operator curve of 0.81 (±0.02 s.d., $n = 336$)) from 336 boosted regression tree models. Areas with a high probability of dengue occurrence are shown in red and areas with a low probability in green. c, Cartogram of the annual number of infections for all ages as a proportion of national or subnational (China) geographical area.

statistics indicated high predictive performance of the BRT ensemble mean map with area under the receiver operating characteristic (AUC) of 0.81 (±0.02 s.d., $n = 336$) (see Supplementary Information, section C). Predicted risk in Africa, although more unevenly distributed than in other tropical endemic regions, is much more widespread than suggested previously. Africa has the poorest record of occurrence data and, as such, increased information from this continent would help to define better the spatial distribution of dengue within it and to improve its derivative burden estimates. We found high levels of precipitation and temperature suitability for dengue transmission to be most strongly associated among the variables considered with elevated dengue risk, although low precipitation was not found to limit transmission strongly (see Supplementary Information, section C). Proximity to low-income urban and peri-urban centres was also linked to greater risk, particularly in highly connected areas, indicating that human movement between population centres is an important facilitator of dengue spread. These associations have previously been cited (Gubler, 1998), but have not been demonstrated at the global scale and highlight the importance of including socioeconomic covariates when assessing dengue risk.

We estimate that there were 96 million apparent dengue infections globally in 2010 (Table A14-1). Asia bore 70% (67 (47–94) million infections) of this burden, and is characterized by large swathes of densely populated regions coinciding with very high suitability for disease transmission. India (Chakravarti et al., 2012; Kakkar, 2012) alone contributed 34% (33 (24–44) million infections) of the global total. The disproportionate infection burden borne by Asian countries is emphasized in the cartogram shown in Figure A14-2c. The Americas contributed 14% (13 (9–18) million infections) of apparent infections worldwide, of which over half occurred in Brazil and Mexico. Our results indicate that Africa's dengue burden is nearly equivalent to that of the Americas (16 (11–22) million infections, or 16% of the global total), representing a significantly larger burden than previously estimated. This disparity supports the notion of a largely hidden African dengue burden, being masked by symptomatically similar illnesses, under-reporting and highly variable treatment-seeking behaviour (Endy et al.,

TABLE A14-1 Estimated Burden of Dengue in 2010, by Continent

	Apparent	Inapparent
	Millions (credible interval)	Millions (credible interval)
Africa	15.7 (10.5–22.5)	48.4 (34.3–65.2)
Asia	66.8 (47.0–94.4)	204.4 (151.8–273.0)
Americas	13.3 (9.5–18.5)	40.5 (30.5–53.3)
Oceania	0.18 (0.11–0.28)	0.55 (0.35–0.82)
Global	96 (67.1–135.6)	293.9 (217.0–392.3)

2011; Gubler, 1998; Kakkar, 2012). The countries of Oceania contributed less than 0.2% of global apparent infections.

We estimate that an additional 294 (217–392) million inapparent infections occurred worldwide in 2010. These mild ambulatory or asymptomatic infections are not detected by the public health surveillance system and have no immediate implications for clinical management. However, the presence of this huge potential reservoir of infection has profound implications for: (1) correctly enumerating economic impact (for example, how many vaccinations are needed to avert an apparent infection) and triangulating with independent assessments of disability adjusted life years (DALYs) (Murray et al., 2012); (2) elucidating the population dynamics of dengue viruses (Cummings et al., 2009); and (3) making hypotheses about population effects of future vaccine programmes (Johansson et al., 2011) (volume, targeting efficacy, impacts in combination with vector control), which will need to be administered to maximize cross-protection and minimize post-vaccination susceptibility.

The absolute uncertainties in the national burden estimates are inevitably a function of population size, with the greatest uncertainties in India, Indonesia, Brazil and China (see full rankings in Supplementary Table 4). In addition, comparing the ratio of the mean to the width of the confidence interval (Hay et al., 2010) revealed the greatest contributors to relative uncertainty (see full rankings in Supplementary Table 4). These were countries with sparse occurrence points and low evidence consensus on dengue presence, such as Afghanistan or Rwanda (see Figure A14-2a), or those with ubiquitous high risk, such as Singapore or Djibouti, for which our burden prediction confidence interval is at its widest (see Supplementary Information, section D, Figure 2). Therefore, increasing evidence consensus and occurrence data availability in low consensus countries and assembling new cohort studies, particularly in areas of high transmission, will reduce uncertainty in future burden estimates. Our approach, uniquely, provides new evidence to help maximize the value and cost-effectiveness of surveillance efforts, by indicating where limited resources can be targeted to have their maximum possible impact in improving our knowledge of the global burden and distribution of dengue.

Our estimates of total infection burden (apparent and inapparent) are more than three times higher than the WHO predicted figure (Supplementary Information, section E). Our definition of an apparent infection is broad, encompassing any disruption to the daily routine of the infected individual, and consequently is an inclusive measurement of the total population affected adversely by the disease. Within this broad class, the severity of symptoms will affect treatment-seeking behaviours and the probability of a correct diagnosis in response to a given infection. Our definition is therefore more comprehensive than those of traditional surveillance systems which, even in the most efficient system, report a much narrower range of dengue infections. By reviewing our database of longitudinal cohort studies, in which total infections in the community were

documented exhaustively, we find that the biggest source of disparity between actual and reported infection numbers is the low proportion of individuals with apparent infections seeking care from formal health facilities (see Supplementary Information, section E, Fig. 5 for full analysis). Additional biases are introduced by misdiagnosis and the systematic failure of health management information systems to capture and report presenting dengue cases. By extracting the average magnitude of each of these sequential disparities from published cohort and clinical studies, we can recreate a hypothetical reporting chain with idealized reporting and arrive at estimates that are broadly comparable to those countries reported to the WHO. This is most clear in more reliable reporting regions such as the Americas. Systemic under-reporting and low hospitalization rates have important implications, for example, in the evaluation of vaccine efficacy based on reduced hospitalized caseloads. Inferences about these biases may be made from the comparison of estimated versus reported infection burdens in 2010, highlighting areas where particularly poor reporting might be strengthened (see Supplementary Information, section E).

We have strived to be exhaustive in the assembly of contemporary data on dengue occurrence and clinical incidence and have applied new modelling approaches to maximize the predictive power of these data. It remains the case, however, that the empirical evidence base for global dengue risk is more limited than that available, for example, for *Plasmodium falciparum* (Gething et al., 2011) and *Plasmodium vivax* (Gething et al., 2012) malaria. Records of disease occurrence carry less information than those of prevalence and, as databases of the latter become more widespread, future approaches should focus on assessing relationships between seroprevalence and clinical incidence as a means of assessing risk (Anders and Hay, 2012). Additional cartographic refinements are also required to help differentiate endemic from epidemic-prone areas, to determine the geographic diversity of dengue virus types and to predict the distributions of future risk under scenarios of socioeconomic and environmental change.

The global burden of dengue is formidable and represents a growing challenge to public health officials and policymakers. Success in tackling this growing global threat is, in part, contingent on strengthening the evidence base on which control planning decisions and their impact are evaluated. It is hoped that this evaluation of contemporary dengue risk distribution and burden will help to advance that goal.

Methods

Assembly of the Occurrence Database and Its Quality Control

Occurrence data comprised of point or polygon locations of confirmed dengue infection presence derived from both peer-reviewed literature and HealthMap alerts (Brownstein et al., 2008; Freifeld et al., 2008) (see Supplementary

Information, section A). An occurrence was defined as one or more laboratory or clinically confirmed infection(s) of dengue occurring at a unique location (a 5 km × 5 km pixel) within one calendar year. All occurrence data underwent manual review and automatic quality control to ensure information fidelity and precise geo-positioning. In total, 9,648 and 1,622 occurrence locations were obtained from literature searches and HealthMap, respectively. After the quality control procedures, our final data set contained 8,309 occurrence locations (5,216 point locations and 3,093 small polygon centroids) spanning a period from 1960 to 2012. We assume any record of dengue occurrence, regardless of its age, represented an environment permissible for the disease, as dengue has expanded from a focal disease in Asia to a cosmopolitan disease of the tropics.

Explanatory Covariates

We assembled gridded global data for a suite of eight explanatory covariates. The covariates were chosen based on factors known or hypothesized to contribute to suitability for dengue transmission (see Supplementary Information, section B). These covariates included: (1) annual maximum and minimum precipitation variables from a Fourier processed (Scharlemann et al., 2008) synoptic annual series interpolated from global meteorological stations (Hijmans et al., 2005); (2) a biological model combining the effects of temperature on the extrinsic incubation period of dengue virus and lifespan of the *Aedes aegypti* vector to quantify the dengue-specific temperature suitability for transmission (Focks et al., 1993a,b; Gething et al., 2012); (3) Fourier-processed annual average normalized difference vegetation index (Hay et al., 2009); (4) categorical demarcations of urban and peri-urban areas (Hay et al., 2009); (5) an urban accessibility metric defining the travel time to nearest city of 50,000 people or more by land- or water-based travel (Nelson, 2008); and (6) an indicator of relative poverty derived from the finest geographic scale data available for economic productivity and adjusted for purchasing power parity (Nordhaus, 2006). No covariate grids were shown to be adversely affected by multicollinearity (see Supplementary Information, section B) and were standardized to ensure identical spatial resolution, extent and boundaries. For point records, covariate values corresponded to the pixel value containing the location of the point. For polygon occurrence records, covariate values were averaged across the whole polygon.

Predicting the Probability of Occurrence (Risk) of Dengue Transmission

We used a boosted regression tree (BRT) approach to establish a multivariate empirical relationship between the probability of occurrence of a dengue virus infection and the environmental conditions sampled at each site from the covariate suite. The BRT method has been shown to fit complicated response functions efficiently, while guarding against overfitting, and is therefore widely used for

vector and disease distribution mapping (Elith et al., 2006; Stevens and Pfeiffer, 2011). The BRT approach combines regression trees (Breiman, 1984) with gradient boosting (Friedman, 2001), whereby an initial regression tree is fitted and iteratively improved upon in a forward stage-wise manner (boosting) by minimizing the variation in the response not explained by the model at each iteration (see Supplementary Information, section C).

Like other niche mapping approaches, the BRT models require not only presence data but also absence data defining areas of disease absence and potentially unsuitable environmental conditions at unsampled locations. Because data on absence of disease are not definitive, pseudo-absence data estimate areas of disease absence instead. No consensus approach has been developed to optimize the generation of pseudo-absence data and we therefore created an evidence-based probabilistic framework for generating pseudo-absences, incorporating the main biasing factors in pseudo-absence generation, namely: (1) geographical extent; (2) number; (3) contamination bias; and (4) sampling bias. To represent areas of absence, n_a pseudo-absence points (Chefaoui and Lobo, 2008; Lobo and Tognelli, 2011; Stokland et al., 2011) were randomly generated based on dengue presence or absence certainty measures at a national or subnational level (Brady et al., 2012). Pseudo-absence locations were restricted to a maximum distance μ from any recorded presence site (Barbet-Massin et al., 2012; VanDerWal et al., 2009). Additionally, to compensate for "contamination" of true but unobserved presences within the generated pseudo-absences (Ward et al., 2009), n_p pseudo-presence points were generated using the same procedure used to generate the pseudo-absences. Variation in the parameter set $\pi = \{\mu, n_a, n_p\}$ resulted in independent samples of the possible states of the real distribution, with all parameter combinations representing a null distribution of possible states. Therefore, rather than using an individual parameter combination from π, we created an ensemble (Araújo and New, 2007) of 336 BRT models spanning reasonable ranges in π and evaluated the central tendency as the mean across all 336 BRT models (see Supplementary Information, section C). The final ensemble BRT model was used to predict a global map of the probability of occurrence of dengue virus infection at a 5 km $\times$ 5 km resolution.

Estimation of Dengue Burden and Populations at Risk

Formal literature searches were conducted for serological dengue virus incidence surveys. Inclusion criteria were restricted to longitudinal surveys of seroconversion to dengue-virus-specific antibodies carried out in parallel with active symptom surveillance in a defined cohort. The surveys were abstracted, standardized and geopositioned (see Supplementary Information, section D). In total, 54 dengue incidence surveys were collected. Of these, 39 contained information about the ratio of inapparent to apparent infections.

The empirical relationship between incidence and the probability of occurrence was represented using a Bayesian hierarchical model. We defined a negative binomial likelihood function (Hilbe, 2011) with constant dispersion and a rate characterized by a highly flexible data-driven Gaussian process prior (Banerjee et al., 2004). The Gaussian process prior was parameterized with a quadratic mean function and a squared exponential covariance function (Banerjee et al., 2004). Uninformative hyperpriors were assigned hierarchically to the prior parameters and the full posterior distribution determined by Markov Chain Monte Carlo (MCMC) sampling (Patil et al., 2010). The entire model was fitted separately for apparent and inapparent infection incidences, with missing inapparent to apparent ratio values imputed in the MCMC. Using human population gridded data for the year 2010 (Balk et al., 2006), estimates of apparent and inapparent dengue infections were calculated nationally, regionally and globally. These estimates were then compared to national clinical cases reported to the WHO and differences between our cartographic estimates of infections and the WHO surveillance estimates were reconciled in a comparative analysis addressing key factors in traditional surveillance under-reporting (see Supplementary Information, section E).

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Contributions

S.I.H. and J.J.F. conceived the research. S.B. and S.I.H. drafted the manuscript. S.B. drafted the Supplementary Information with significant support on sections A (O.J.B., C.L.M.), B (J.P.M., G.R.W.W.), C (P.W.G.), D (O.J.B., T.W.S.), and O.J.B. wrote section E. J.S.B. and A.G.H. provided HealthMap occurrence data and advice on its provenance. O.J.B. reviewed all the occurrence data. S.B. did the modelling and analysis with advice from J.M.D., P.W.G., and

S.I.H. J.P.M. created all maps. All authors discussed the results and contributed to the revision of the final manuscript.

Competing Financial Interests

The authors declare no competing financial interests.

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A15

CIRCUMPOLAR POPULATIONS, CLIMATE AND ENVIRONMENTAL CHANGE, AND THE IMPACT ON INFECTIOUS DISEASE PATTERNS

Alan J. ***Parkinson***[75]

The Arctic Environment and Populations

The Arctic is home to 4 million people of whom almost half reside in the northern part of the Russian Federation. People in the Arctic live in social and physical environments that differ from their more southern dwelling counterparts. Approximately 400,000 (10 percent) of persons are of indigenous ancestry, half of whom live in the northern part of the Russian Federation (Parkinson, 2009; Stefansson Arctic Institute, 2004).

The indigenous populations of northern Canada, Alaska, Greenland, and the northern Russian Federation generally reside in remote isolated communities consisting of 150 to several thousand inhabitants. In some regions, the only access to communities is by small aircraft or boat in summer and by small aircraft and snow machine in winter. Arctic communities, once isolated, are now very much a part of the global village we all live in and are as vulnerable to health

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threats as any other community on the globe. Through their unique relationship with nature, many of these peoples are more vulnerable to health threats generated by climate change.

These communities often have little economic infrastructure and are still largely dependent on subsistence harvesting of wildlife resources from terrestrial, fresh water, and marine ecosystems for a significant proportion of their diet. Food security is often dependent on subsistence wildlife migration patterns, predictable weather, and some method of food storage. In these remote regions, access to public health and acute care systems is often marginal and poorly supported.

The health of indigenous peoples of the circumpolar region has improved over the last 50 years or so. Much of this improvement can be attributed not only to the implementation of prevention and treatment activities that have resulted in reductions in morbidity and mortality from infectious diseases, such as tuberculosis, and the vaccine-preventable diseases of childhood, but also to the provision of safe water supplies and sewage disposal in many communities.

However, life expectancy of the indigenous populations of Alaska, northern Canada, Greenland, and the northern Russian Federation is lower than that of the respective national populations. Infant mortality remains higher than respective populations of the United States, northern Canada, Greenland, and northern Russian Federation (Young and Bjerregaard, 2008).

Mortality rates for heart disease and cancer were once lower among the indigenous populations of the United States, Canada, and northern European countries, but are now similar to their national rates. According to the U.S. CDC the cancer incidence rate is 1.5 times higher for Alaska Natives than the general U.S. population.

However, it is evident that the indigenous populations of Alaska, Canada, and Greenland have much higher rates of unintentional injury and suicide. Unintentional injuries have always been a fact of life for those who live close to the land. These have often been related to hunting (animal attacks, shootings, and boating accidents) and hypothermia. With modernization, motor vehicle accidents and house fires have recently assumed more importance.

Other health concerns of indigenous populations of the north include the high prevalence of certain infectious diseases such as hepatitis B, tuberculosis, *Helicobacter pylori*, respiratory syncytial virus in infants, influenza, and sexually transmitted infections, as well as the potential health impacts associated with exposure to environmental pollutants through the traditional food supply, the health impacts of rapid economic change and modernization, and now the health impacts of climate change.

Climate and Environmental Change

The Arctic has warmed substantially more than the rest of the world over the last century, principally in recent decades. Figure A15-1 shows the global

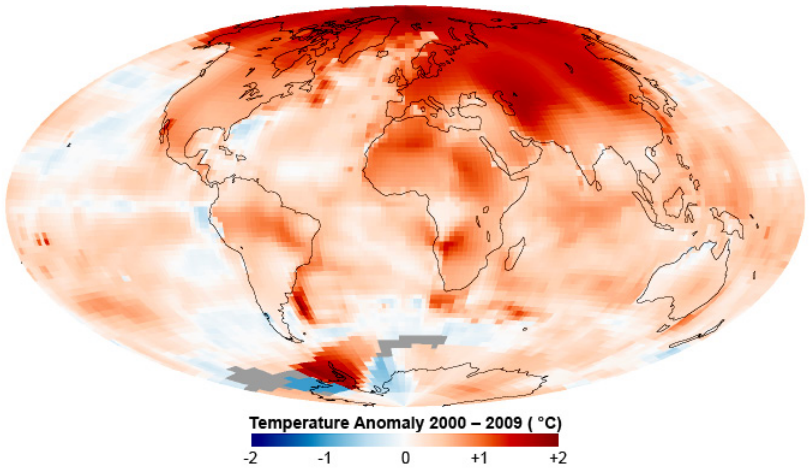

FIGURE A15-1 Global temperature anomalies for 2000–2009 compared to 1951–1980. Global temperatures were on average about 0.6°C higher than they were 1951–1980. The Arctic, however, was about 2°C warmer.
SOURCE: NASA image by Robert Simmon based on GISS surface temperature analysis data, including ship and buoy data from the Hadley Centre. Caption by Adam Voiland.
The Climate of 2012 report: http://www.ncdc.noaa.gov/bams-state-of-the-climate/2012.php
The State of the Climate in 2012 is a supplement to the August 2013 issue of the Bulletin of the American Meteorological Society (BAMS Vol. 94, No. 8).

temperature anomalies for 2000–2009 compared to 1951–1980. Global temperatures were on average about 0.6°C higher than they were 1951–1980. The Arctic, however, was about 2°C warmer. Arctic climate models project continued warming with a 3–7°C mean increase by 2100 (Symon et al., 2005).

The greatest warming will occur in the winter months. The mean annual precipitation will also increase, and continued melting of land and sea ice is expected to increase river discharge and contribute to a 1 m sea level rise by 2100, which will greatly impact many low-lying coastal communities not only in the Arctic but worldwide.

Climate change is already impacting indigenous communities of the Arctic. Indigenous people have reported that the weather is less predictable than in recent memory (Furberg et al., 2011; Huntington and Weller, 2005). There is already a considerable impact on the sea and coastline in many regions of the Arctic. The average extent of sea ice in summer has declined by 15–20 percent over the last 30 years. The sea ice is getting thinner. There has been a significant loss of multiyear ice over the last decade (www.nsida.org). Ice is important for hunting and fishing. It provides easy access to open water, a platform to hunt from—not only for indigenous people but also for the prey they hunt. Thin ice means fewer

seals, walrus, and whales to hunt, impacting diet nutrition and cultural well-being (Brubaker et al., 2011). Thin ice also may increase unintentional injury and death by drowning to those traveling the surface to hunting grounds (Fleischer et al., 2013). Reduction in sea ice will have widespread effects on the marine ecosystem, coastal climate, human settlements, and subsistence activities. The reduction in sea ice has, for the first time, created ice-free shipping lanes to the northwest from Labrador to the Bering sea, and to the northeast from the Bering sea to Norway, representing fuel saving short cuts for transportation by sea, and access to oil gas and mineral reserves once inaccessible (Arctic Council, 2009). This traffic is projected to increase rapidly. Benefits to isolated communities will include construction of military bases and the development of other industrial and commercial ventures such as tourism, which will result in infrastructure support and employment. Public and private services will increase to support emerging economies. However, these ventures will affect population distribution, dynamics, culture, and local environments and will challenge the traditional subsistence way of life for many communities and lead to accelerated and long-term cultural change, which will create additional stress on an already vulnerable population.

Delayed freeze-up, lack of the sea ice barrier, and increased storm intensity have accelerated coastal erosion and damage to water and sanitation systems, forcing some communities in northwestern Alaska to evacuate during storm events and to consider eventual permanent relocation (Brubaker et al., 2011). Such storm events also place residents at higher risk for unintentional injury and for chronic stress. Fear for safety and security will have long-term effects on mental and behavioral health in these communities. The movement of rural residents to urban centers is occurring in some regions of the circumpolar north (Driscoll et al., 2010; Stefansson Arctic Institute, 2004). This is currently being driven by economic, educational, and health care opportunities. However, this trend may accelerate due to the impact of climate change.

For many communities, the river is a byway that connects a community to inland-based subsistence resources such as caribou, salmon trout, waterfowl, and wild berries. With warming has come widespread thawing of shallow permafrost resulting in the collapse of tundra into the rivers. This increased erosion changes river flow, increases turbidity, and restricts access to upriver hunting grounds. Rivers are becoming wider, shallower, warmer, and dirtier—affecting navigation, critical fish habitat, and water quality and quantity when used as a community water source (Brubaker et al., 2011; Evengård et al., 2011).

Lakes are also changing. Some are expanding with water from thawing permafrost; others are shrinking as an underlying ice lens thaws and drains the lake (Smith et al., 2005). Warmer water allows new vegetation to grow; algae, aquatic plants, and mosses flourish, creating problems if the lake is used as a community water source.

As warming temperatures move northward, associated plants and wildlife will follow. Biologic responses to a warming Arctic are expected to outpace those

at lower latitudes. Spring will occur earlier and the growing season will be longer. The tree line is projected to reach the Arctic Ocean in most of Asia and western North American by the end of this century. This is likely to lead to a near loss of tundra vegetation in these areas with important consequences for many types of wildlife (Weller, 2005). Thus, climate change is likely to have a significant impact on key terrestrial species used as subsistence food by shifting range and abundance of key species such as caribou, moose, water fowl, and sea birds. The health impacts of a decline in the proportion of traditional food consumed by the indigenous population may be significant. A shift away from a traditional diet to a more western diet, higher in carbohydrates and sugars, has been associated with increased levels of cardiovascular disease, diabetes, vitamin-deficiency disorders, dental cavities, anemia, obesity, and lower resistance to infection.

Climate and Environmental Change and Infectious Diseases

It is well known that climate and weather affect the distribution and risk of many vector-borne diseases such as malaria, Rift Valley fever, plague, and dengue fever in tropical regions of the globe. Weather also affects the distribution of food- and water-borne diseases and emerging infectious diseases such as West Nile virus, Hantavirus, and Ebola hemorrhagic fever (Haines et al., 2006). Less is known about the impact of climate change and the risk and distribution of infectious diseases in Arctic regions. It is known that Arctic populations have a long history of both endemic and epidemic infectious diseases (IOM, 2008; Parkinson and Butler, 2005). However, with the introduction of antimicrobial drugs, vaccines, and public health systems, morbidity and mortality due to infectious diseases have been greatly reduced. The impact of climate on the incidence of these existing infectious disease challenges is unknown. In many Arctic regions, however, inadequate housing and sanitation are already important determinants of infectious disease transmission. The cold northern climate keeps people indoors, amplifying the effects of household crowding, smoking, and inadequate ventilation. Crowded living conditions increase person-to-person spread of infectious diseases and favor the transmission of respiratory and gastrointestinal diseases and skin infections.

Impact on the Water and Sanitation

In many communities in the north, the built infrastructure is supported on permafrost. Loss of this support will result in damage to water intake systems and pipes and may result in contamination of community water supplies and damage to water and sanitation infrastructures and distribution systems, forcing communities to rely more on untreated (or traditional) water sources (Brubaker et al., 2011; Evengård et al., 2011). This may result in an increase in clinic visits and hospitalizations for various “water washed” infectious diseases, those commonly

prevented by hand washing such as gastroenteritis, respiratory infections caused by respiratory syncytial virus (RSV), influenza, skin infections, impetigo, and boils caused by MRSA (Brubaker et al., 2011; Hennessy et al., 2008; Wenger et al., 2010). A study in western Alaska demonstrated two to four times higher hospitalization rates among children less than 3 years of age for pneumonia, influenza, and childhood RSV infections in villages where the majority of homes had no in-house piped water, compared with villages where the majority of homes had in-house piped water service. Likewise, outpatient multiple-resistant *Staphylococcus aureus* infections and hospitalizations for skin infections among persons of all ages were higher in villages with no in-house piped water service compared to villages with water service (Hennessy et al., 2008; Wenger et al., 2010).

Lack of water for hygiene may also contribute to the transmission of zoonotic pathogens such as *Giardia*, *Cryptosporidium*, and *Echinococcus* from the environment to people. The climate-related northern expansion of the boreal forest in Alaska and northern Canada has favored the steady northward advance of the beaver, potentially extending the range of *Giardia*, a parasitic infection of beaver that can infect other mammals, including humans, who consume untreated surface water. *Giardia* is currently well established in northern climates where cooler, wetter conditions favor survival and transmission of cysts. This parasite is the most significant enteric protozoan in the entire North American Arctic (Jenkins et al., 2013). In Alaska, rates of giardiasis have been consistently two times higher than is found overall in the United States (Yoder et al., 2012a). It is possible that warming temperatures will decrease environmental survival of *Giardia* cysts. However, this will likely be offset by increased transmission through changes in animal reservoir dynamics, regional hydrology, and flooding events caused by heavy rain, snowfall, and melting, leading to outbreaks of waterborne infections.

Elevated runoff from snow melt and increased precipitation could also exacerbate contamination of water supplies with *Cryptosporidium* cysts and oocysts (Davidson et al., 2011). The association between infection and increased precipitation is well recognized. In a recent outbreak in two towns in northern Sweden, more than 50,000 residents developed *Cryptosporidium*-related gastroenteritis after drinking contaminated municipal water following heavy rainfall that overwhelmed water purification systems (Evengård et al., 2011). However, compared to giardiasis, cryptosporidiosis in Arctic populations appears relatively uncommon. In Alaska, for example, the mean annual incidence (1.0 and 0.8/100,000) is almost three times lower than the U.S. average (Yoder et al., 2012b). The lack of livestock, and apparent low level of infection in both marine and terrestrial wildlife in these regions, suggests that zoonotic transmission of cryptosporidiosis may be uncommon in Arctic regions.

Alveola echinococcosis caused by *Echinococcus multilocularis* was common in two regions of northwestern Alaska prior to 1986 (State of Alaska, 2003). Only one case has been reported in northern Canada (Jenkins et al., 2013). *Echinococcus multilocularus* maintains a cycle in foxes and voles. Disease in humans was

mainly associated with contact with sled dogs. However, improvements in housing, water and sanitation, sled dog lot management, and the transition from dog sled teams to snow machines have largely eliminated dog-to-human transmission in Alaska. Climate change will influence the transmission of *E. multilocularis* through the effects on the distribution and abundance of rodent intermediate hosts and the sylvatic definitive host—the Arctic fox. Increased precipitation might lead to increased stability and density of rodent populations facilitating transmission of *E. multilocularis*. However, increased frequency of severe weather events may decrease overall transmission. These events are occurring in parallel with other drivers of disease emergence, landscape change, and translocation of hosts. *E. multilocularis* was recently detected in Svalbard in the Norwegian Arctic following introduction of a suitable intermediate host likely from shipping (Henttonen et al., 2001). Such events will increase in frequency with the opening of ice-free shipping lanes across the Arctic bringing increasing cargo, tourist traffic, and other flora and fauna to regions once inaccessible to invasion from the sea, requiring a continued vigilance for this disease in these regions (Jenkins et al., 2011).

The Northern-strain cystic hydatid disease is caused by *Echinococcus granulosus*, which maintains a cycle that includes an adult cestode stage in the definitive host such as wolf, coyote, fox, or dog, and a larval cestode stage in an intermediate host in cervids such as moose, deer, caribou, and reindeer. Humans usually acquire the infection via exposure to eggs that are shed in canid feces and are an accidental host. In Alaska, the first human case was recorded in 1941. Human hydatid disease is reportable in Alaska; peak numbers of cases were detected from 1953 to 1973, nearly all of which were in Alaska Natives (State of Alaska, 2003). Similarly in Canada, 99 percent of 141 cases in the 1950s occurred in indigenous peoples. Today, cases of cystic hydatid disease occur infrequently in North America, in part, as a result of improving housing, water and sanitation infrastructure, and the gradual phasing out of sled dogs as a method of transportation in these regions (Jenkins et al., 2013). Populations of cervid hosts are already being affected by climate change. Caribou populations in the Arctic are declining due to secondary effects of climate and landscape changes (Kerby and Post, 2013). Increased precipitation and extreme weather events will likely contribute to further declines in population and parasite transmission in Arctic regions.

Impact on the Food Supply

Some infectious diseases are unique to the Arctic and lifestyles of the indigenous populations and may increase in a warming Arctic. For example, many Arctic residents depend on subsistence hunting, fishing, and gathering for food—and on a predictable climate for food storage. Traditional food storage methods often include aboveground air-drying of fish and meat at ambient temperature, belowground cold storage on or near the permafrost, and fermentation. Changes in climate may prevent the drying of fish or meat, resulting in spoilage. Similarly, loss

of the permafrost may result in spoilage of food stored below ground (Brubaker et al., 2011).

Climate change could exacerbate the potential for the food and/or waterborne transmission of toxoplasmosis in the Arctic (Jenkins et al., 2013). Toxoplasmosis is caused by infection with *Toxoplasma gondii*, a widespread protozoan parasite of mammals and birds. Members of the cat family are the only known definitive host for the sexual infectious stages (oocysts) of *T. gondii*; however, the asexual encysted stage is found in muscle tissues of animals and can serve as the main reservoirs of infection in cat-free areas. Humans become infected by ingesting raw or insufficiently cooked meat and foods that have come into contact with infected meat; by, indirectly or directly, ingesting cysts from soil, such as items that have come into contact with cat feces (unwashed vegetables); or transplacentally in humans from a mother to her fetus.

A serosurvey conducted among the Inuit of Nunavik showed a seroprevalence of 60 percent (Messier et al., 2009). Because of the absence of a felid host in Nunavik, it is unclear how *Toxoplasma* infection would be maintained in this region of the Arctic. It would appear to require a nonfelid definitive host, possibly rodents or various migratory species (e.g., barren ground caribou, birds, marine mammals) with terrestrial runoff feeding into a marine cycle. It is also possible that it could be maintained by carnivores and/or vertical transmission (marine mammals, herbivores). The recent discovery of *Toxoplasma* in polar bears and Arctic foxes in Svalbard underscores the widespread nature of this infection (Elmore et al., 2012). It has been hypothesized that this infection was introduced to this region by migratory birds. The prevalence in polar bears in Svalbard, the Barents Sea Region, and Eastern Greenland areas has doubled in the last decade (now 46 percent), and detection in ring seals for the first time highlights the predator–prey cycles in this region, and increasing risk to populations that rely on marine mammals for food. In the Arctic, the consumption of undercooked meat from marine mammals seems a much more important risk factor for human infection than drinking water. A recent serosurvey among Inuit in northern Quebec showed that 80 percent of Inuit with a dietary preference for dried meat from sea mammals were seropositive compared to 10 percent among ethnic Cree in the same community, who preferred cooked terrestrial mammals (Messier et al., 2009).

Another important meat-borne parasite in the Arctic is *Trichinella*, commonly responsible for outbreaks related to the consumption of undercooked bear or walrus meat (Davidson et al., 2011). The most common species is *T. nativa*, which, unlike other *Trichinella* species (such as *Trichinella* T6), survives freezing. In addition, smoking, drying, fermenting, or salting are not reliable methods for killing the parasite, thus placing the consumer at risk of infection. The geographical distribution of cold-tolerant versus freeze-tolerant *Trichinella* sp. follow the January isothermal lines (–5°C for *T. nativa*). Thus, shifts in host diversity and environmental temperature could lead to altered distribution. There is no current

evidence that climate change has contributed to an increase in *Trichinella* prevalence in Alaska or northern Canada. Loss of sea ice could interfere with resting, feeding, and breeding of marine mammals. The decline in sea ice has already resulted in large haulouts of walruses on beaches in northwestern Alaska and may contribute to increased transmission of *Trichinella* to other land or marine scavengers and carnivores.

In the Arctic, human infections caused by *Brucella suis* biovar IV have been linked to the consumption or processing of raw caribou meat, and the infection has been shown to be endemic in many caribou and reindeer herds across the Arctic (Hueffer et al., 2013). This is in contrast to infection in other parts of the United States where the most common route of transmission is through the consumption of raw dairy products or meat. However, there is little data on the prevalence of brucellosis in humans or wildlife not only in Alaska, but also in other Arctic regions. In Alaska, there have been 17 human cases reported since 1973. Reporting in wildlife is complicated by the absence of a standardized diagnostic test for different animal species. Other *Brucella* spp. can also infect other land and marine mammals. While human infections caused by a marine *Brucella* found in seals (*B. pinnipedialis*) has been documented, evidence for the direct transmission from seals to humans has yet to be established, as does the risk of infection to those who depend on marine mammals as a subsistence food source.

Past outbreaks of anthrax among cattle and reindeer have resulted in more than 13,000 burial grounds in Russia containing the carcasses of infected animals. More than half of these are located on permafrost in Siberia. There is concern that with a warming of the Arctic, melting permafrost in these regions will expose many of these burial sites together with anthrax spores that will result in an epizootic among grazing animals and increase the risk of infection in humans who come into contact with infected animal products (undercooked meat, hides, bone) (Revich et al., 2012).

Impact on Vector-Borne Diseases

Vector-borne diseases are those transmitted to humans, or between humans, via an arthropod vector. In Sweden, the incidence of tick-borne encephalitis (TBE) has substantially increased since the mid-1980s (Lindgren and Gustafson, 2001). This increase corresponds to a trend of milder winters and an earlier onset of spring, resulting in an increase in the tick population (*Ixodes ricinus*) that carries the virus responsible for TBE and other potential pathogens (Skarphédinsson et al., 2005). Similar movement of TBE has been documented in northern northwestern Russia where *Ixodes persulcatus* is the predominant vector. This movement corresponds to the estimated climate-induced changes in the *I. persulcatus* habitat (Revich et al., 2012; Tokarevich et al., 2011). In northeastern Canada, climate change is projected to result in a northward shift in the range of *Ixodes scapularis*, a tick that carries *Borrelia burgdorferi*, the etiologic agent of

Lyme disease. The current northern limit of *Ix. scapularis* is southern Ontario, including the shoreline of Lake Erie and the southern coast of Nova Scotia. Some temperature-based models show the potential for a northward expansion of *Ix. scapularis* above 60°N latitude and into the Northwest Territories by 2080 (Ogden et al., 2006). Alaska, once thought to be tick free (Zarnke et al., 1990), is now reporting the presence of the moose winter tick (*Dermacentor albipictus*), which transmits anaplasmosis in moose and elk herds in southwestern Alaska, as well as dog ticks (*Dermacentor variablis* and *Rhipicephalus sanguineus*)—both vectors of Rocky Mountain Spotted Fever in south central and interior Alaska (Beckman, 2013). While it may be predicted that the warming of Alaska may be contributing to this recent invasion, tick distribution is influenced by additional factors such as habitat suitability and dispersal patterns, which can affect the accuracy of these predictions. The contribution of climate change-induced alterations in vector range to human disease, thus, depends on many other factors such as land use practices, human behavior (suburban development in wooded areas, outdoor recreational activities, transport of pets, use of insect repellents, etc.), and human population density, as well as adequacy of the public health infrastructure.

Linkage Between Climate and Infectious Diseases

For most diseases that we consider to be climate sensitive, we have very little data on the relationship between weather climate and infectious disease emergence in the Arctic. Much can be learned by promptly investigating outbreaks that may be climate related. For example, outbreaks of gastroenteritis caused by *Vibrio parahaemolyticus* have been related to the consumption of raw or inadequately cooked shellfish collected from seawater at temperatures higher than 15°C (Figure A15-2). Prior to 2004, the most northerly outbreak occurred in northern British Columbia in 1997. However, in July 2004, an outbreak of gastroenteritis caused by *V. parahaemolyticus* was documented among cruise ship passengers consuming raw oysters while visiting an oyster farm in Prince William Sound, Alaska (McLaughlin et al., 2005). The outbreak investigation documented an increase of 0.21°C per year in the July-August water temperature since 1997, and reported that 2004 was the first year that the oyster farm water temperature exceeded 15°C in July. This event provides direct evidence of an association between rising seawater temperature and the onset of illness. Warmer temperatures may allow infected host animal species to survive winters in larger numbers, increase in population, and expand their range of habitation, thus increasing the opportunity to pass infections to humans. For example, milder weather and less snow cover may have contributed to a large outbreak of Puumala virus infection in northern Sweden in 2007 (Figure A15-3). Puumala virus is endemic in bank voles, and causes hemorrhagic fever with renal syndrome in humans (Pettersson et al., 2008). Similar outbreaks have been noted in Finland and in the Russian Federation (Makary et al., 2010; Revich, 2008).

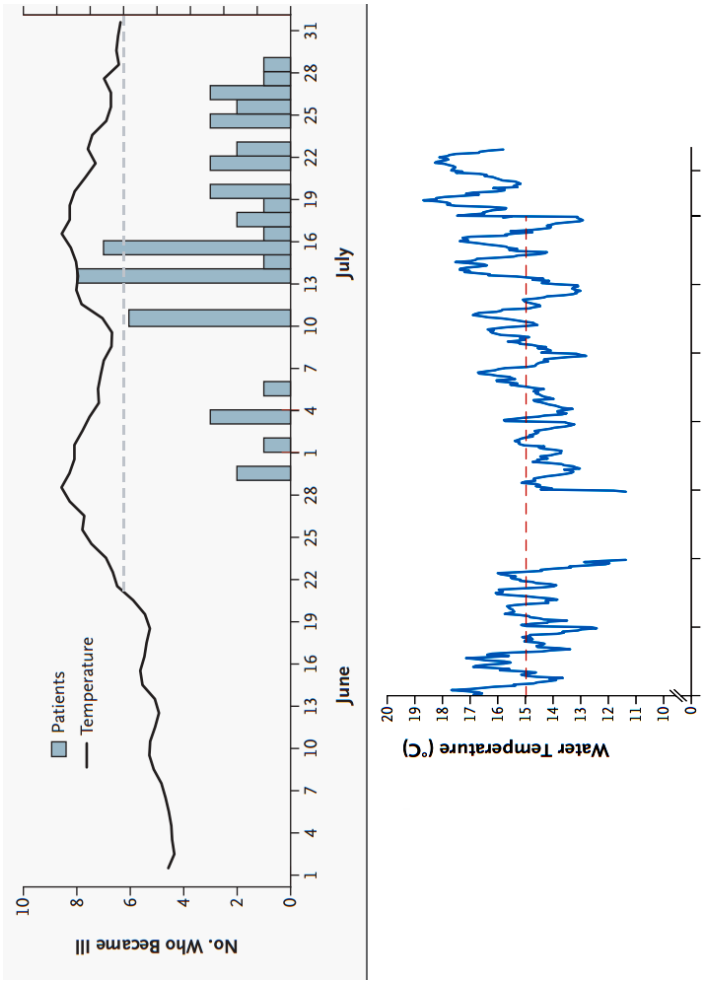

FIGURE A15-2 Climate-related outbreak of *Vibrio parahaemolyticus* gastroenteritis, Alaska 2004. Graph shows the mean daily water temperature at an oyster farm in Prince William Sound Alaska, together case patients by date of consumed farmed oysters. The sea water temperature had increased by 0.21°C per year since 1997 ($r^2 = 0.14$, $P < 0.001$) reaching an optimal temperature for bacterial growth, above 15°C, in oysters in June 2004.
SOURCE: McLaughlin et al., 2005.

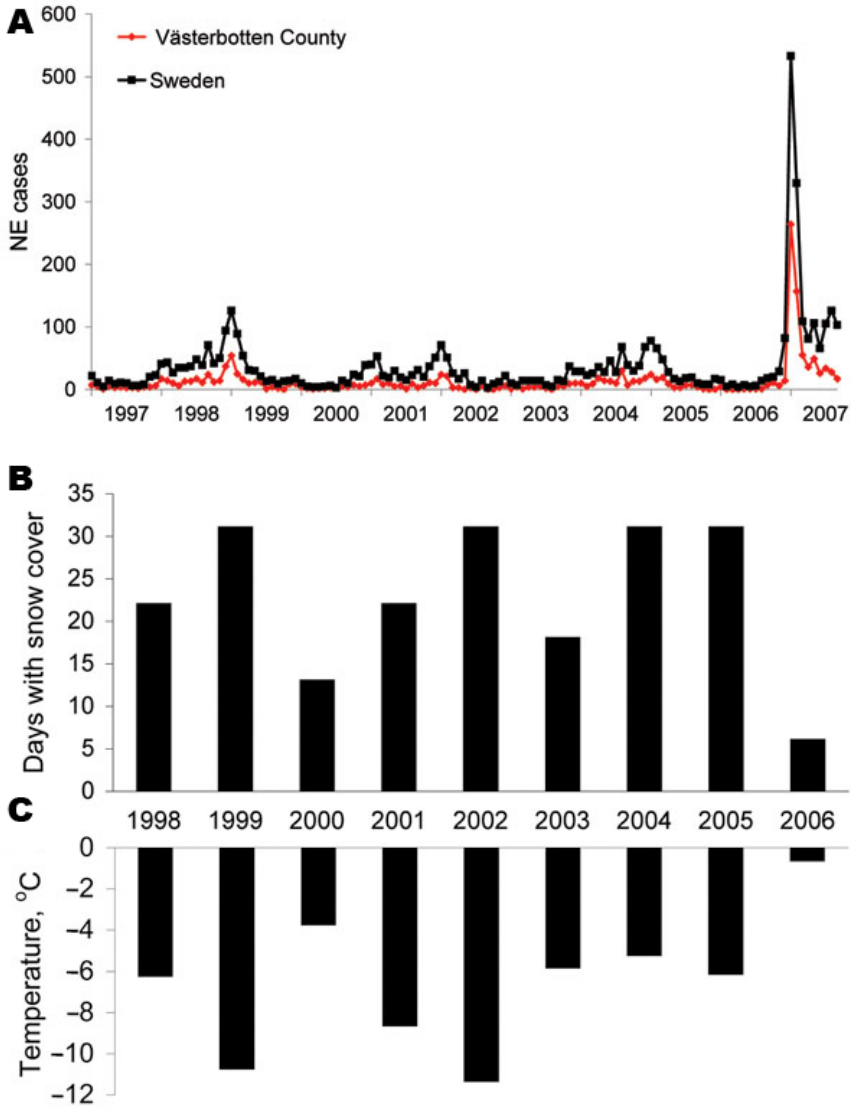

FIGURE A15-3 Climate-related outbreak of Puumala virus infection in Sweden 2007. (A) Monthly incidence of nephropathia epidemica (NE) in Sweden and Västerbotten County, Sweden, January 1997–September 2007. Also shown are climate conditions, December 1998–2006, in the NE outbreak area of Västerbotten County, Sweden. (B) Number of days with a snow cover. (C) Average temperature.
SOURCE: Pettersson et al., 2008.

Recommended Actions

It is apparent that for many of these diseases the risk to human and animal populations is not known, largely because surveillance systems are inadequate, lacking the sensitivity and specificity to be able to determine, with any accuracy, the prevalence of disease in these populations. It is not clear whether this is because of underreporting or underdiagnosis due to the lack of diagnostics, staff issues in remote locations, or logistical difficulties associated with remote specimen collection handling and shipping. Baseline levels of infection in humans and animals are also unknown. More research is needed on establishing current prevalence of infection, determining the disease ecology of these and other emerging pathogens, and the potential impact of climate on disease occurrence in both human and animal populations in Arctic regions. To begin to assess the potential emergence and health impact of climate-sensitive infectious diseases in northern human and animal populations, the following actions need to be undertaken:

1. Enhance the surveillance capacity to monitor potentially climate-sensitive infectious diseases that are likely to have the most impact on human and animal populations. An initial step would include conducting surveys to assess reportable climate-sensitive infectious diseases by Arctic country or northern region. This catalog can then be used to conduct surveillance evaluations for those climate-sensitive infectious diseases with the greatest potential for impacting public or animal health. All facets of each surveillance system should be examined to determine the number of cases identified, case definitions used, data collection, analysis, and reporting and distribution systems used, including feedback to those providing the data.
2. Determine baseline levels of infection by conducting seroprevalence surveys in both human and animal populations. Conduct a survey of available human and animal specimen banks in the circumpolar north. Results could be used to target communities or regions for specific prospective serosurveys and risk factor analysis, and could lead to the implementation of prevention and control outreach, education, and communication activities.
3. Conduct research into the relationship between weather, climate, and infectious disease emergence to guide early detection and intervention by promptly investigating outbreaks that may be climate related.
4. Adopt a "One Health" strategy. Throughout the world the close link between ecosystem health and health of food species and humans has been recognized and is the foundation of the One Health concept. This concept is nowhere more apparent than in the Arctic, making the circumpolar north the place where One Health can be the organizing concept to understand the disease ecology and the potential impact of climate on disease occurrence in both human and animal populations in Arctic

regions (Dudley et al., 2013). The key to capitalizing on the One Health approach is to use and expand interdisciplinary networks to establish and integrate disease surveillance using human, animal, and environmental data to detect emergence of climate-sensitive infectious diseases in human and animal populations.

5. Networks must be expanded. One network that focuses on human health in Arctic populations is the International Union for Circumpolar Health (www.iuch.net), which includes working groups on infectious diseases, and climate change and infectious diseases (www.arcticinfdis.com). A network that could facilitate greater intersectorial cooperation efforts between human, animal, and environmental professionals in the Arctic is the Arctic Council. The Arctic Council (www.arctic-council.org) is a ministerial intergovernmental forum promoting cooperation, coordination, and interaction between the eight Arctic States (the United States, Canada, Denmark/Greenland, Iceland, Norway, Sweden, Finland, and the Russian Federation), including Arctic indigenous populations, on common Arctic concerns such as sustainable development and environmental protection in the Arctic and more recently on climate change (Arctic Council, 2005). The scientific work of the Arctic Council is carried out in six working groups, which include the Arctic Contaminants Action Program, the Monitoring and Assessment Program, Conservation of Arctic Flora and Fauna, Protection of the Marine Environment, Emergency Prevention Preparedness and Response, and Sustainable Development Working Group. Using contacts within the International Union for Circumpolar Health and Arctic Council working group structures allowed the formation of the International Circumpolar Surveillance of Emerging Infectious Diseases (ICS) in 1999 (Figure A15-4). ICS links public health laboratories, institutes, and academic centers across the circumpolar north for the purpose of monitoring and sharing information on infectious diseases of concern, collaborating on research, and prevention and control activities (IOM, 2008; Zulz et al., 2009).
6. Develop communication strategies for data sharing with communities, circumpolar countries, and other organizations and agencies with wildlife, human, and environmental health responsibilities. In the Arctic, systems for monitoring and communicating changes in environment, wildlife, and human health are very limited. Therefore, establishing communication networks, locally, regionally, and internationally, is critical. For example, the Alaska Native Tribal Health Consortium has developed the Local Environmental Observer Network (LEO), a system for sharing information on environmental impacts and community health effects (Brubaker et al., 2013). LEO uses trained community members to document time and location of specific events and encourages communication between communities, academic centers, and resource agencies to increase understanding

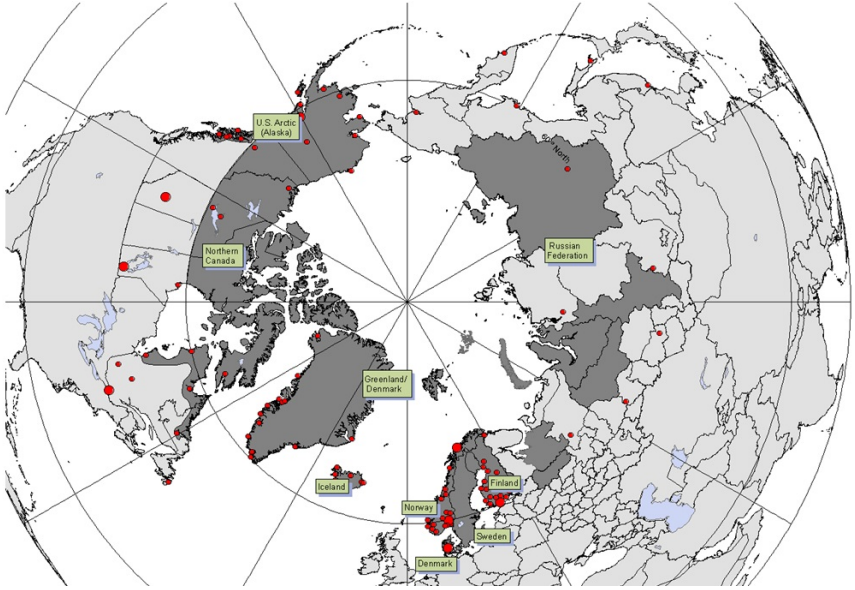

FIGURE A15-4 International Circumpolar Surveillance of Emerging Infectious Diseases. Established in 1998 ICS links public health laboratories, institutes, and academic centers across the circumpolar north for the purpose of monitoring and sharing information on infectious diseases of concern, collaborating on research and prevention and control activities. Participating regions (shown in dark grey), reference laboratories (large red dots), and laboratories (small red dots).
SOURCE: Parkinson, 2009; Zulz et al., 2009.

about climate and other drivers of climate change and to develop adaptation strategies. Such networks can be linked to circumpolar networks such as the Atlas of Community-Based Monitoring (www.arcticcbm.org), which will allow communities and networks to link and expand information sharing and establish collaboration on a circumpolar scale.

Conclusion

Climate change is already affecting indigenous communities of the Arctic. It is well known that in more temperate parts of the world, climate can affect the distribution of many food-, vector- and waterborne infectious diseases. Less is known about the impact of climate change and the risk and distribution of infectious diseases in Arctic regions. Melting permafrost can destabilize water and sanitation infrastructure, resulting in damage to water intake systems and pipes, forcing communities to rely on untreated water sources. This may result in an increase in clinic visits and hospitalizations for various "water-washed" infectious

diseases, those commonly prevented by hand washing such as respiratory infections, skin infections, echinococcosis, and gastroenteritis caused by *Giardia* or *Cryptosporidium*. Many Arctic residents depend on subsistence hunting, fishing, and gathering for food; consequently, changes in climate may increase the potential for the food-borne transmission of toxoplasmosis, trichinosis, and brucellosis in the Arctic. Milder winters and an earlier onset of spring may result in an increase and northward shift in tick populations increasing the incidence of tick-borne diseases in Arctic regions.

It is apparent that for many of these diseases, the risk to human and animal populations is not known, and for most diseases that we consider to be potentially climate sensitive we have very little data on the relationship between weather, climate, and infectious disease emergence. More needs to be done to determine baseline levels of infection and to enhance surveillance capacities in Arctic countries for those infectious diseases that are likely to be potentially climate sensitive, and could have the most impact on human and animal populations.

More research needs to be done on establishing the relationship between weather, climate, and infectious disease emergence to guide early detection and intervention. The Arctic provides a unique opportunity to use a One Health approach as an organizing concept to understand the disease ecology and the potential impact of climate on disease occurrence in both human and animal populations in Arctic regions and to expand local, regional, and international networks to increase interdisciplinary collaboration and understanding about climate change and infectious disease emergence, prevention, and control.

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A16

CLIMATE CHANGE AND HUMAN HEALTH: A ONE HEALTH APPROACH[76]

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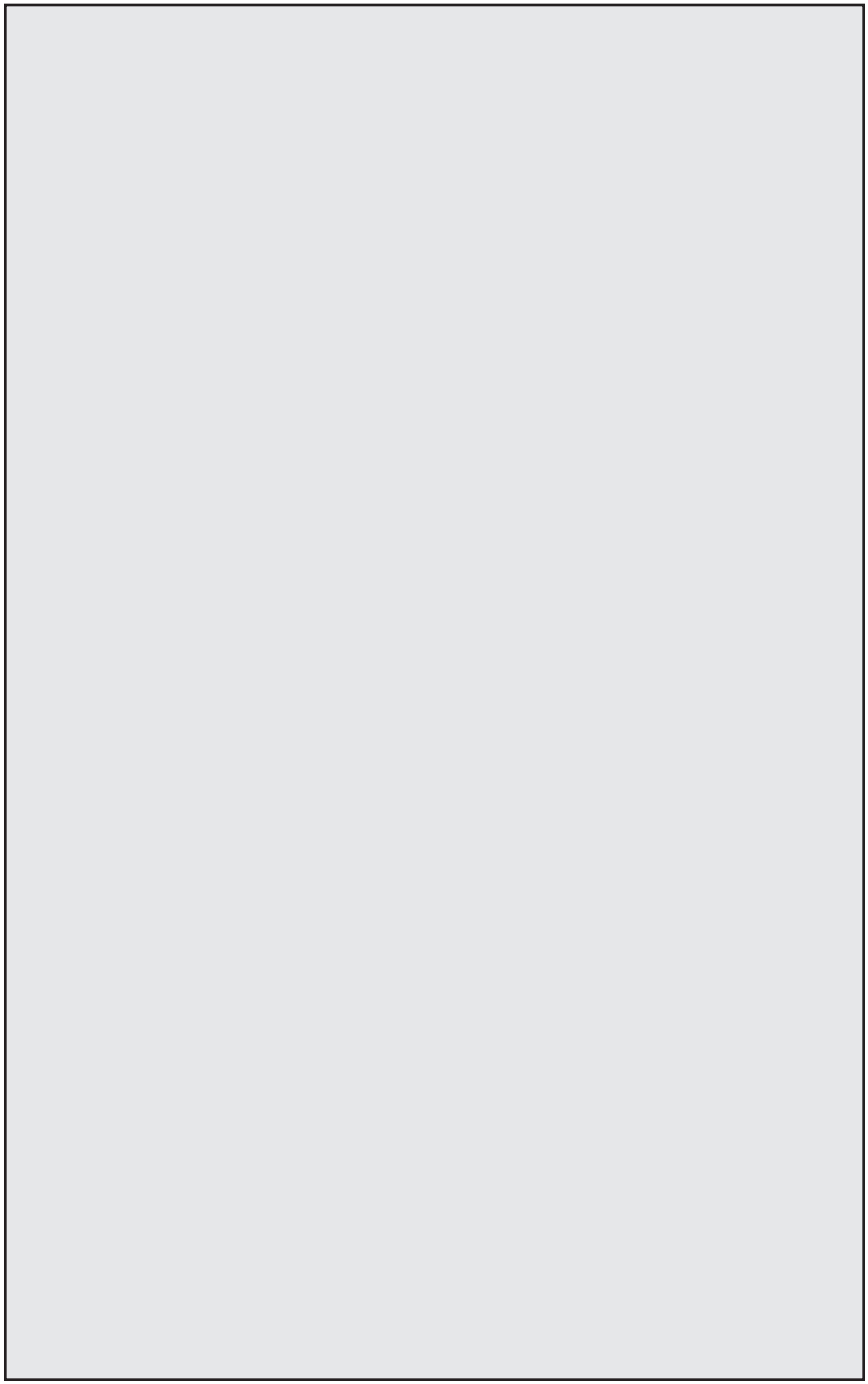

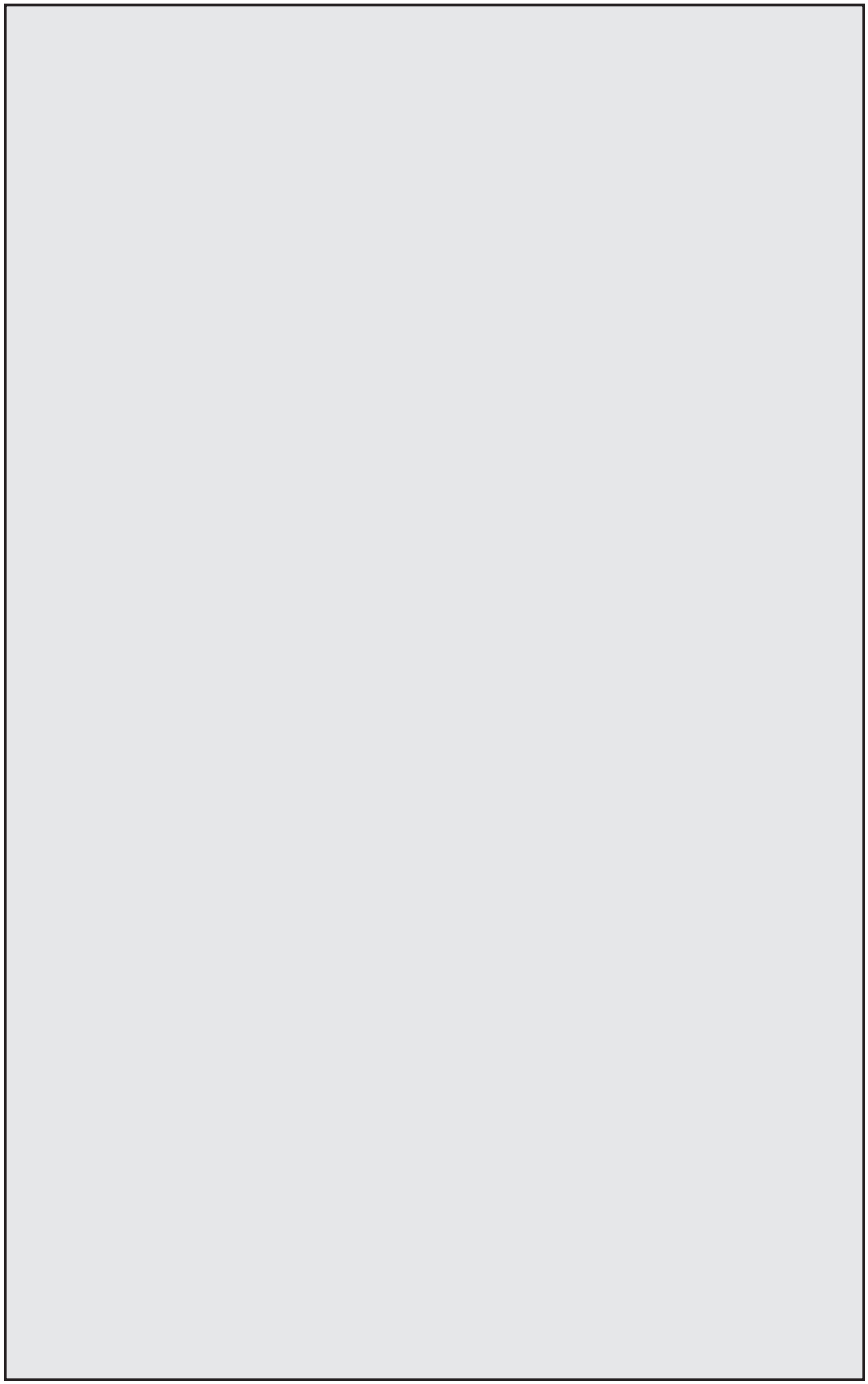

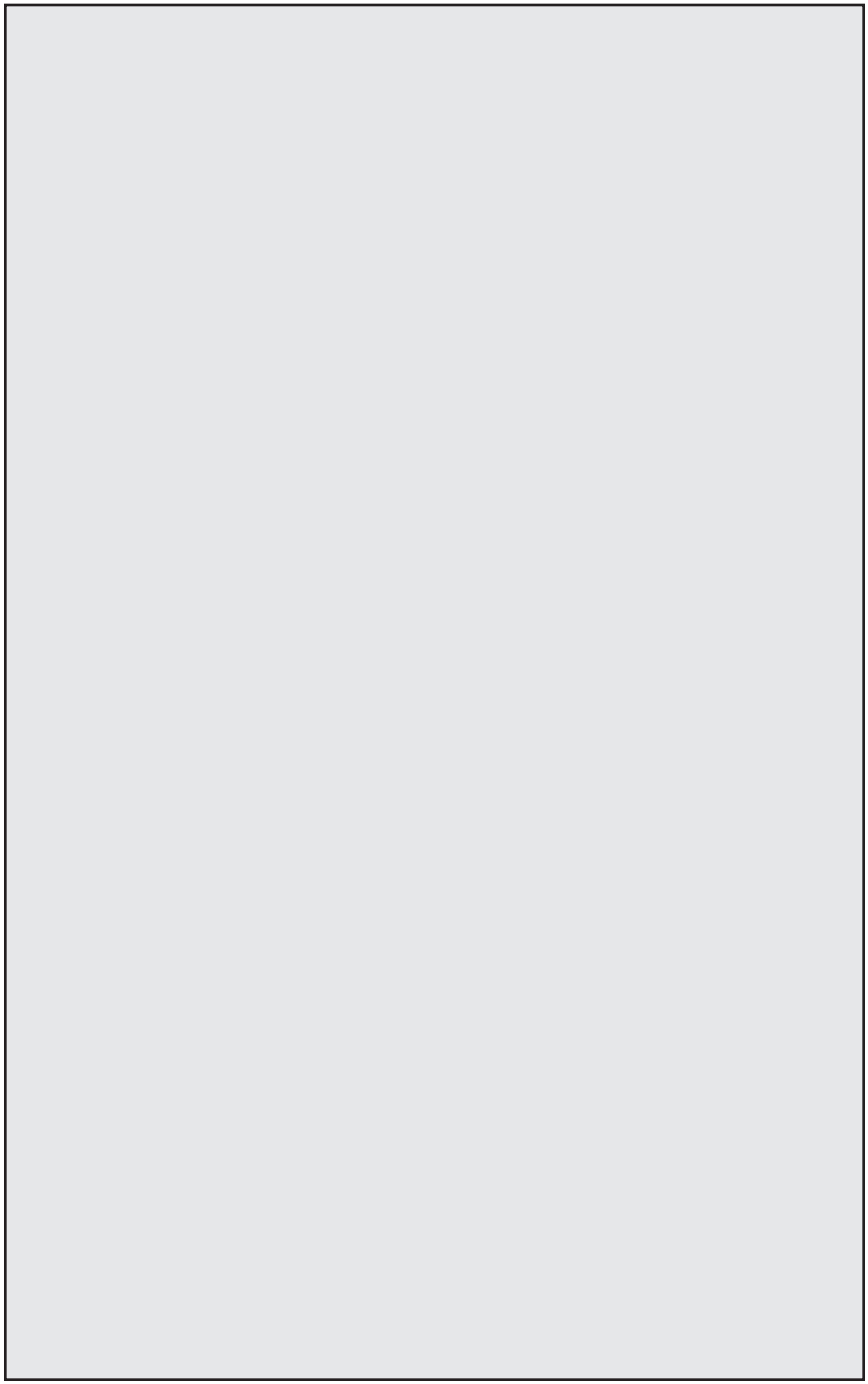

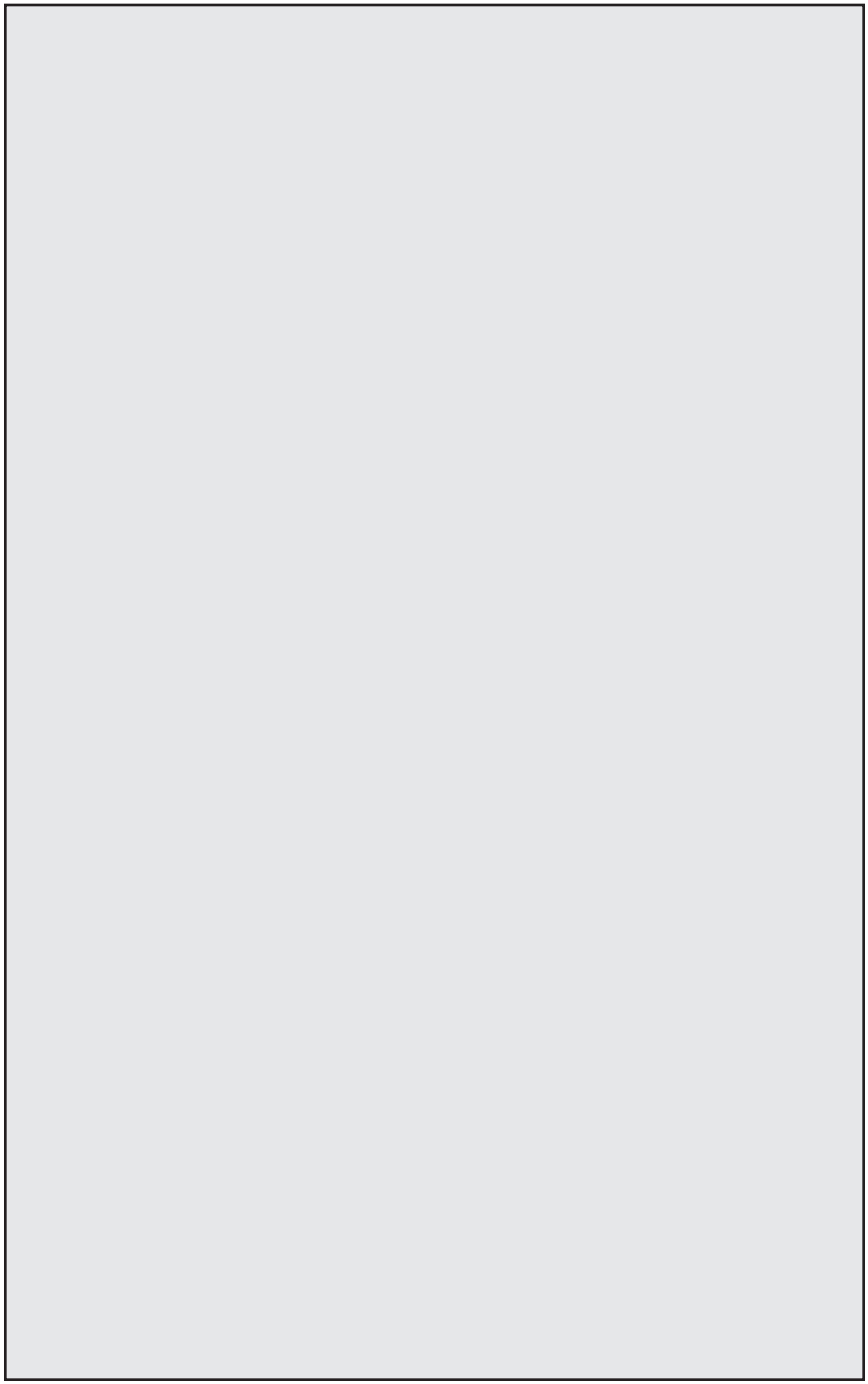

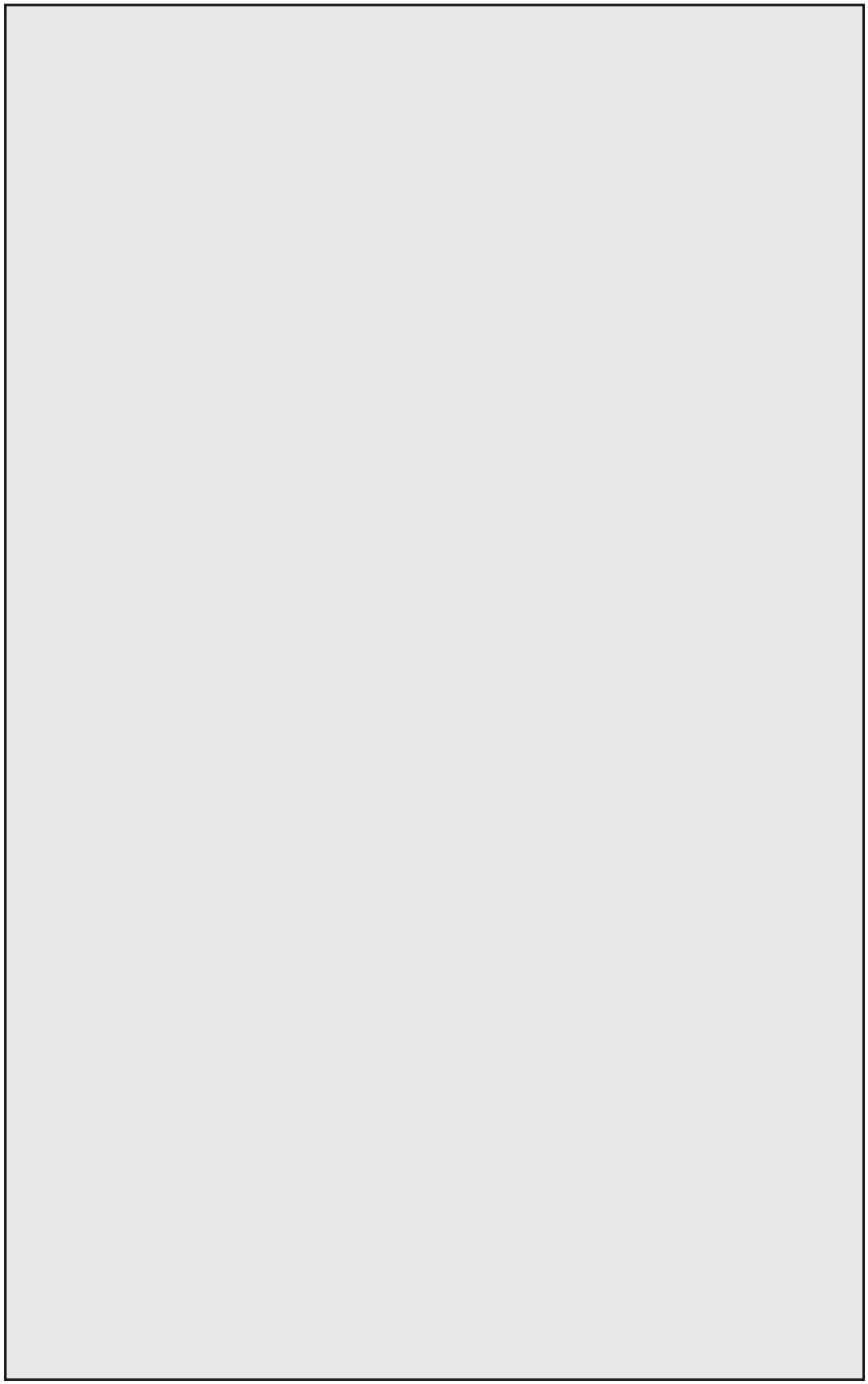

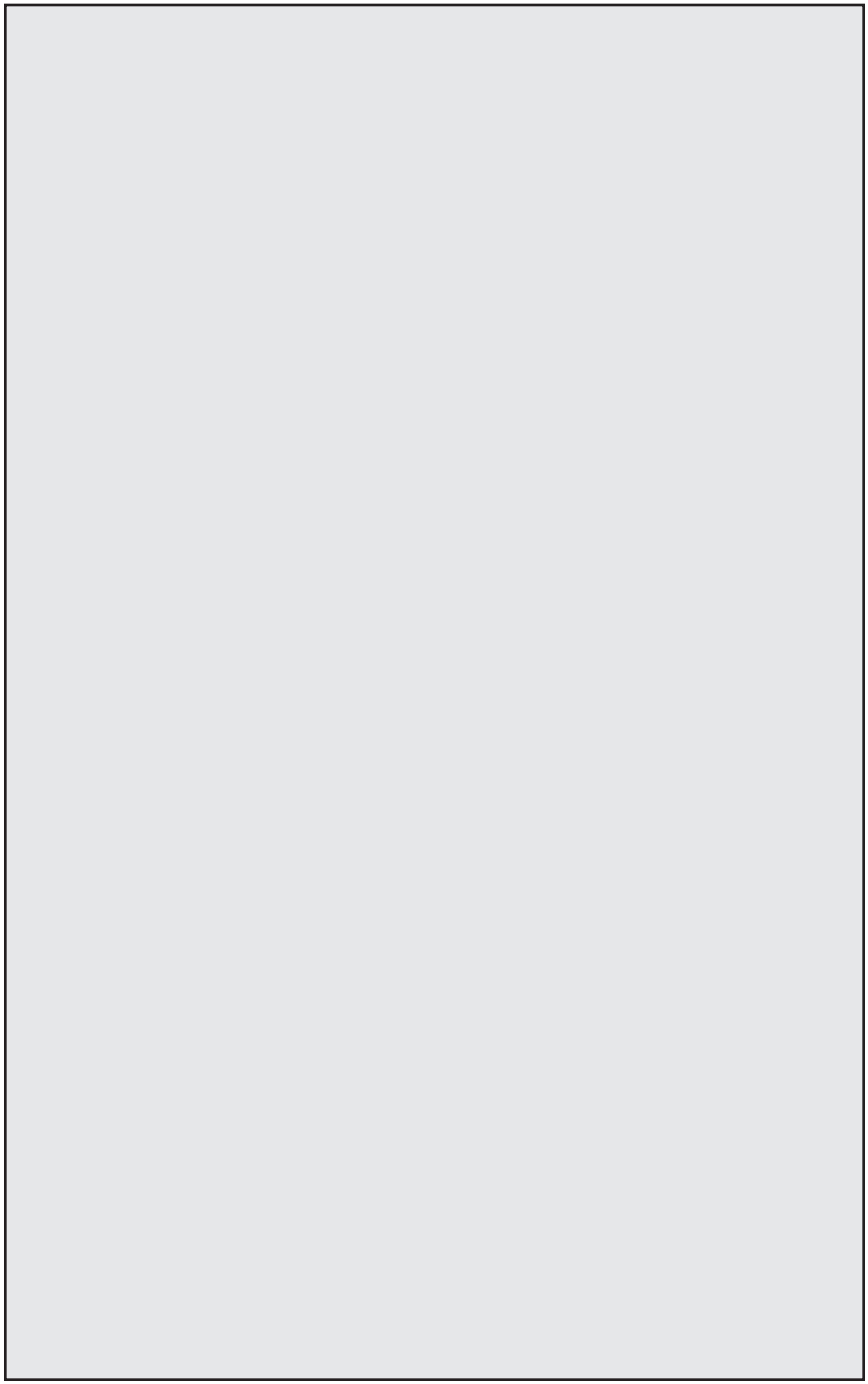

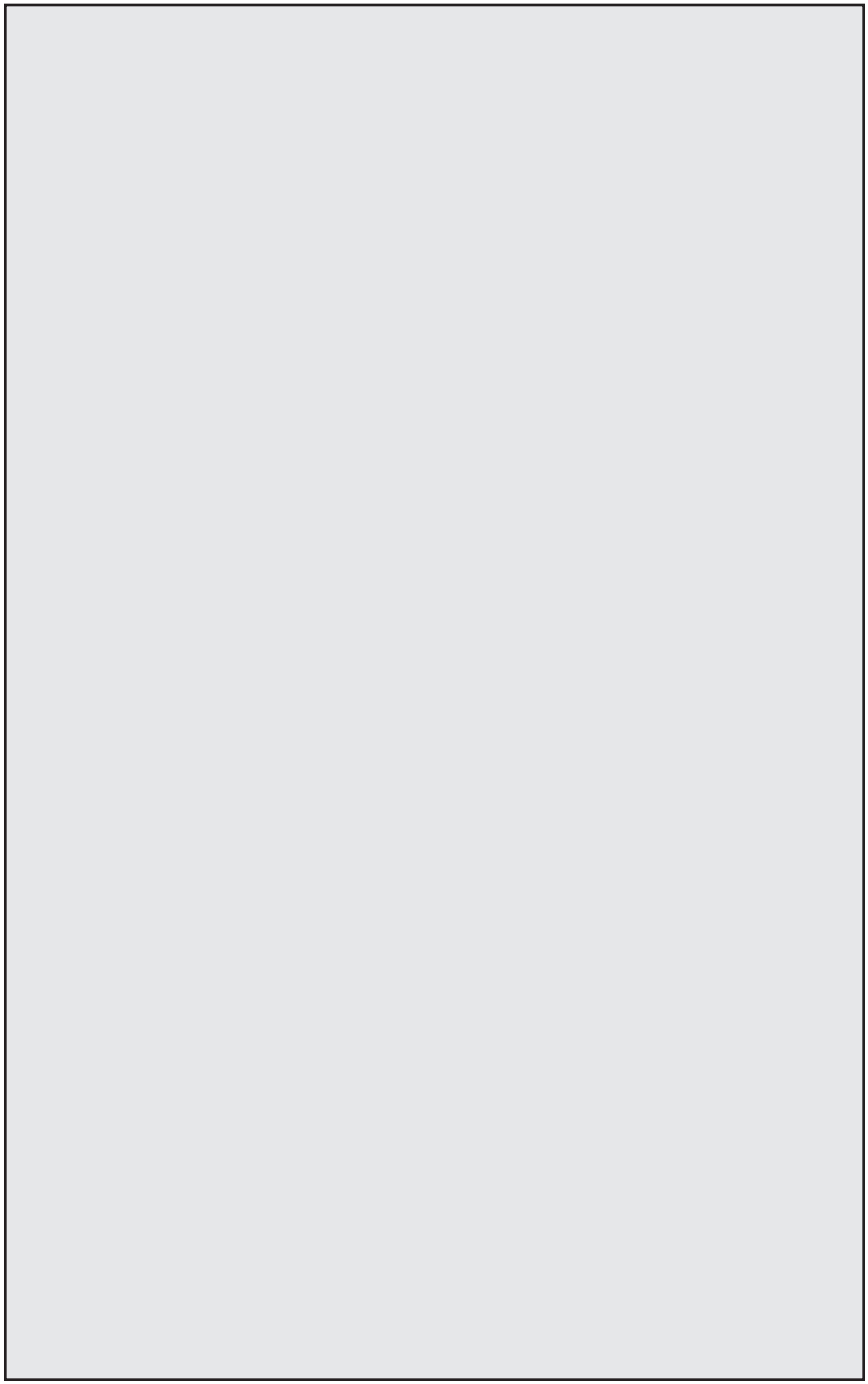

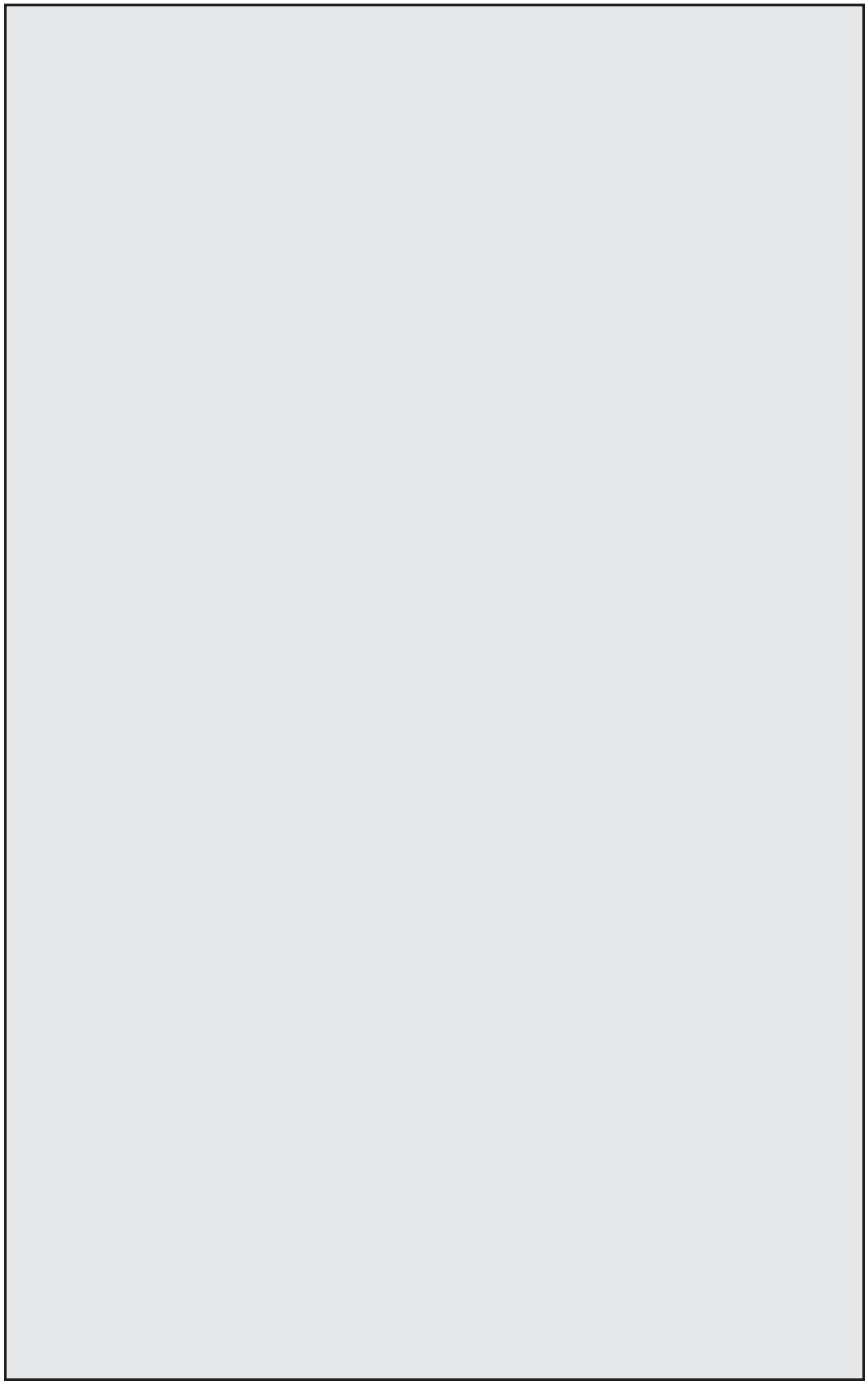

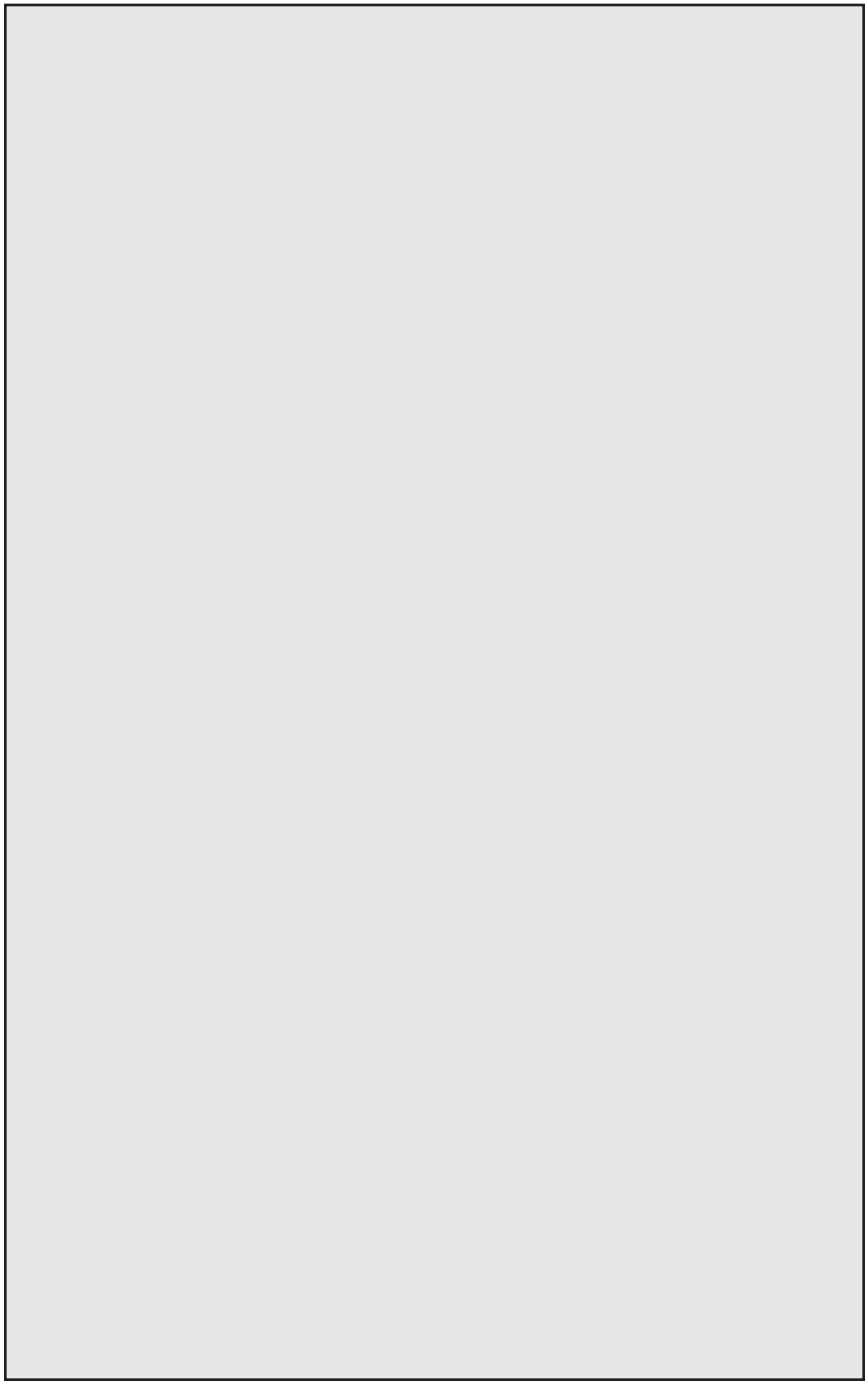

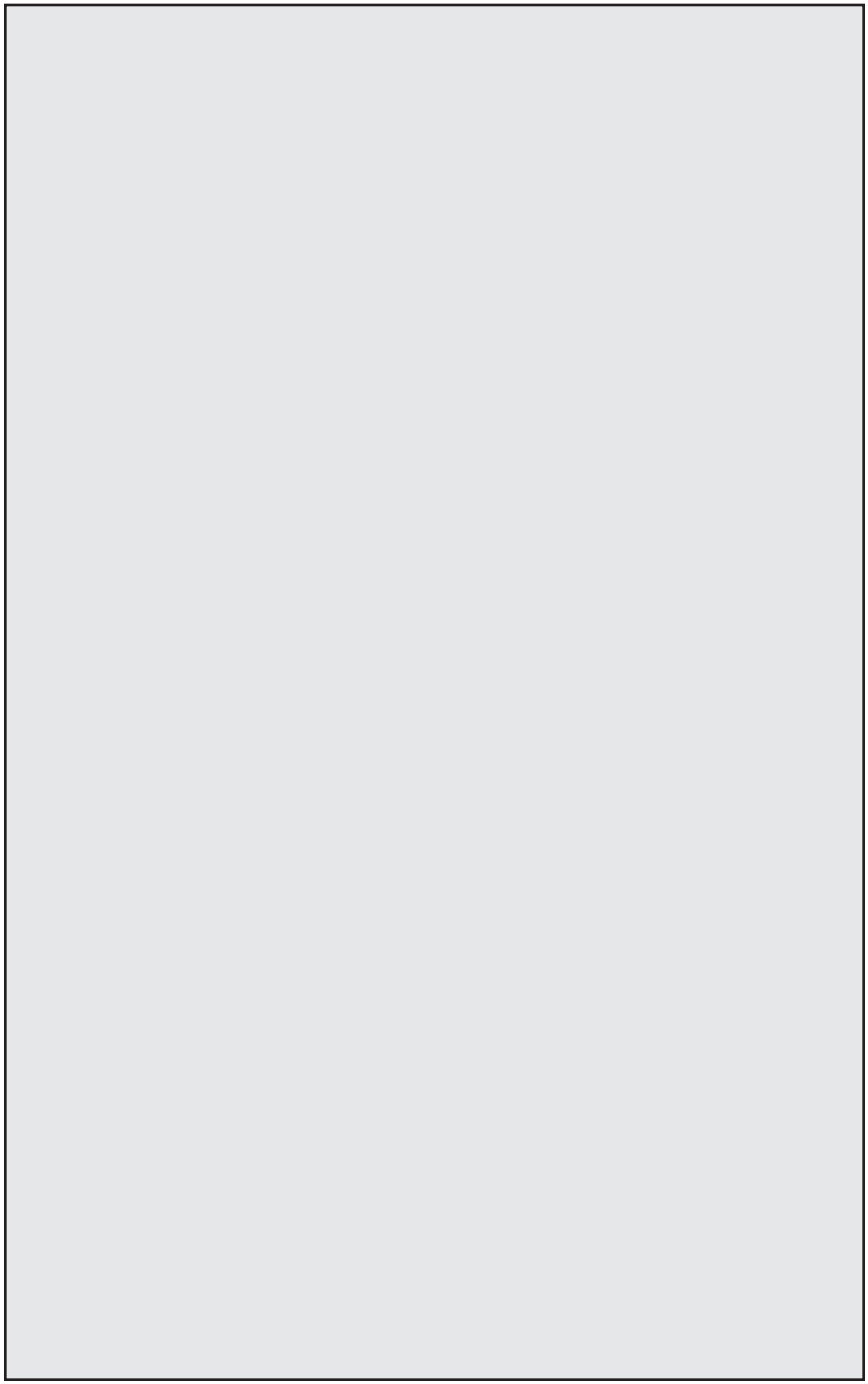

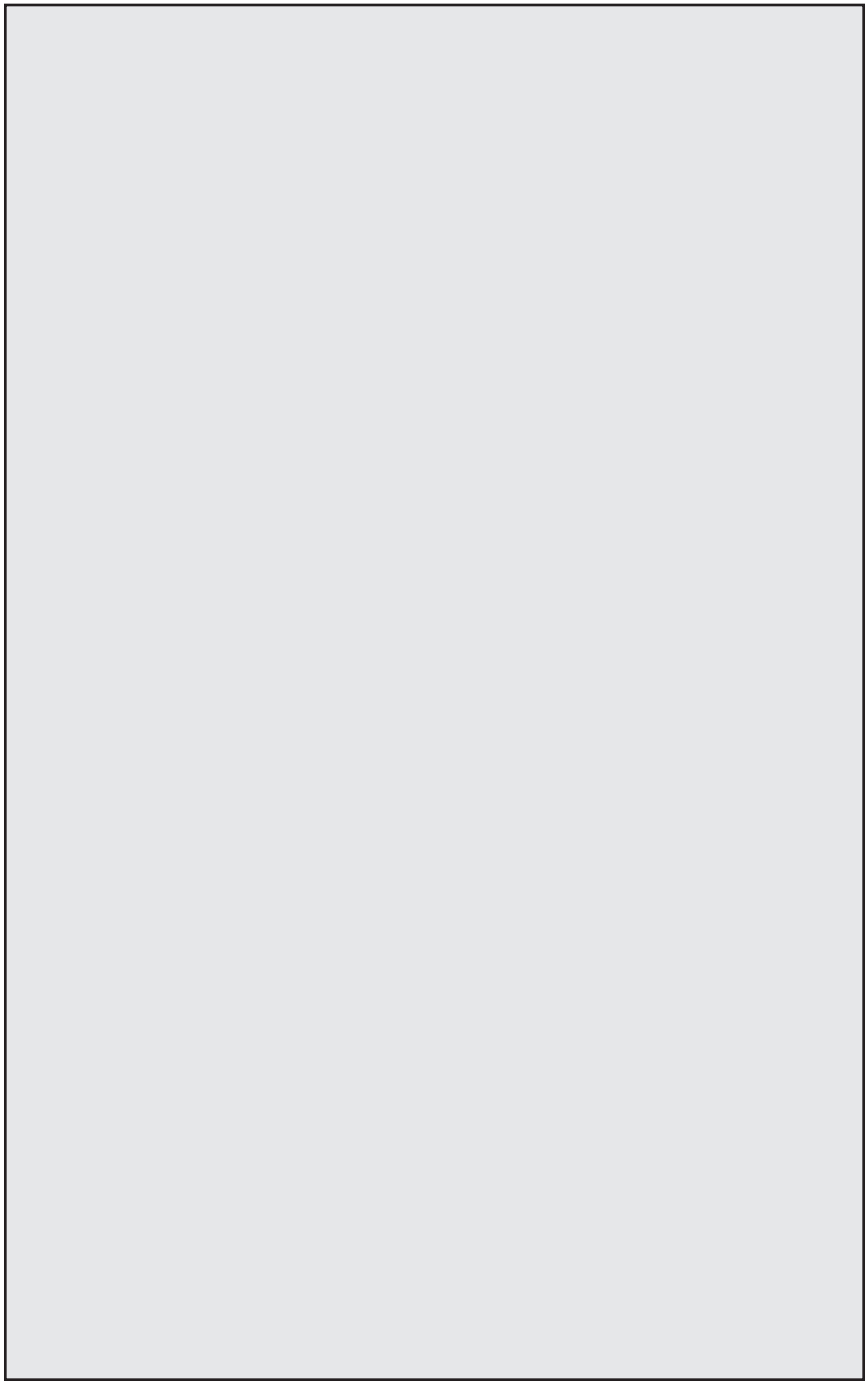

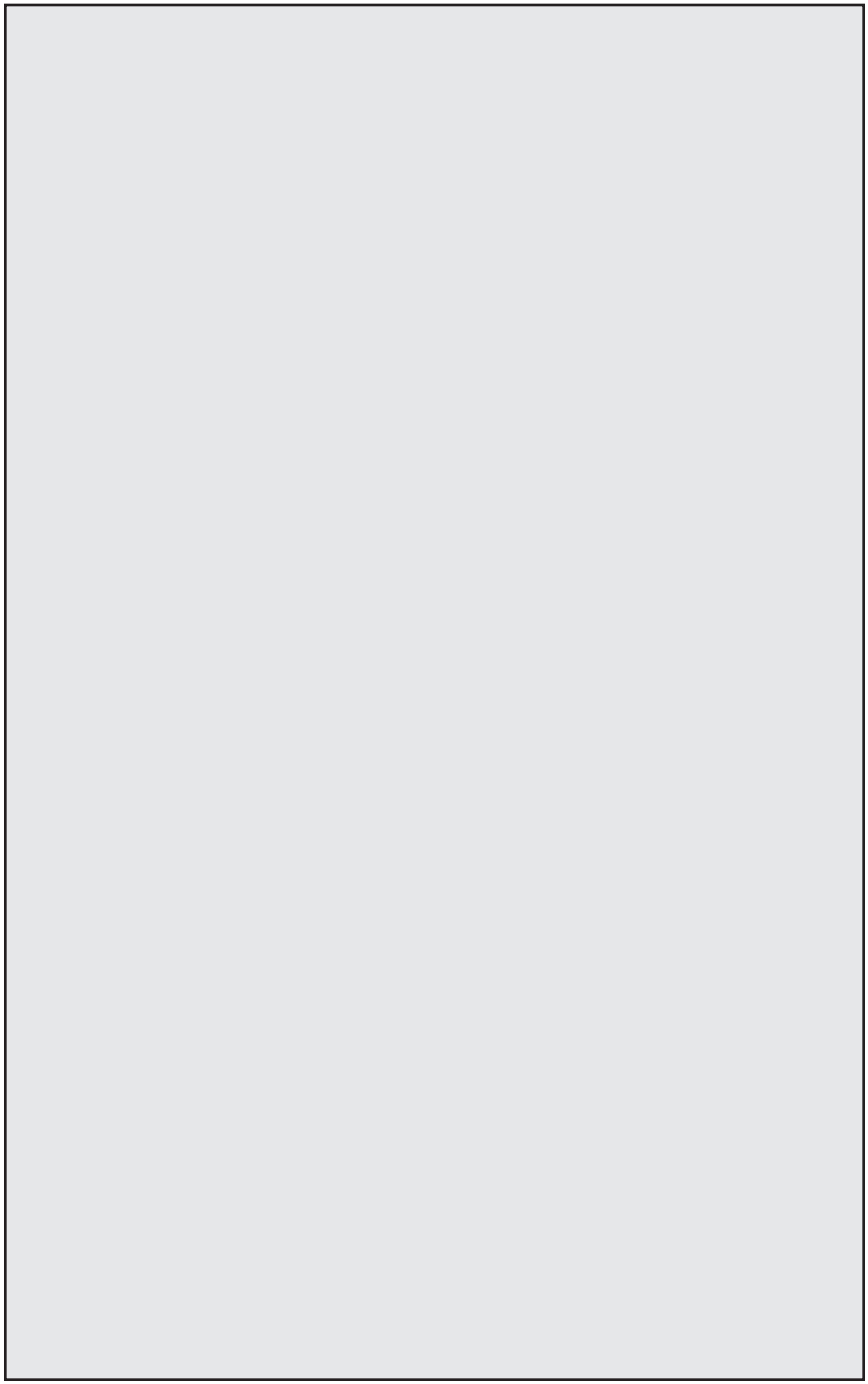

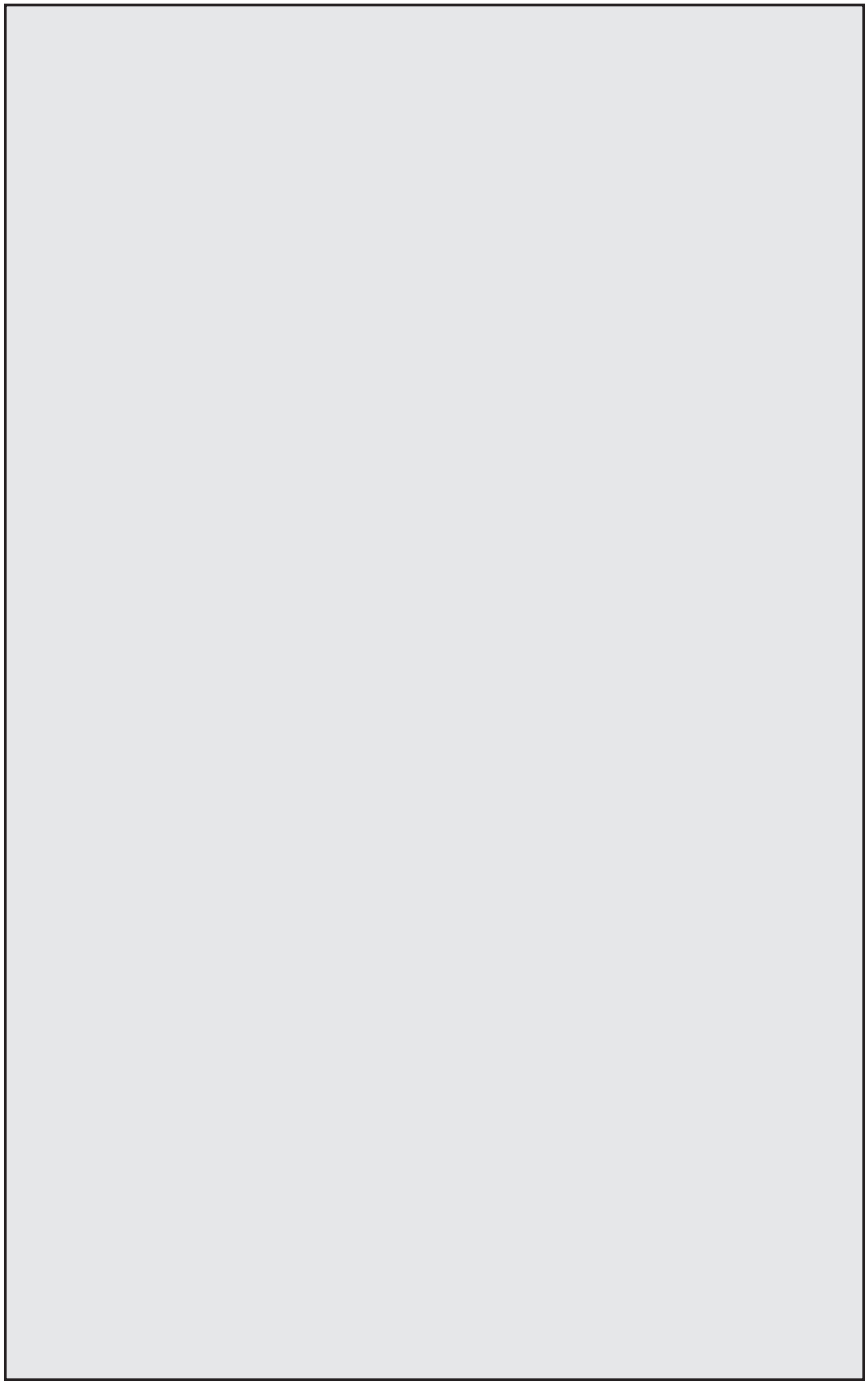

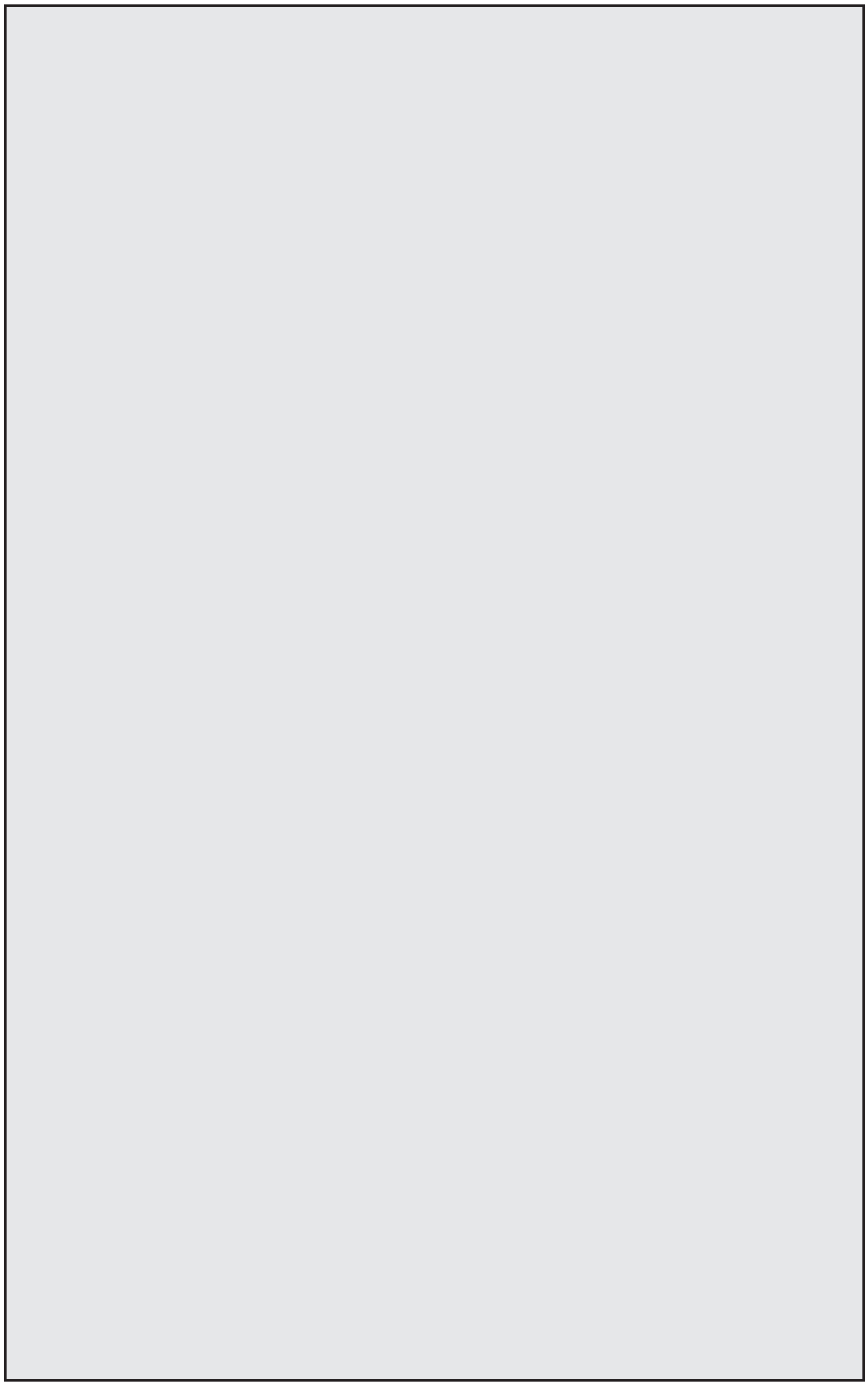

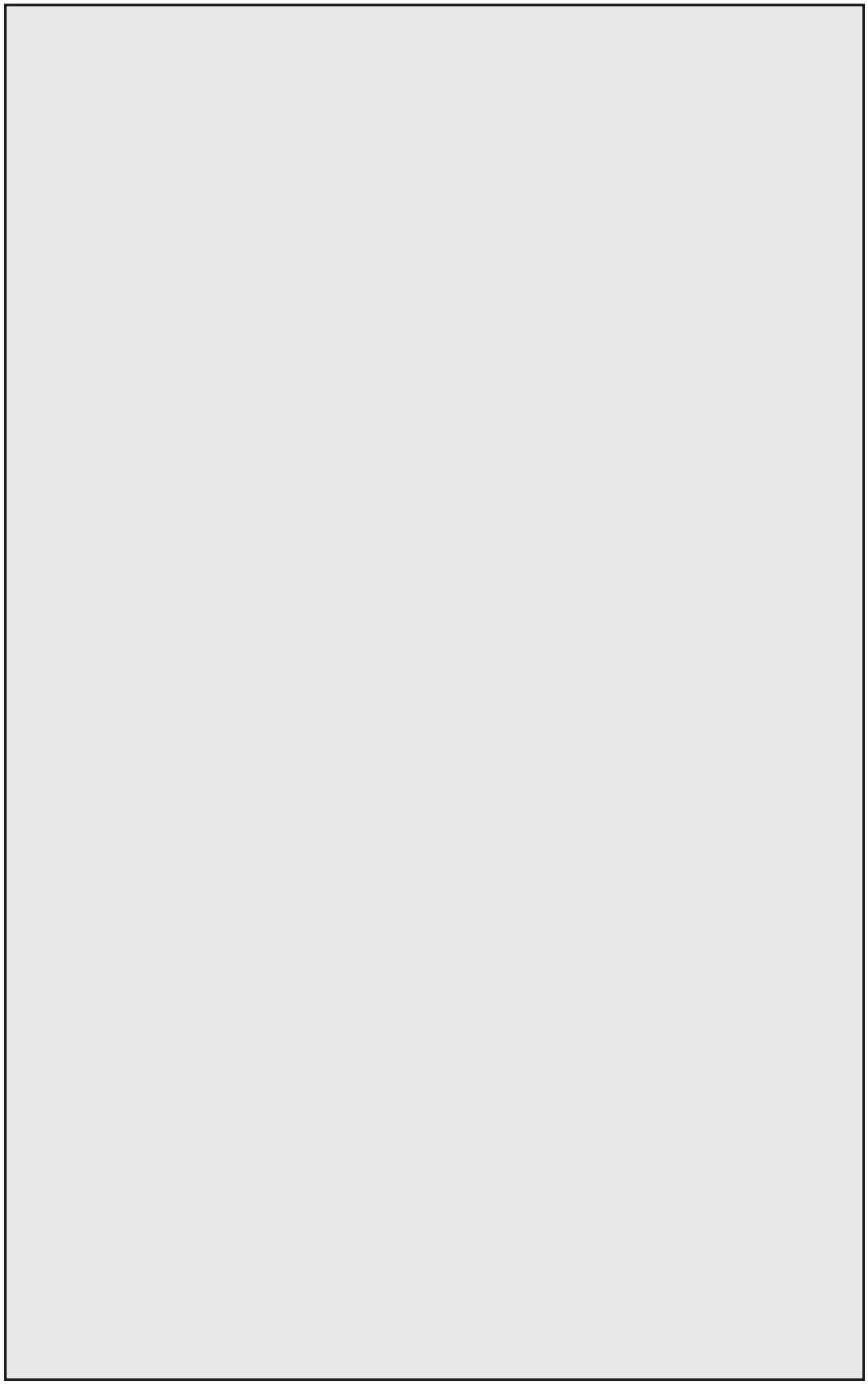

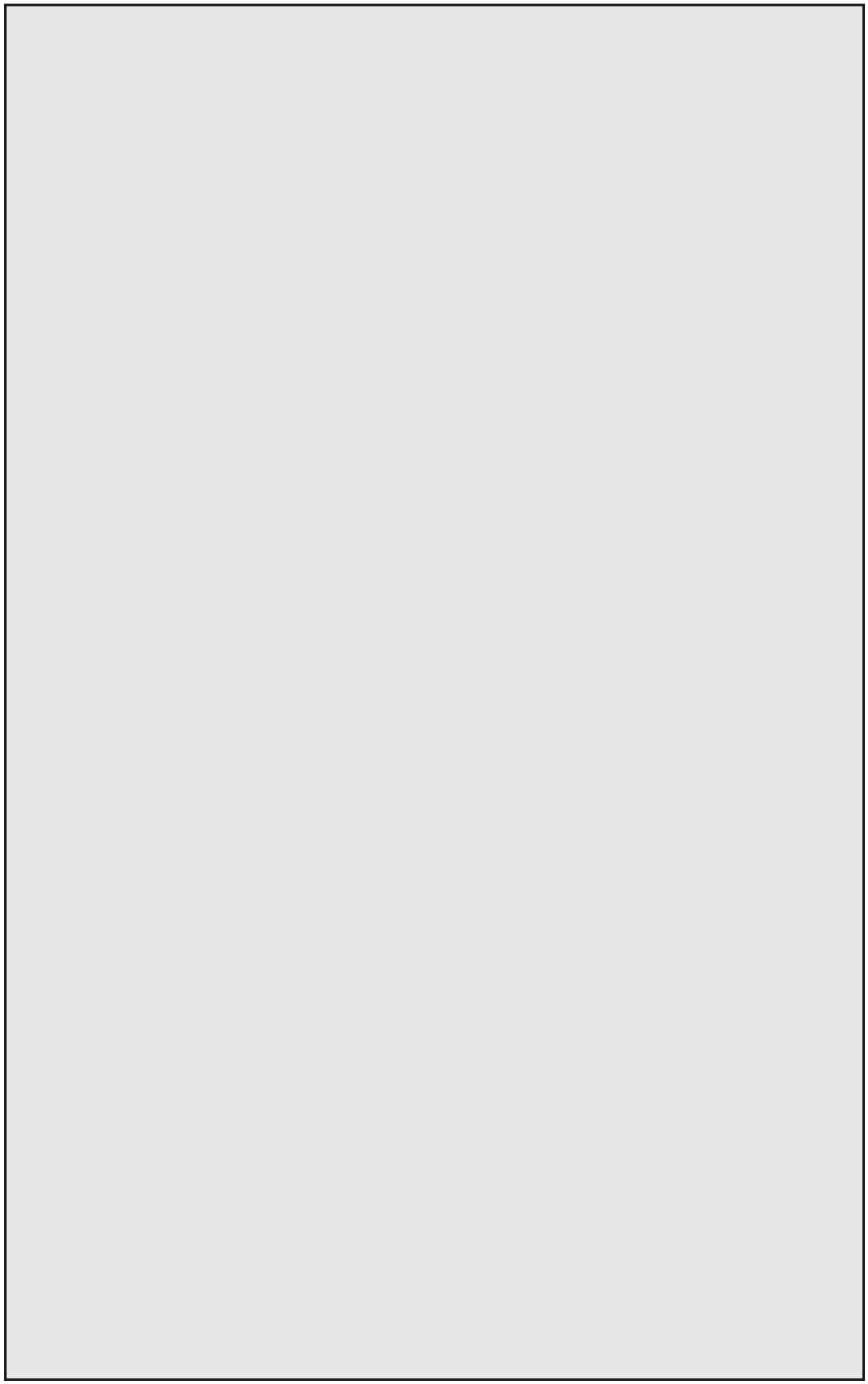

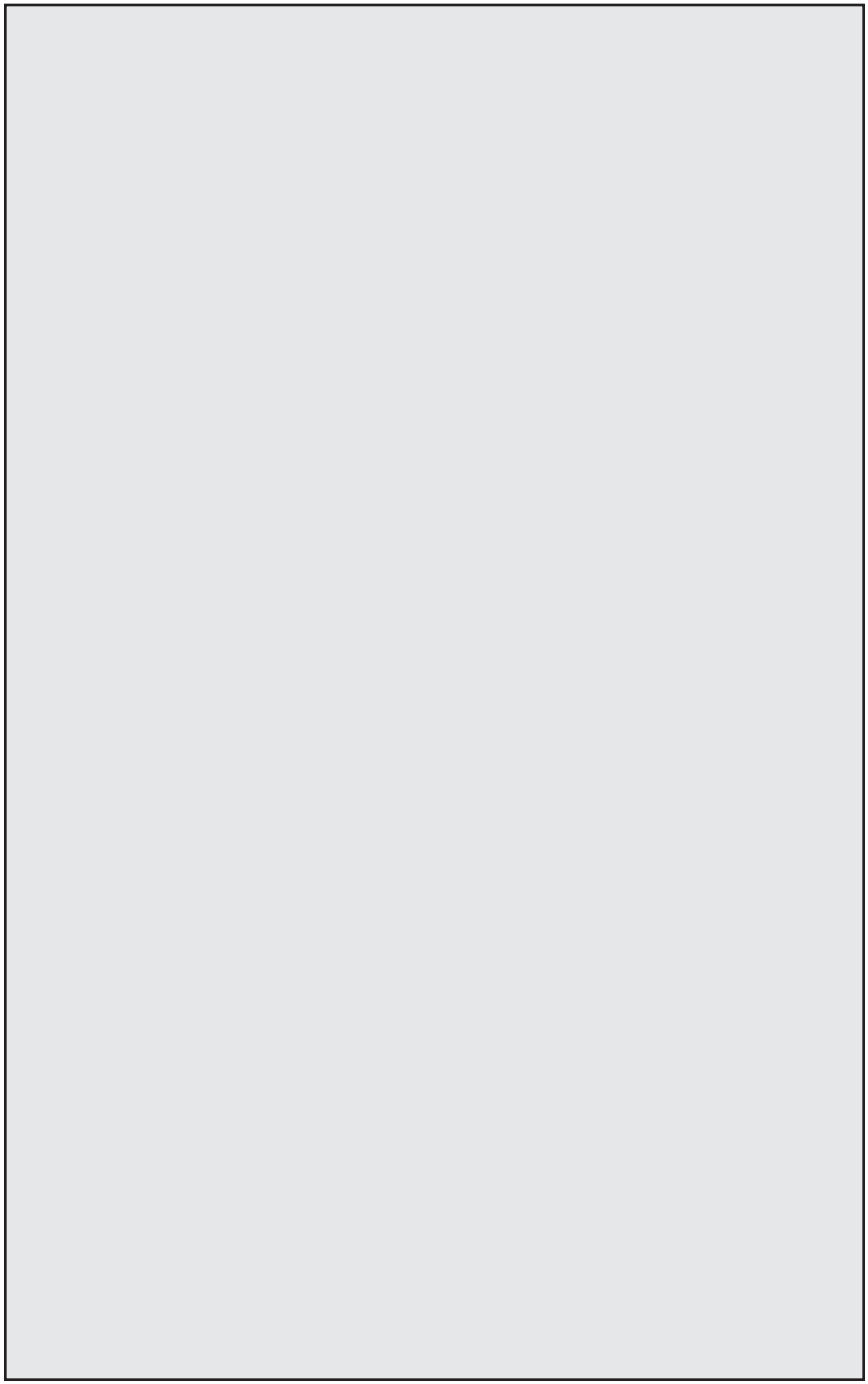

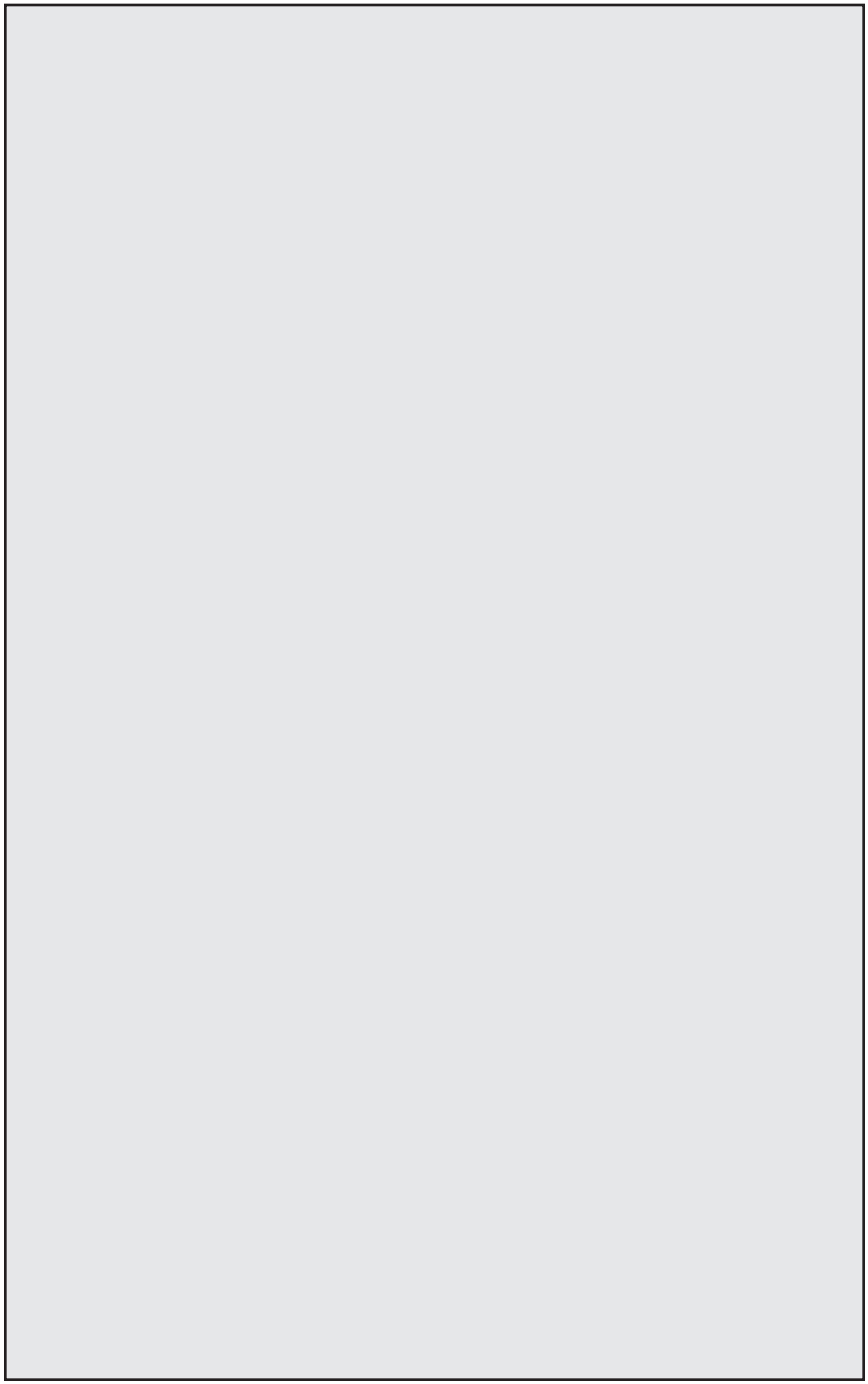

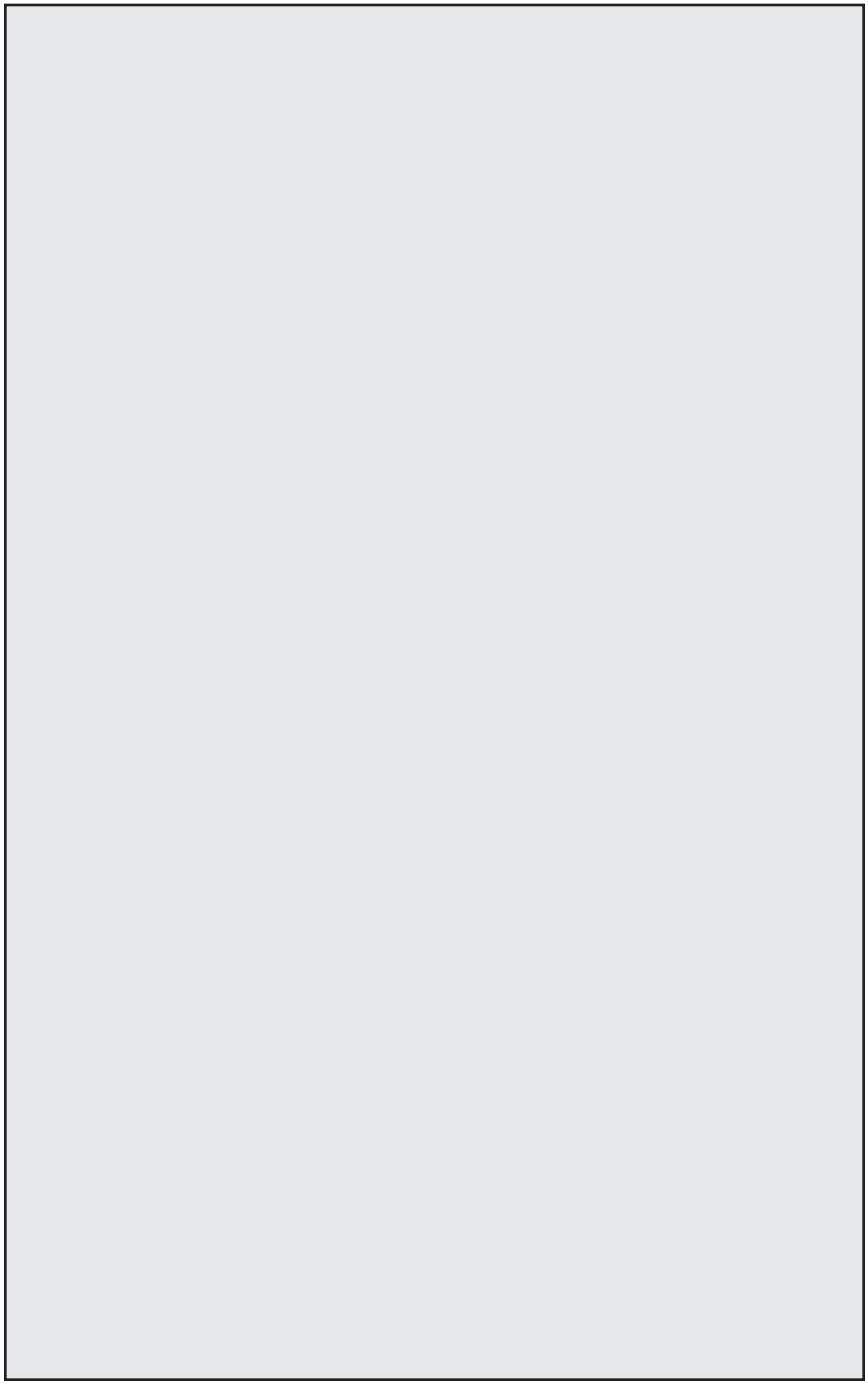

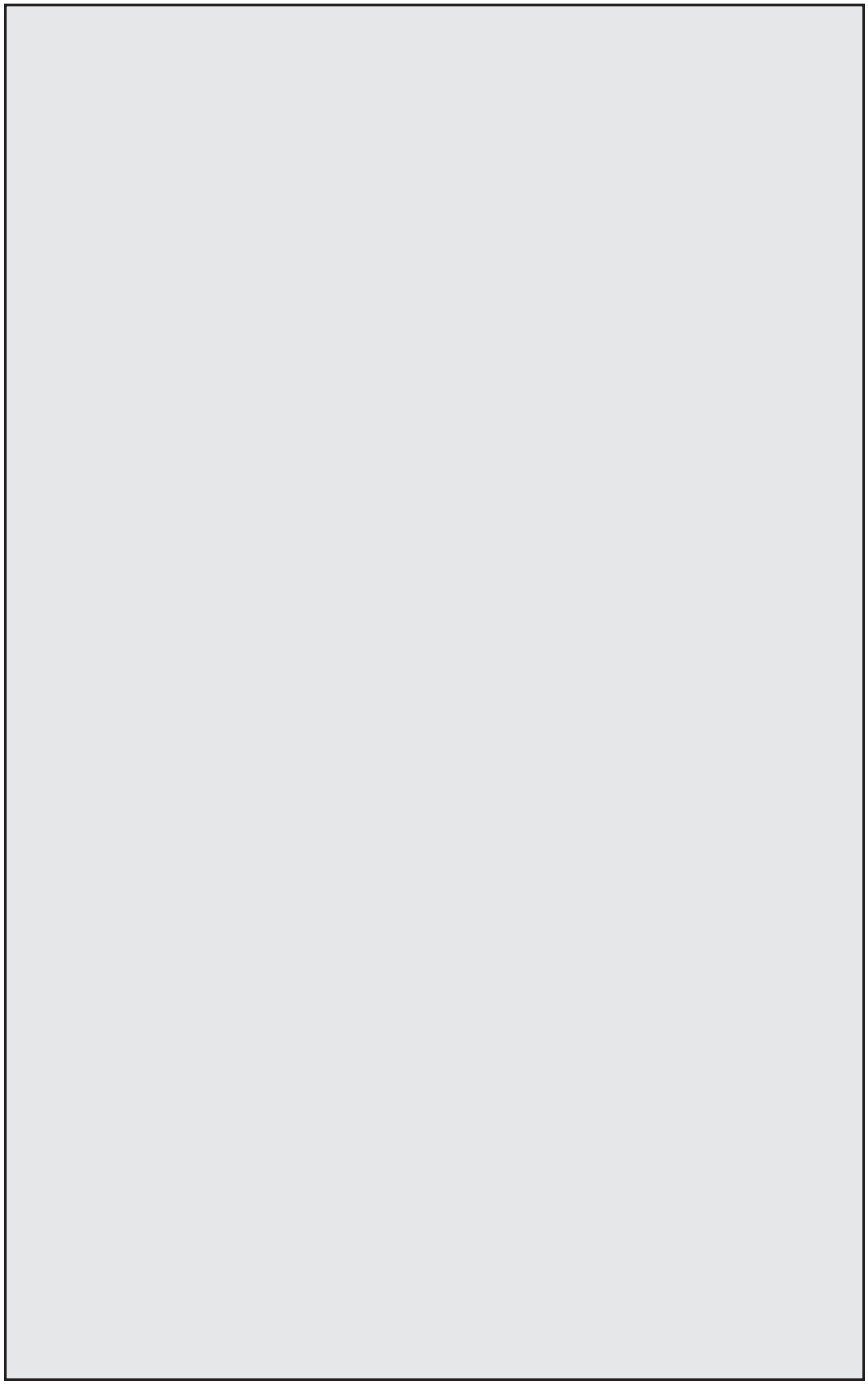

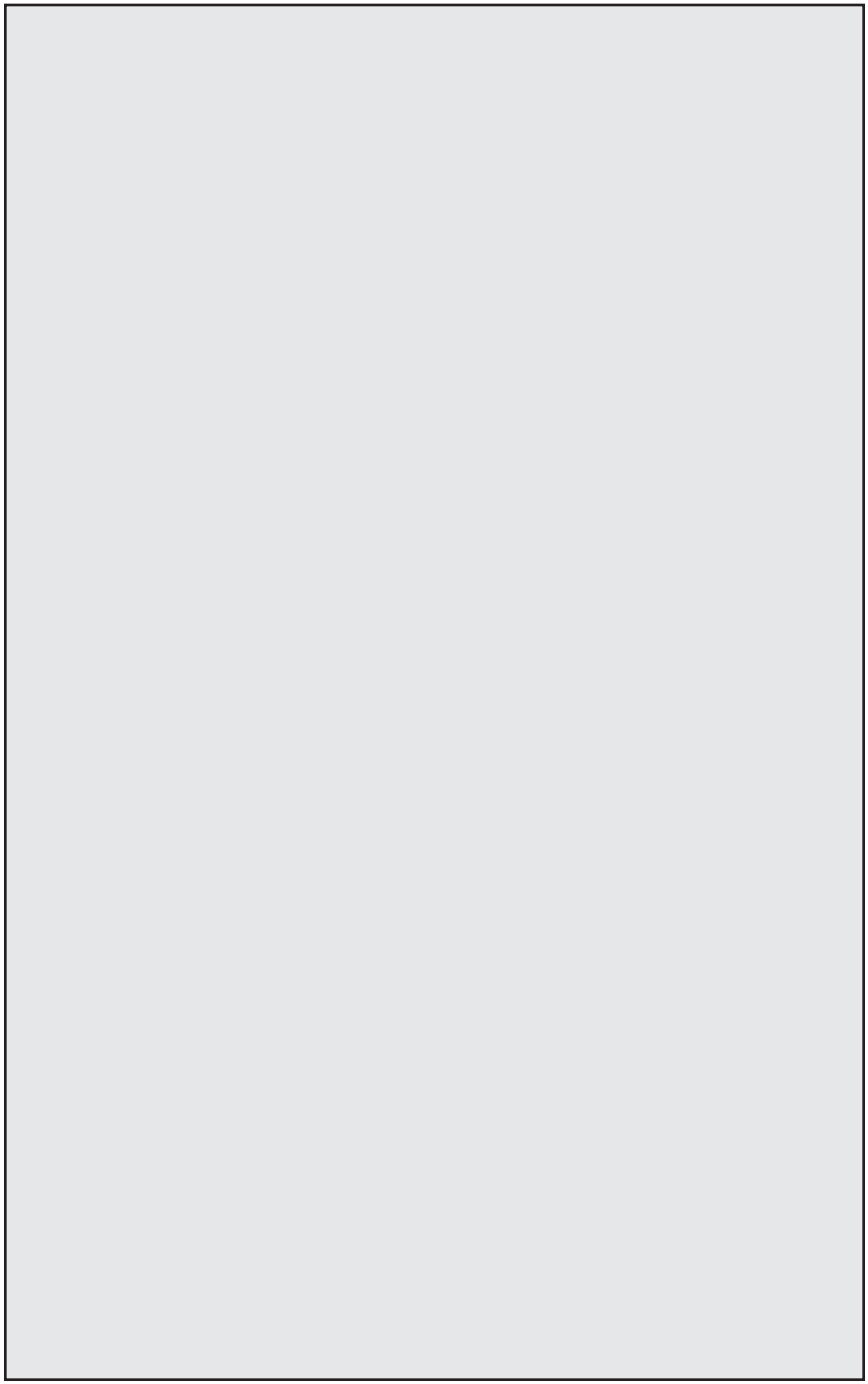

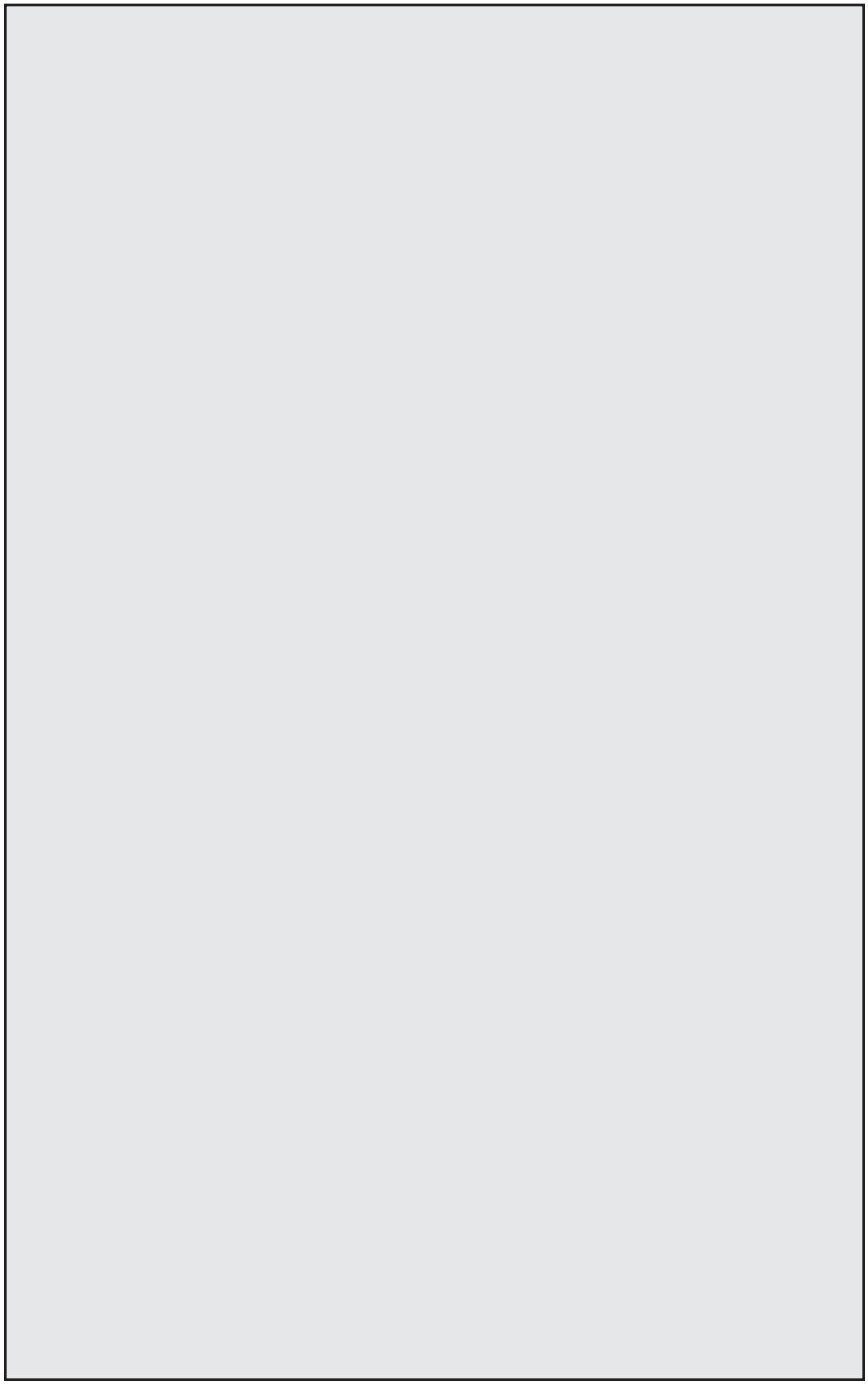

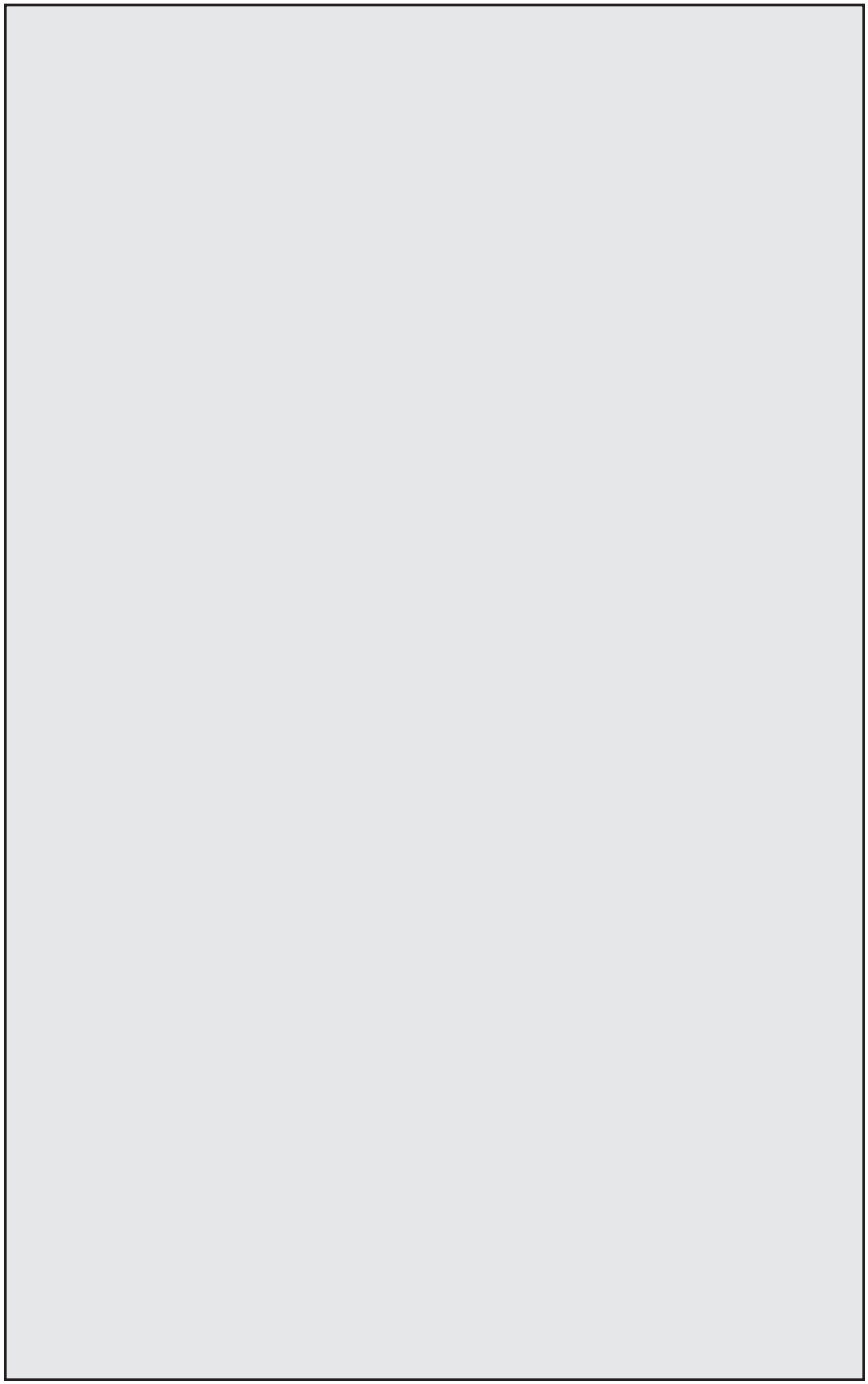

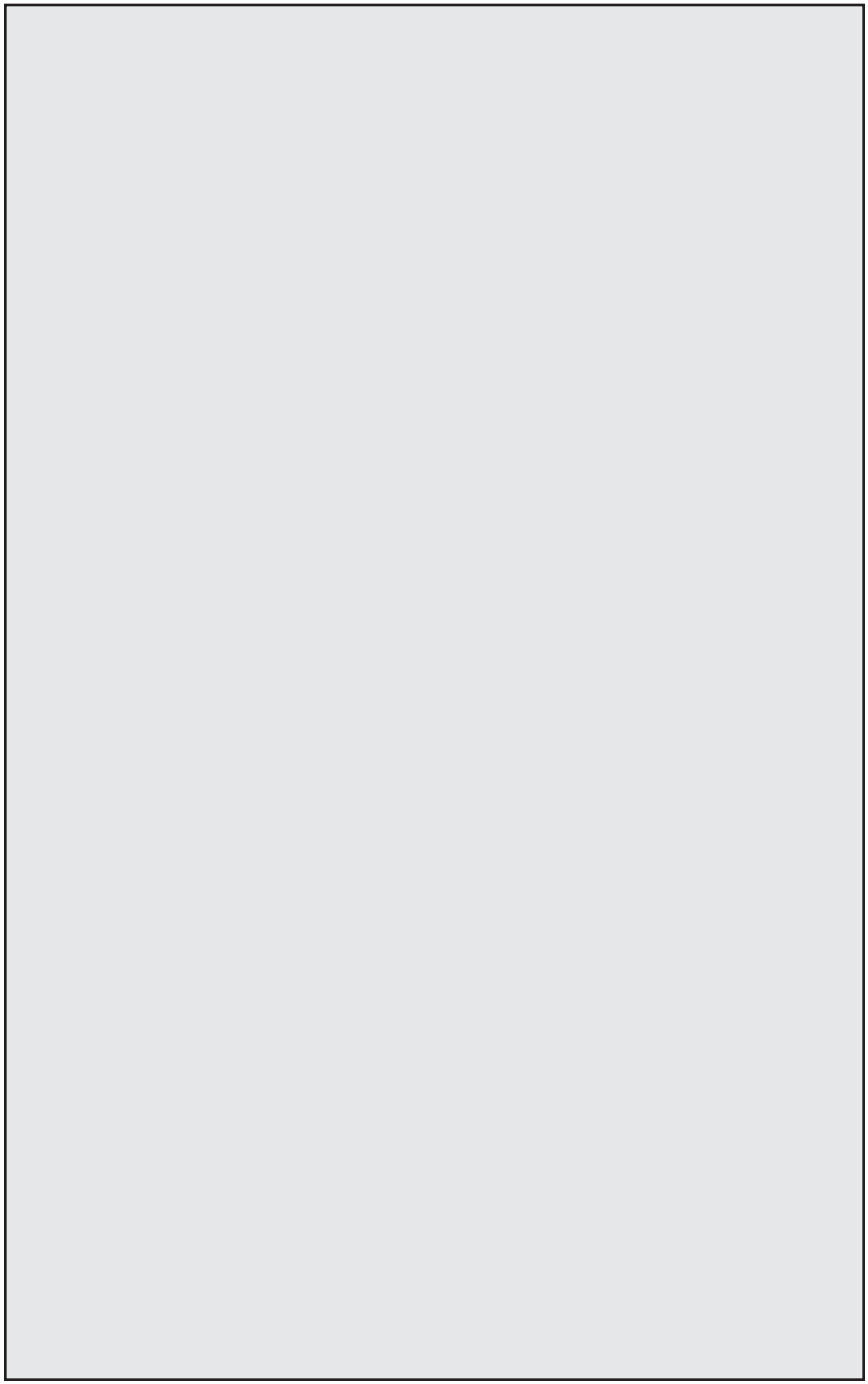

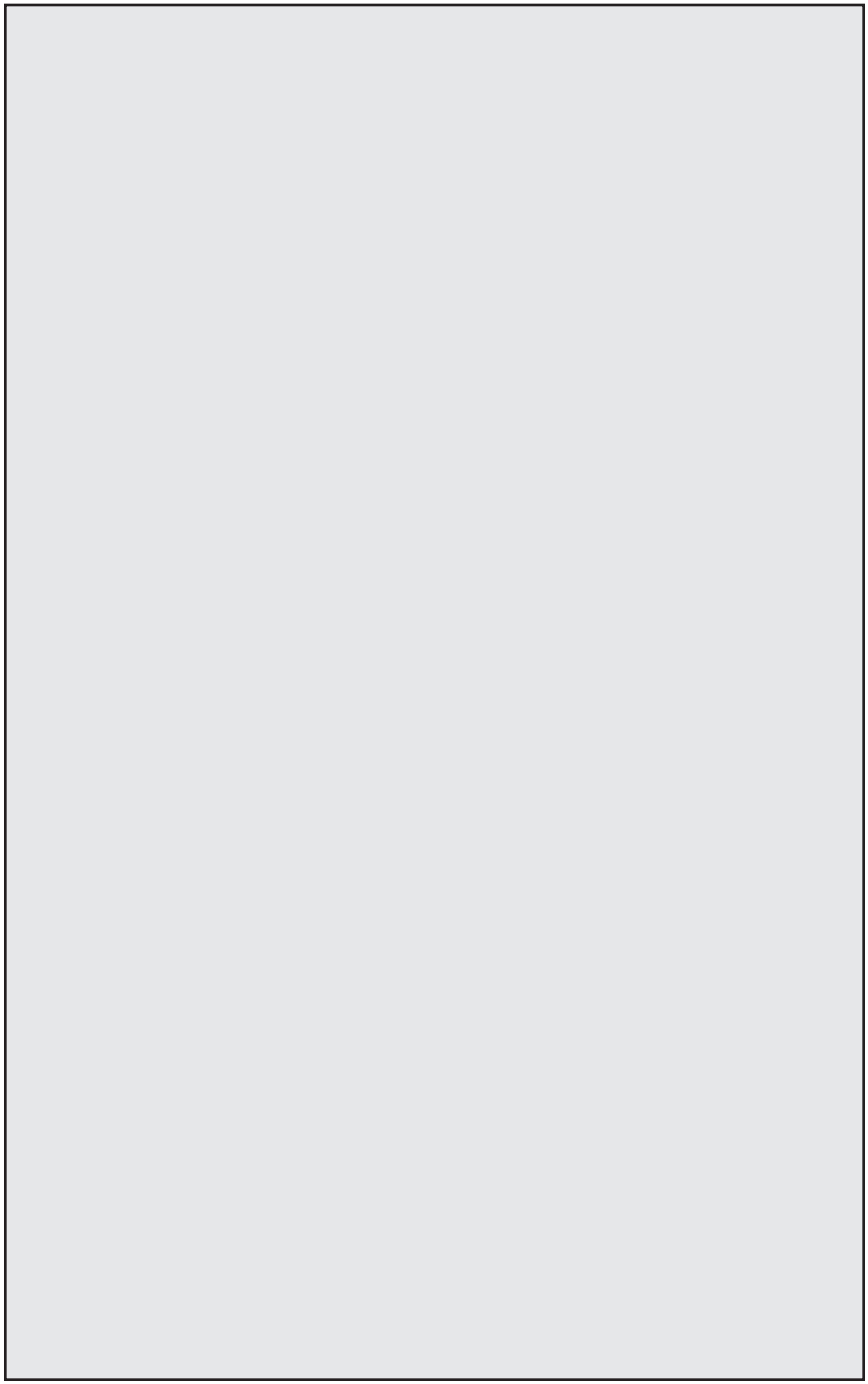

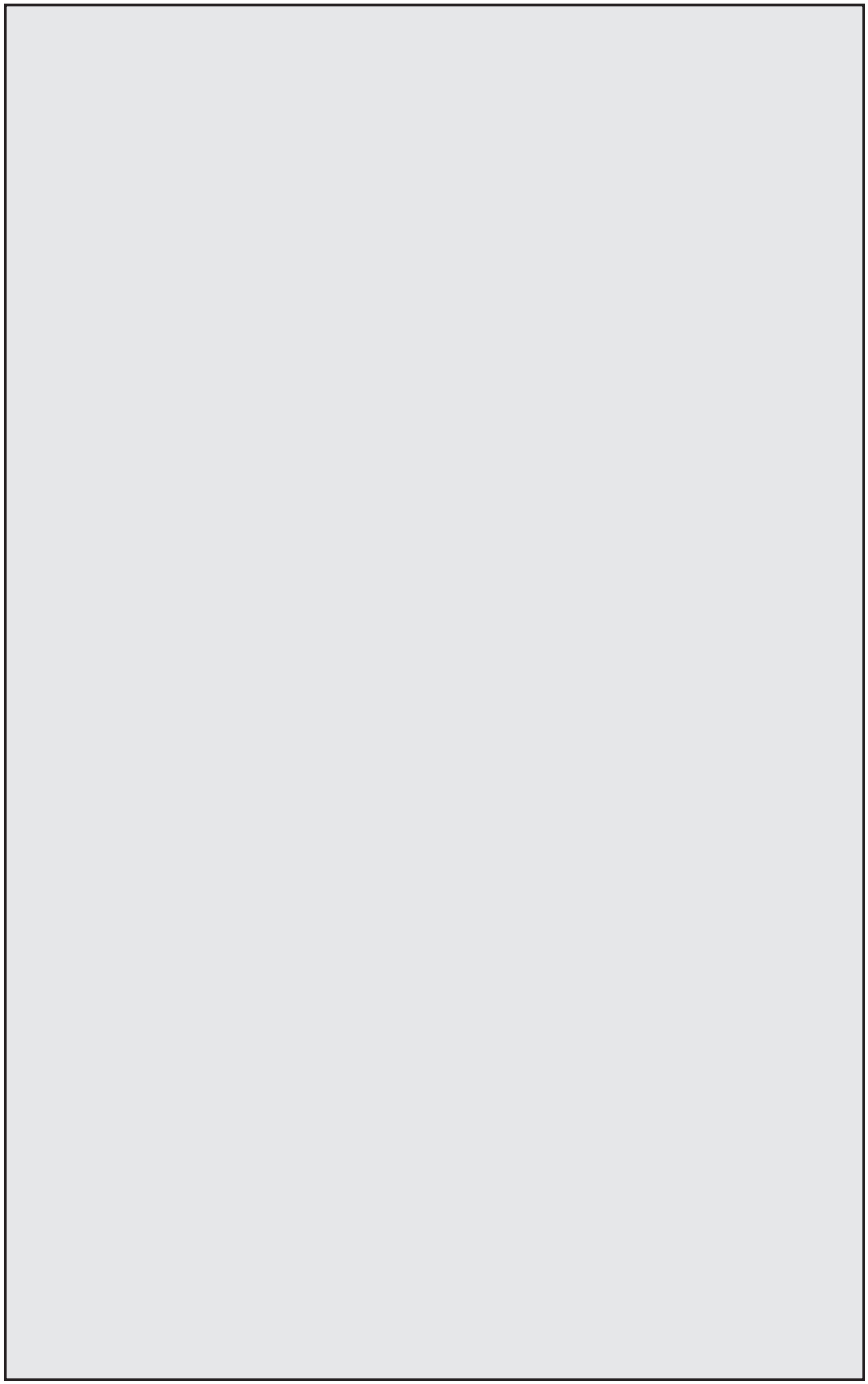

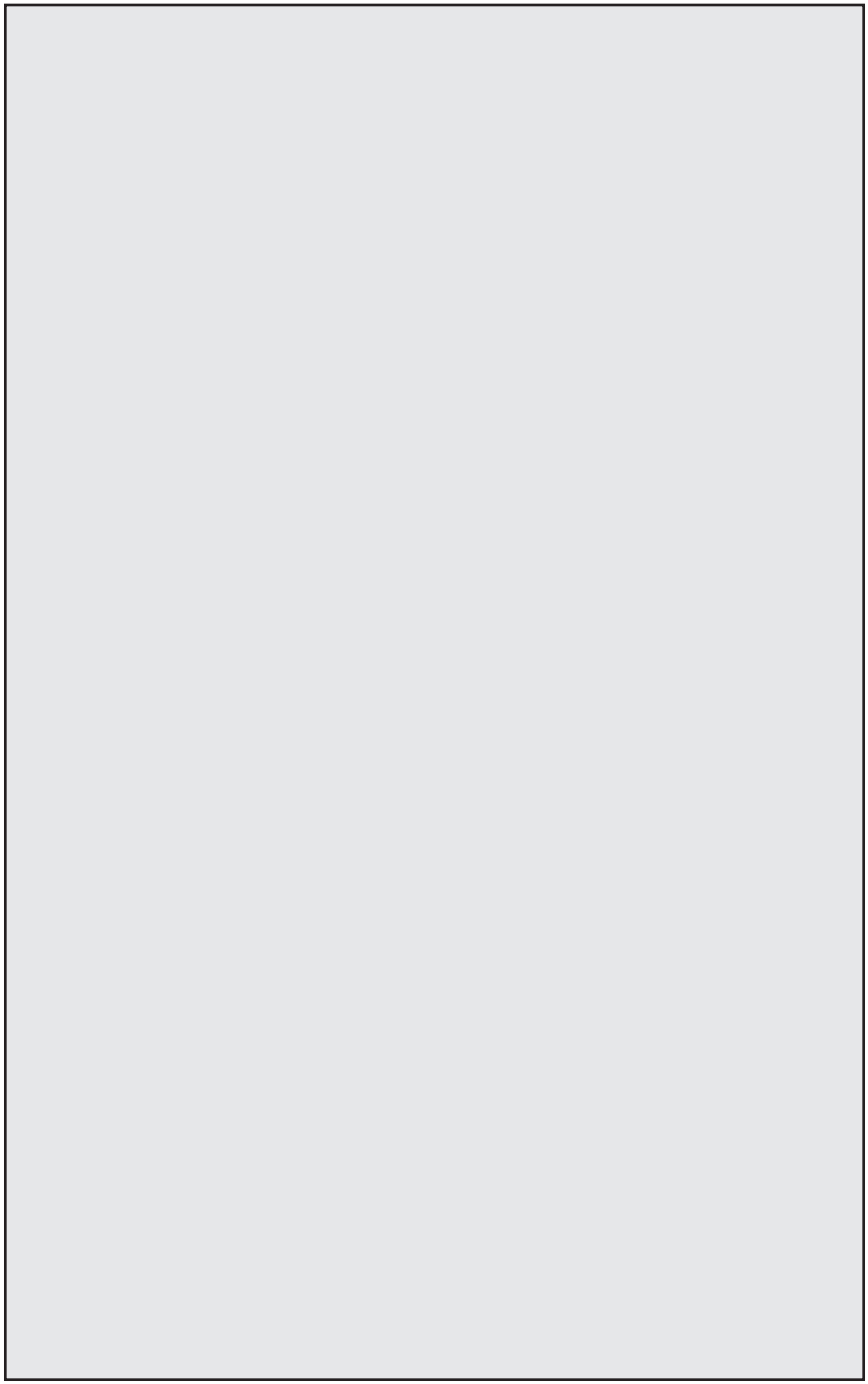

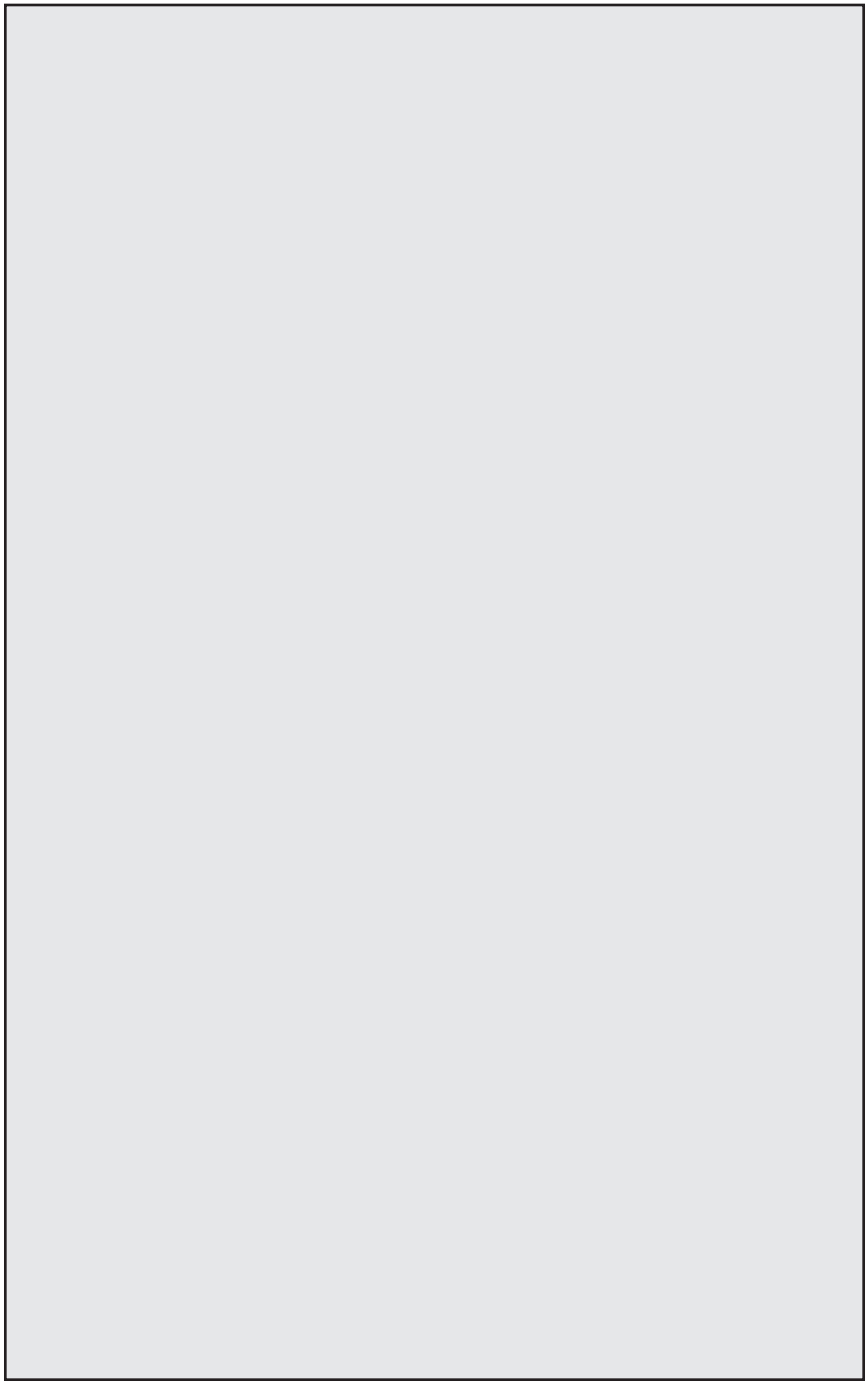

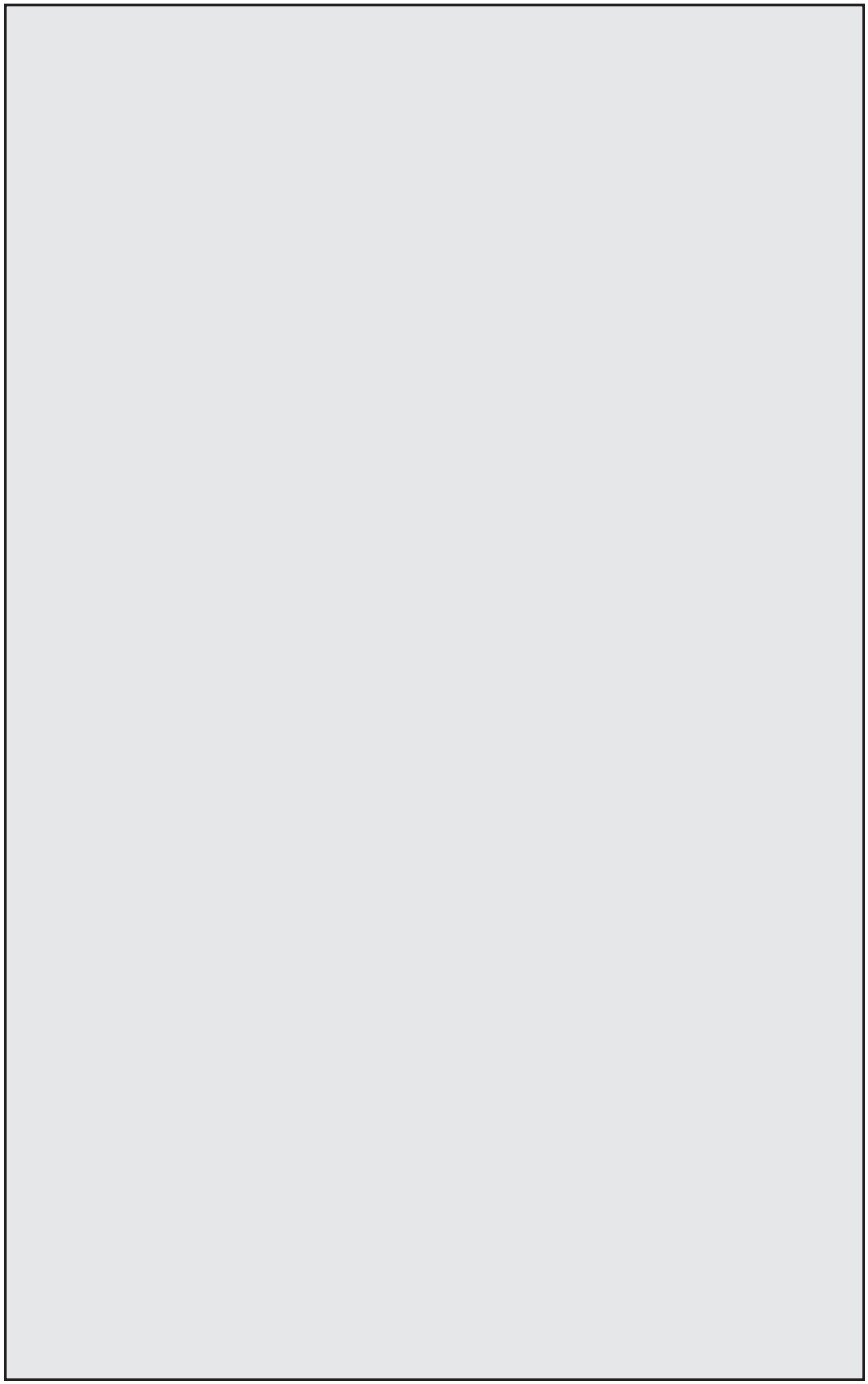

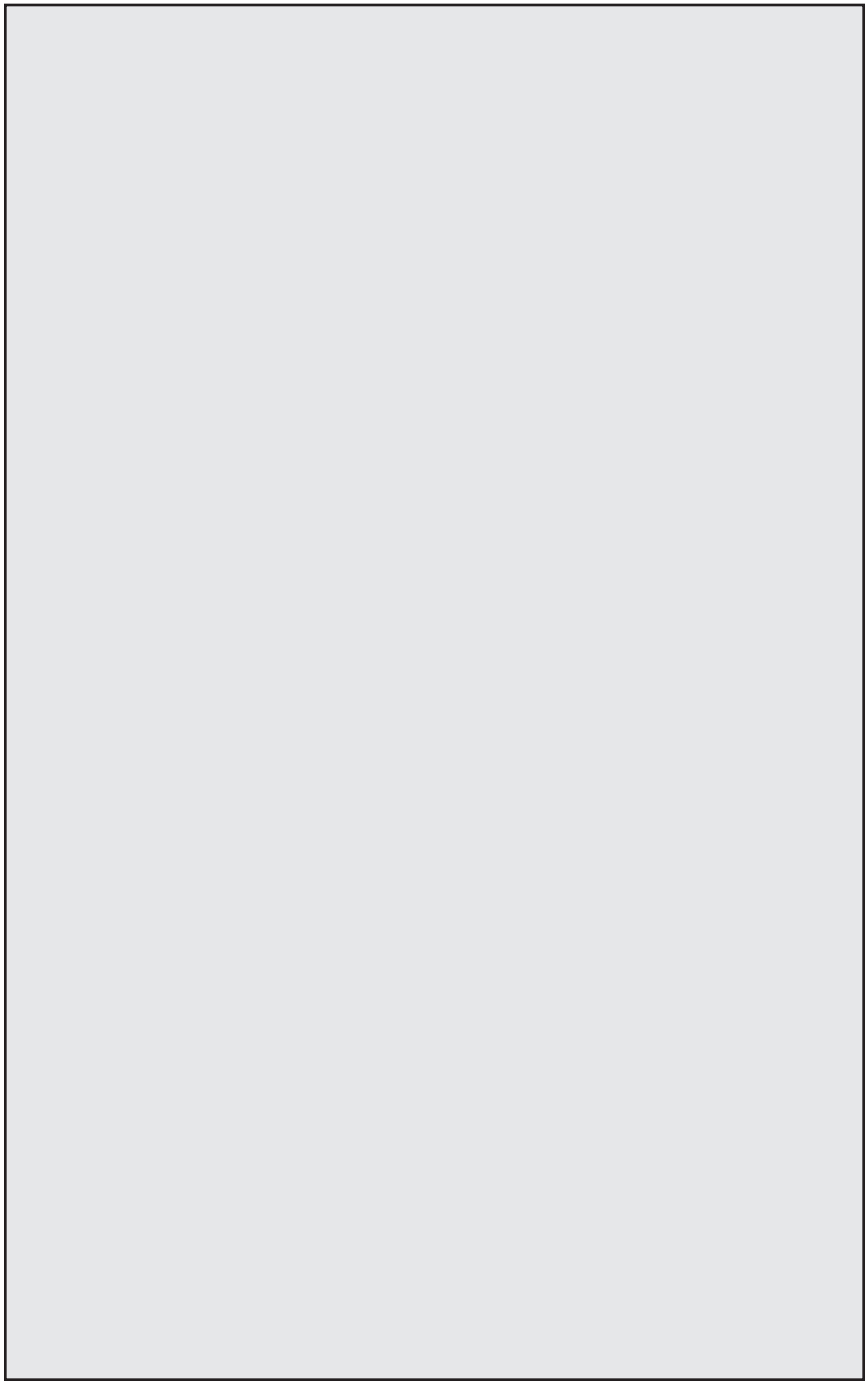

A17

IMPACTS OF CLIMATE CHANGE ON PLANT DISEASES: NEW SCENARIOS FOR THE FUTURE

*Marco **Pautasso***[78] *and Michael J. Jeger*[79]

Abstract

In this overview, we selectively discuss recent literature on the development of new scenarios of the impacts of climate change on plant health. The literature on human health is much larger than the one on plant health, but plants are essential to human health and well-being. Impacts of climate change on plant health have been mostly studied for North America and Europe, although research has also taken place in South America, Asia, and Australasia. New scenarios will need to take into account not just the expected temperature and precipitation trends, but also the increased likelihood of introduction of exotic plant pathogens due to long-distance plant trade networks. The example of *Phytophthora ramorum* shows that historical factors and the distribution of the hosts are important and need to be considered in new scenarios too. At the same time, there is scope for integration in such scenarios of human responses to climate change (e.g., large-scale plantations of biofuel crops), effects of extreme weather events, the uncertainty in precipitation shifts, and climate change modifications of plant host defence systems. More precise and useable prediction will come from scenarios including the diversity of strategies available to prevent and manage the emergence of exotic plant pathogens under changing environmental conditions.

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Keywords: global change, migration pathways, network epidemiology, *Phytophthora ramorum*, plant health

Introduction

Plants are essential for human health and well-being, not only because they provide ecosystem services such as photosynthesis, food production, evapotranspiration, and carbon storage, but also due to their cultural, psychological, and aesthetic benefits (Pearson-Mims and Lohr, 2000; Bringslimark et al., 2009; Eyles et al., 2010; Russell et al., 2013). Plants are vital to human beings, but plant health is an understudied issue. About 90,000 items are retrieved with Google Scholar using the keyword *plant health*, whereas the same search engine retrieves about 1,640,000 publications when searching for *human health*, or about 18 times more material (as of October 2013, no time limits). The difference is even more pronounced when searching the same keywords in Web of Science (~1,000 (plant health) vs. ~28,000 (human health) findings, or ~28 times more material in human medicine).

Interestingly, when searching for *plant disease* and for *human disease*, there are still more findings for human beings compared to plants, but the ratio is only about four, both for Google Scholar (~356,000 vs. ~1,510,000 findings, respectively) and for Web of Science (~3,700 vs. 16,000 findings, respectively). Whereas there appear to be more publications using the keyword *human health* than *human disease*, the opposite is the case for *plant health* and *plant disease* (Figure A17-1). This is likely to be due to the traditional focus of plant pathologists on specific plant diseases.

The recent development of the One Health concept calls for more recognition of the interconnections between the health of human beings, animals, and ecosystems and for common approaches among researchers and practitioners in the three domains (Pautasso et al., 2012b). A study of whether epidemic models can be used to represent the diffusion of topics among disciplines suggests a potential for interdisciplinary collaboration between researchers in human and plant epidemiology (Kiss et al. 2010), but there is still little overlap between the two areas, for example, in terms of curricula (Gómez et al., 2013). Nonetheless, there is increasing recognition that integrating ecological considerations into human epidemiology and public health is likely to bring many benefits (Preston et al., 2013), just as this has been the case for plant disease and pest management (Kogan, 1998).

Patz et al. (this volume) provide an excellent overview of the importance of the environment for human health. Three recent examples specific to plant health are:

- The report of increased human mortality following widespread ash tree mortality in the Midwest of the United States due to the introduction from Asia of the Emerald Ash Borer, which led to more severe heat waves (Donovan et al., 2013);
- A study showing the benefits for child health and nutrition of retaining patches of forest in Malawi (Johnson et al., 2013); and

- A call for multidisciplinary research to tackle the increasing challenge posed by human pathogens harboured by plants (Fletcher et al., 2013).

Given the number of plant species on the planet (estimated at about 420,000; Crane, 2004), plant health is a rather more complex issue than human health, where there is only a single host species to be kept healthy, except for zoonotic diseases. Plants range from annual weeds (that germinate and develop to maturity and death in a few months) to long-lived trees, able to cope with diseases for decades, at the same time sustaining an intricate ecosystem in their canopy and roots. The diversity of plant life forms is matched by a variety of plant pathogen strategies, which translates into a corresponding diversity of plant pathosystems (Ingram, 2002). Moreover, there are fundamental differences between human and

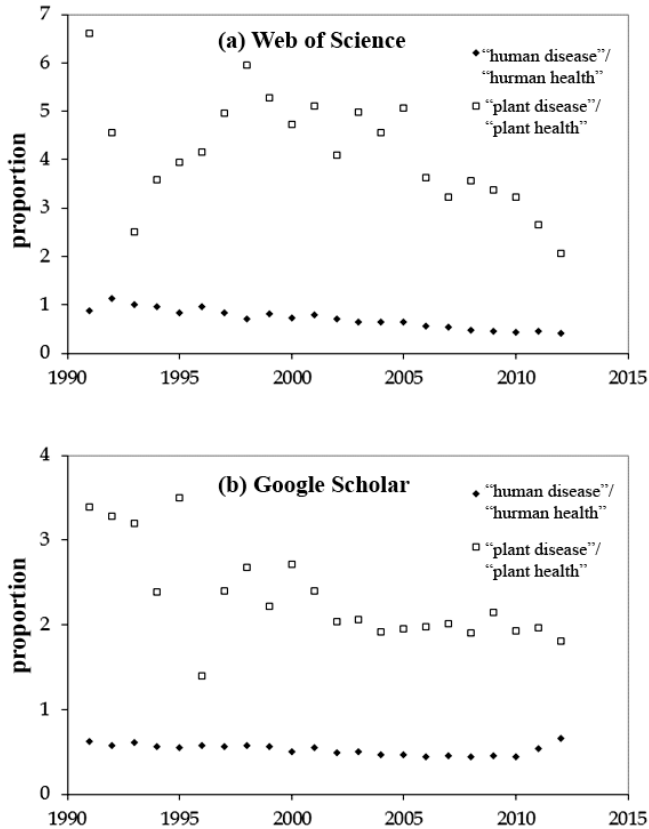

FIGURE A17-1 Number of publications retrieved in (a) Web of Science and (b) Google Scholar using the keyword *human disease* relative to the number of publications retrieved using the keyword *human health*, and for *plant disease* in comparison with *plant health* (1991–2012, as of October 2013).

plant health because of emotive and ethical considerations. The death of every child is a tragedy, but we do not hesitate to harvest vegetables, long before these plants have completed their life cycle. While there has been a long-standing philosophical debate about the definition of human health, plant health is also understudied from a conceptual perspective (Döring et al., 2012).

Plants are traditionally seen as sedentary organisms, living their whole life at the location where they germinated. This makes it unlikely that a tree in, say, Washington, D.C., might move temporarily to a tropical location and then come back with a tropical disease, as many people now sometimes do (Richaud et al., 2013). However, human beings have developed a trade network of plants for planting, seed, and other plant material that has grown rapidly over the last decades and is now global in scope (Dehnen-Schmutz et al., 2010). Some plants for planting might travel more in their life span than many humans do. This pathway has become the major route of invasion for forest pathogens and pests, both in North America (Liebhold et al., 2012) and in Europe (Santini et al., 2013). Most published research on global change in general (Pasgaard and Strange, 2013) and on the effects of climate change on plant health in particular (Andrew et al., 2013) is indeed from North America and Europe, although research on the topic has also taken place in South America, Australasia, and Asia (Chakraborty et al., 1998; Ganley et al., 2011; Ghini et al., 2011; Savary et al., 2011a). There is thus the need for more empirical studies and scenarios of climate change impacts on plant health from other continents.

The diversity of plant pathosystems makes it difficult to achieve successful generalizations about the effects of climate change on plant health, because specific scenarios are needed (Savary et al., 2011b). Nonetheless, comparative epidemiology can deliver useful insights also on the likely effects of climate change (West et al., 2012). Moreover, many plant pathogens are nowadays dispersed artificially due to long-distance trade in plants, so scenarios of the effects of climate change on such pathogens need to take into account that their introduction into areas newly suitable from a climatic point of view will be facilitated by plant trade. Without increasing global trade and the associated movements of pathogens, climate change would be less of a problem for health, and this is likely to apply to both human beings and plants (Engering et al., 2013). However, for plants, increased trade in seed of food crops would be necessary anyway following climate shifts to support new crops being grown in regions previously unsuitable.

As an example, take *Phytophthora ramorum*, the oomycete responsible for Sudden Oak Death in California (Rizzo et al., 2005) and for Sudden Larch Death in the British Isles (Brasier and Webber, 2010). This quarantine pathogen, which was unknown to science until 2001 (Werres et al., 2001), has been intercepted a number of times in shipments of ornamental plants among European countries (EFSA PLH, 2011). Border interceptions of plant pathogens are probably the tip of the iceberg, given that only a fraction of the massive amounts of traded plants

can be inspected (Brasier, 2008). In Britain, *P. ramorum* findings are concentrated in the southwestern part of the country. This could reflect the distribution of

- The hosts—The pathogen affects plants that are typically found in Cornwall, from holm oak (*Quercus ilex*) to *Rhododendron ponticum* (an exotic shrub), but also more widespread species such as heath (*Calluna vulgaris*) and bilberry (*Vaccinium myrtillus*) (Purse et al., 2013);
- The initial foci of introduction—Whether these were nurseries or historic gardens in Cornwall is likely, but remains to be demonstrated (Xu et al., 2009);
- Climatic suitability—The western part of Britain is generally milder and wetter (EFSA PLH, 2001; Chadfield and Pautasso, 2012); or
- A combination of these three issues.

This example confirms that climate plays an important role also in determining the distribution of exotic plant pathogens (Ireland et al., 2013), but also that historical factors and the host distribution are important and need to be considered in new scenarios too (Croucher et al., 2013; Liebhold et al., 2013). The 2013 *P. ramorum* outbreaks in thousands of hectares of Japanese larch (*Larix kaempferi*) plantations in southwestern Scotland underline the importance of establishing the climatic suitability to exotic plant pathogens of entire countries. In this case, the Scottish region with the majority of outbreaks (now an infection "red zone") was the only part of Scotland considered at high risk from *P. ramorum*.

Assessing regional plant disease risk helps prioritizing monitoring also under changing environmental conditions. One interesting insight achieved by modellers of *P. ramorum* in California is that predictive modelling is more reliable if based not just on data on where the pathogen has been detected, but also on where the pathogen has not been detected (absences) (Václavík and Meentemeyer, 2009; Pautasso, 2013b). Scenarios of the future distribution of plant pathogens are thus likely to be fraught with considerable uncertainty, because there are few data available on the absences of plant pathogens under changed climatic conditions.

The evidence base (and lack thereof, i.e., knowledge gaps) on plant health and climate change has been summarized many times before, so there is no lack of reviews of the literature on the topic (e.g., Coakley et al., 1999; Garrett et al., 2006, 2012; Jeger et al., 2011; Newton et al., 2011; Sturrock et al., 2011; Boonekamp, 2012; Dixon, 2012; Ghini et al., 2012; Chakraborty, 2013; Pangga et al., 2013; Juroszek and von Tiedemann, 2013). In this overview, we make one more attempt at reviewing such literature, but also take into account the related body of knowledge on exotic plant pathogens. Our main point is that prediction of the effects of climate change on plant health is likely to fail without considering at the same time the effects of globalization on the likelihood of introduction of plant pathogens (Figure A17-2). We also provide a summary of strategies with which to respond to emerging plant diseases. We argue that these strategies are

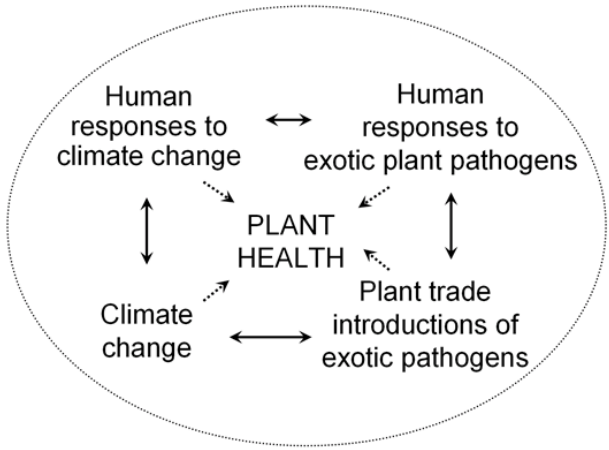

FIGURE A17-2 New scenarios of climate change impacts on plant health will need to take into account the likely introductions of exotic plant pathogens due to increased plant trade, as well as human responses to both climate change (e.g., large-scale cultivation of biofuels) and exotic plant pathogens.

likely to gain even more importance in the presence of changing environmental and climatic conditions.

New Scenarios to Predict Plant Health Under Climate Change

New plant health scenarios under climate change need to integrate likely developments of global trade taking place at the same time as the predicted changes in climate. Scenarios linking climate change and global trade are a subset of those predicting plant health under global change, because global change is not just driven by climate change and long-distance trade, but also by urbanization, pollution, and land use change (Gregory and Ingram, 2000). These drivers are fuelling each other. For example, the more land is converted from tropical forest to agriculture, the more there will be carbon emissions, and the likelier it will become that the most severe climate change scenarios will take place. Similarly, further urbanization spurs increased long-distance trade, which leads to increased pollution, including greenhouse gas emissions.

Plant health is also the outcome of various interacting factors, including host–pathogen interactions, host and pathogen migration, the action of vectors, and environmental and human influences. However, establishing how the various plant health components are influencing each other is less straightforward than with global change, not just because of the variety of pathosystems (Sutherst et al., 2011). For example, landscape connectivity can make it more likely that

exotic pathogens will disperse, but it will also tend to maintain host genetic diversity, which can result in enhanced resilience of plant hosts in the face of a new disease. Variation in host genetic diversity also influences plant phenology, which can affect host–pathogen interactions, such as by shifting the main period of host susceptibility away from (or closer to) the main period of pathogen virulence (Dodd et al., 2008; Grulke, 2011; Caffarra et al., 2012). Similar mismatches between plants and their pollinators can affect plant and ecosystem health (Ogawa-Onishi and Berry, 2013).

An additional complication is that each of these components, whose interactions result in the continuum between plant health and plant disease epidemics, is affected by each of the global change drivers (Anderson et al., 2004; Pautasso et al., 2012a). Researchers have started investigating the outcome of such interactions, but we are still far away from a comprehensive understanding of how various pathosystems will behave under changing environmental conditions. We know though that climate change effects deleterious to plant health are likely to result in enhanced climate change, because of the resulting increased carbon emissions due to such things as large-scale tree mortality (Kurz et al., 2008; Hicke et al., 2013), although in the long term these emissions may be compensated by forest regrowth. Not only plant health scenarios, but also climate change models, need to include this kind of feedback.

To make realistic predictions about the feedbacks between climate change and plant health, scenarios also have to take into account that climate change will result not just in changed average conditions, but also in the increased frequency of extreme events (Garrett, 2008; Reichstein et al., 2013). Heat waves, wind storms, drought, and floods can all affect plant health (and food safety) both indirectly, by moving the environmental conditions outside of the optimal physiological window for many plant species, and directly, by affecting the likelihood and severity of plant disease epidemics (Marvin et al., 2013). Floods and heavy rains dramatically increase moisture and can thus increase the prevalence of leaf and soil pathogens, but they can also contribute in dispersing plant pathogens in air currents, transported soil, and water droplets (Munkvold and Yang, 1995). Drought and heat waves, conversely, favour secondary parasites because they weaken plants, and make viral epidemics more likely as insect vectors are favoured by dry and warm conditions (Rosenzweig et al., 2001).

Some extreme weather events are reported to be on the rise (e.g., extreme rain events in India between the 1950s and 2000; Goswami et al., 2006), but (due to the many confounding factors) it is difficult to establish whether plant disease epidemics due to extreme weather events are also becoming more frequent. What is apparent, despite the differing survey effort in various countries, is a shift in first reports of plant pathogens towards the poles, which would suggest an already perceptible influence of climate warming on plant pathosystems worldwide (Bebber et al., 2013). Climate warming is only part of the observed and foreseen climate changes: precipitation and humidity are two other essential variables to

predict the development of future plant pathosystems (Thompson et al., 2013). Unfortunately, the uncertainty of the predicted precipitation regimes under climate change is rather high for many regions, thus making prediction of outcomes for plant pathosystems also insecure (Shaw and Osborne, 2011). Further work is thus needed to model likely shifts in precipitation for regions such as China, Indonesia, the Rocky Mountains, and western tropical Africa.

Uncertainty in future precipitation is an important knowledge gap because scenarios of plant diseases in the presence of increased temperature and precipitation or in the presence of increased temperature and reduced precipitation differ markedly (Kliejunas, 2011). For example, a foliar pathogen such as *P. ramorum* is not likely to become more virulent in the West Coast of the United States in case of increased temperature but decreased precipitation, whereas increased temperature and precipitation are likely to lead to more sporulation, increased inoculum, and thus more likely expansion of Sudden Oak Death into new regions. However, if sexual reproduction does take place in *P. ramorum*, as with some other exotic and homothallic *Phytophthora* species in California, then a wider range of environmental conditions and the potential for greater diversity in virulence may occur (EFSA PLH, 2011; Grünwald et al., 2012). On the contrary, an abiotic tree health issue such as the dieback of yellow cedar (*Chamaecyparis nootkatensis*) in Alaska (which appears to be due to yellow cedar vulnerability to fine-root freezing following reduced snow depth; Hennon et al., 2012) would be exacerbated by increased temperature and reduced precipitation, whereas the tree species might recover in case of increased temperature and precipitation (Hennon and Shaw, 1994; Kliejunas, 2011).

Several reports of increased tree mortality due to more frequent drought have appeared, for example for quaking aspen (*Populus tremuloides*) in North America (Worrall et al., 2013). These reports are worrying, because of the associated carbon emissions and the loss of ecosystem services we normally take for granted from healthy forests. Widespread tree mortality due to more frequent and severe drought is a problem which is likely to take place at the same time as the predicted lack of drinking, agricultural, and industrial water for many regions of the world. Whether precipitation will decrease or not, climate warming is expected to reduce the presence and severity of frost events, and thus to extend the growing season at high altitudes and latitudes (Roos et al., 2011). This phenomenon is likely to make it possible to introduce new crops in such regions, but it is also likely that the cultivation of those crops will be followed by the migration of their associated pathogens (Chakraborty, 2013). What is needed to develop successful scenarios of such shifts in crops and plant pathogens is also an improved understanding of how plant host defence systems will behave in response to increased temperatures (Cheng et al., 2013).

Shifts in the range and severity of plant diseases will also be a consequence of climate change mitigation measures such as large-scale biofuel cultivation. Increased use of plant biomass could provide new opportunities for plant pathogens,

particularly in the case of large-scale deployment of monocultures (Paterson et al., 2013). Even without the threat posed by climate change, there is the need to develop more diverse timber and biomass plantations, so as to diminish the losses due to outbreaks of plant pathogens and pests. In many cases, emerging pathogens affecting crops used to produce biomass are exotic. This is a further reminder that scenarios to predict plant health under climate change need to take into account patterns in the long-distance trade of plants, because such trade networks amplify the likelihood of introducing new plant pathogens.

Integrating Our Responses to Exotic Plant Pathogens in Scenarios to Predict Plant Health Under Climate Change

Expanded cultivation of biofuels, whether this makes sense as a climate change mitigation measure or not, is likely to provide new opportunities for plant pathogens. This makes it clear that, to predict how plant health will develop under changing environmental conditions, we need to take into account human responses to climate change and new plant diseases. A diversity of strategies is available to respond to emerging plant diseases. In general, prevention is better than cure, but prevention is at best difficult for pathogens that are still unknown to science or are understudied. Interdisciplinary approaches between plant pathologists, economists, modellers, and social scientists to develop preventive strategies are important and should be encouraged, as shown by the Rural Economy and Land Use (RELU) project on the growing risks to the U.K. rural economy posed by crop diseases (Mills et al., 2011; Pautasso et al., 2012b; Ilbery et al., 2013).

One way to respond to new plant diseases is to model the spread of exotic plant pathogens in space and time. This was achieved for *P. ramorum* in Britain, taking into account the distribution of the main hosts (deciduous trees such as *Quercus* spp. and heathland) and a realistic reconstruction of the trade in ornamental plants susceptible to the pathogen (Harwood et al., 2009). Such models can help predict the further development of plant disease epidemics under various inspection policies, thus improving the focus of monitoring surveys. There is the need to include changing climatic conditions in such modelling exercises.

The importance of including trade network information in spatial simulation models is exemplified by the 2012 reports from Britain of ash dieback. This disease, caused by the exotic ascomycete *Hymenoscyphus pseudoalbidus* (Gross et al., 2013), is now present throughout much of the distributional range of the host, *Fraxinus excelsior*, and is likely to have arrived to the eastern part of Britain from the European continent through wind-blown spores, due to the reports in East Anglia and Kent of affected mature woodlands. However, the trade in ash saplings contributed to establishing the disease more widely, because the pathogen was detected across the United Kiingdom at recently planted sites (Pautasso et al., 2013b).

Despite the increasing plant health issues associated with movements of plants by the nursery industry, there is still little information about the structure of such plant trade networks. This is of concern, given that network structure, even in the case of small-size networks, has been shown to affect the likelihood of epidemics taking place, particularly in the presence of super-connected individuals (Moslonka-Lefebvre et al., 2011); in the case considered here, nursery sites which act as major hubs in the nursery trade. The amounts of plants shipped within and among continents are massive (for example, millions of ash saplings were imported by the United Kingdom from other European countries between 2002 and 2011), so that only a small fraction of such consignments can be inspected. It is thus sobering that most models of climate change impacts on plant health do not take into account plant trade networks.

The sudden appearance of ash dieback in Britain was not just a wake-up call to improve plant biosecurity (Woodward and Boa, 2013), but also an example of how stakeholder involvement can make a difference in terms of research funds made available to plant health researchers. Following the first reports of the pathogen in the country, a huge public and media outcry made it possible for the U.K. government to find the resources to commit to funding research on ash dieback, despite the climate of austerity and the previous years of cuts to plant pathology departments and institutes. Scenarios to predict plant health in the face of climate change and the introduction of new plant pathogens will thus need to be aware of such potential rapid developments in research capacity. Nevertheless, long-term monitoring and research would be better served by a more secure funding environment. It would be beneficial if botanic gardens and arboreta, traditionally operating with a long-term perspective, could become a sentinel network warning about potential plant health risks before these materialize (Britton et al., 2010).

Because of limited resources, economic considerations are indeed at the heart of any disease management strategy. Although there is increased use of bio-economic models in plant disease management, with promising work on efficient control of plant disease epidemics spreading in networks (Oleś et al., 2012, 2013), there is still the need to apply such approaches in the modelling of climate change impacts on plant pathosystems. This is an important knowledge gap because plant diseases already cause substantial losses to global food production (Savary et al., 2012). In the coming decades, climate change will not happen in a vacuum, but together with a further rise in human population, which will make intensification of agriculture necessary in many regions. New scenarios of climate change impacts on plant health need to take into account such shifts in cultivation intensity.

Further intensification of agriculture is just one of the land use changes potentially affecting how climate change will influence plant pathosystems. Particularly important and underexplored in scenarios is the assisted migration of plant species to enable them to cope with the rapid climate warming. There has been

little consideration in the assisted migration debate among conservation biologists that such plant translocations could result in the inadvertent long-distance movement of plant pathogens (Garbelotto and Pautasso, 2012). One practical way to respond to both climate change and to the likely effects of climate change on plant health would be to decrease emissions of greenhouse gases (Pautasso et al., 2010), but there is little evidence for the moment that such a decrease may happen soon, so it is likely that scenarios of climate change impacts on plant health based on current emission trends may be more realistic than those expecting a drop in emissions.

Long-term monitoring of (i) carbon emissions, (ii) climate change effects on plant health, and (iii) the literature on this important topic is essential to inform scenarios with the most updated information from experiments and surveys (Jeger and Pautasso, 2008). For example, there is evidence that fungi are increasingly mentioned in the climate change literature of the last two decades. A similar increasing trend in the proportion of papers mentioning fungi was reported also for the literature on disease, health, infection, and immunity (Pautasso, 2013a). It is possible that such a pattern in the literature reflects an increased importance of fungi as human pathogens.

Much of the literature on climate change impacts on crop health has focused on a handful of widespread crops (e.g., grape, potato, oilseed rape, rice, soybean, and wheat; Luck et al., 2011; Bregaglio et al., 2013; Siebold and Tiedemann, 2013; van der Waals et al., 2013). Similarly, most of the available literature on exotic tree diseases is about a few pathogens (e.g., *P. ramorum*, *P. cinnamomi*, and *P. cactorum*) (Pautasso et al., 2013a). There is the need to increase our epidemiological knowledge of less studied pathosystems that might become problematic under changing environmental conditions, including increased CO_2 levels (Kaczynski and Cooper, 2013). This knowledge includes how such pathogens will respond to changing climates and plant trade patterns, but also how we are likely to respond to such changes in pathogen behaviour (in agro- vs. wild ecosystems), and the associated uncertainties (Gouache et al., 2013).

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A18

WATER QUALITY AND HEALTH FOR A SUSTAINABLE SOCIETY

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Abstract

Sustaining high-quality aquatic ecosystems is critical for ensuring global biohealth. However, critical knowledge gaps limit our ability for efficient and effective management of human and natural water systems to ensure human health. We recommend a major program in water and health, promoting water quality diagnostic tools and pathogen discovery focusing on key exposure pathways. This program should:

1. **Fill key knowledge gaps necessary for using the quantitative microbial risk assessment framework:**
   a. **Critical water quality diagnostic tools should be used to address exposure assessment for recalcitrant and emerging pathogens, which includes exploration of the water microbiome along the human exposure pathway.**
   b. **Health risks should be calculated and known for all waters in the United States.**
2. **Develop a framework for transdisciplinary research with respect to biohealth linked to water systems. System dynamics methodology should be used to:**
   a. **Create and explore the theoretical couplings between the various components of water systems (including the socioeconomic [health] and biophysical [water quality]).**
   b. **Develop and operationalize indicators for assessing and managing key linkages among various components of human and natural systems.**

Background

Water is one of the most critical of the world's life support systems. Water quantity and quality are inextricably linked with global biohealth. Biohealth is the health of all animals, humans, and plants (including the microbiome) on Earth linked to a healthy biosphere. High-quality, functioning aquatic ecosystems support sustainable plant, animal, and human communities and provide critical services to humans, from food and drinking water to industry and recreation. In the last 60 years we have seen a great acceleration of population growth in people and

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animals, land use change, use of fertilizers, and water use as well as the global transport of humans and animals. This has led us into the Anthropocene, in which continued water quality degradation as demonstrated by increased eutrophication and fecal contamination associated with microbial hazards and antibiotic resistance is a global phenomenon. This degradation in global water quality and quantity is exacerbated by climate change and extreme events. Despite our investment in infrastructure and better environmental protection policies, water pollution shows a continual and dramatic impact on health in the developed world and devastates communities in the developing world. Waterborne diseases in humans are characterized by pathogens that are persistent, potent, excreted at high numbers, and often zoonotic. Waterborne disease outbreaks of *Clostridium difficile* and Guillian-Barré syndrome in Europe and the United States are emerging. Rare amoeba associated with high mortality in children are showing up in association with tap water. Waterborne poliovirus and cholera have not been controlled, and zoonotic diseases including bacteria such as *E. coli* 0157H7, *Campylobacter*, and *Salmonella*; parasites like *Giardia* and *Cryptosporidium*; and new emerging viruses like *Cyclovirus* remain global threats to animal and human health.

Animal and human health can be addressed through targeted monitoring and management strategies using the quantitative microbial risk assessment (QMRA) framework and molecular tools. Point and diffuse pollution sources and specific hazards are now identifiable using technology such as microbial source tracking. In addition, system dynamics models can improve decision making regarding complex systems by using integrated socioeconomic, water quality, and health data to couple human and water systems, thereby explicitly linking human health and well-being with ecosystems services.

In the future, it will be more important than ever to operationalize QMRA and develop system dynamics models in order to effectively and efficiently mitigate the impacts of climate, an aging infrastructure (or lack thereof), and the global changes that are now occurring to protect and restore the biohealth of the planet.

Key scientific questions around water quality and health remain:

- How is water quality changing and affecting human health?
- What are the sources of emerging, recalcitrant, and problematic pathogens?
- How does ecosystem health relate to human health?
- How do we restore and protect water systems to protect the biohealth of the planet?

We recommend a major program in water and health, promoting water quality diagnostic tools and pathogen discovery focusing on key exposure pathways. These data then must be used within community-based and health risk

frameworks to improve decision making for enriching the future of our complex human-coupled water systems and health.

Waterborne Disease: Emerging and Zoonotic Pathogens

Waterborne disease problems seem to have been solved in the United States, yet large or dramatic outbreaks continue to occur in both drinking water systems and recreational waters. Understanding the exposure pathways (Figure A18-1) that move pathogens from humans and animals into water and back to susceptible populations via drinking water, recreational water, and food is critical due to emerging, recalcitrant, and problematic infectious agents associated with human or animal wastes and the water environment.

Waterborne outbreaks continue to occur in the United States, and these are the "plane crashes" for the water industry and for communities. From 1971 to 2008 in the United States, more than a half million people (576,853 persons) were ill during 747 documented waterborne outbreaks caused by bacteria (15 percent), viruses (9 percent), protozoa (19 percent), and chemicals (11 percent) (Haas et al., 2014). The etiological agents causing acute gastrointestinal illness in a large percentage of the outbreaks were not identified (45 percent), and those with multiple types of pathogens were less than 1 percent. In the last decade, outbreaks in community drinking water have decreased and averaged about five

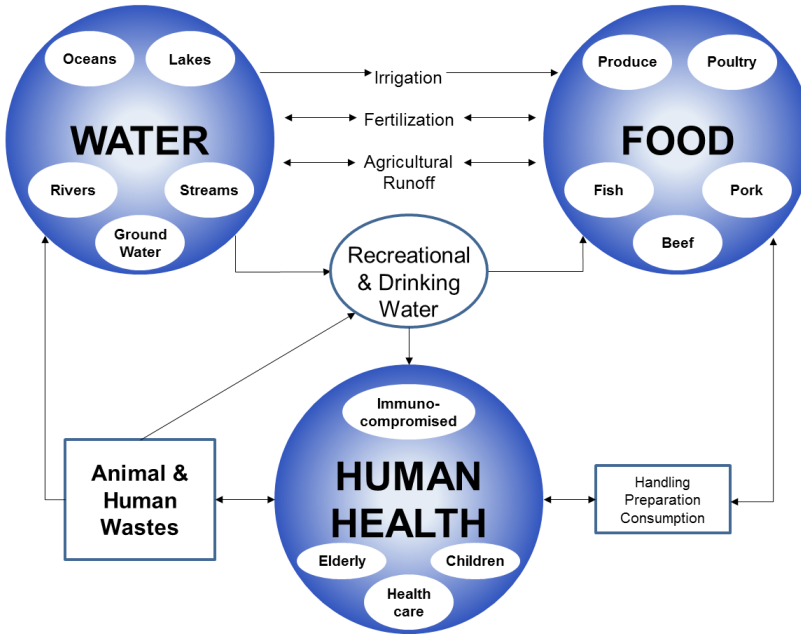

FIGURE A18-1 Exposure pathways in the human-water coupled system.

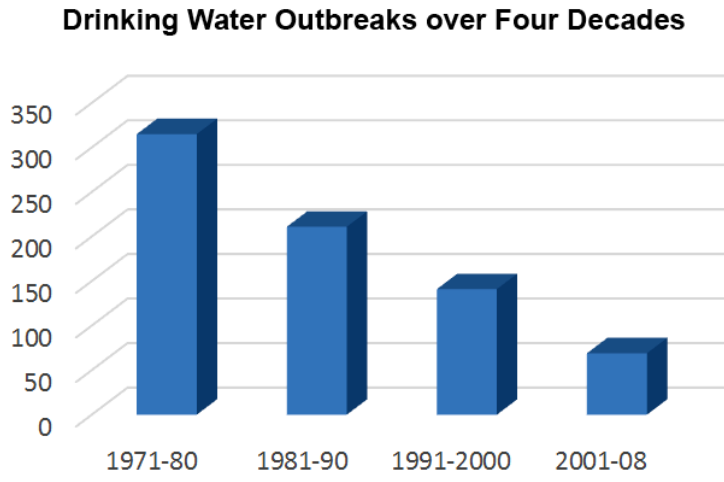

FIGURE A18-2 Outbreaks in drinking water in the United States.

per year (Figure A18-2) with more outbreaks associated with multiple pathogens and animal manure or human sewage as the source of the pathogens. In ambient recreational waters where outbreaks are much more difficult to identify, no such decrease in disease is evident (Figure A18-3), and in the last few years between 5 and 15 outbreaks have occurred (Haas et al., 2014).

The outbreak data do not capture endemic waterborne disease risks, referred to as the iceberg because most of these cases go unreported (the tip being the reportable outbreaks). There are several estimates of endemic waterborne disease risks:

- 12 million cases/year (Eisenberg et al., 2006),
- 16 million cases/year (Messner et al., 1996), and
- ~19 million waterborne illnesses/year for community water systems in the United States (5.4 million illnesses from groundwater and 13 million illnesses from surface water systems) (Reynolds et al., 2008).

New disease concerns emerge every year as a result of water contamination. A waterborne cluster of 24 cases of Guillain-Barré syndrome (GBS) along the U.S.-Mexico border near Yuma, Arizona, was identified in 2011 due to *Campylobacter* (AZ Department of Health, http://www.azdhs.gov/diro/pio/news/2011/110718_Yuma_GBS.pdf). The first documentation of waterborne disease caused by *Clostridium difficile* was due to sewage contamination of tap water (Kotila et al., 2013). *Nagleria fowleri* infections associated with high mortality

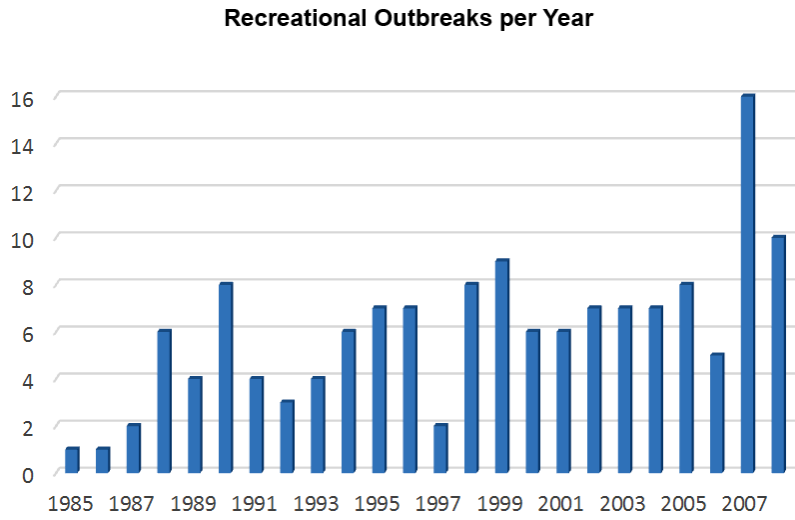

FIGURE A18-3 Outbreaks in ambient recreational water per year in the United States.

in children are now showing up in association with tap water.[81] Waterborne poliovirus and cholera have not been controlled, and zoonotic diseases including *E. coli* 0157H7, *Campylobacter*, and *Salmonella*, and parasites like *Giardia* and *Cryptosporidium,* remain global threats to animal and human health. Finally, concerns about antibiotic resistance are coming to the forefront, and studies on polluted water show that these markers are prolific (Ashbolt et al., 2013).

Emerging viral diseases in humans are now a new threat to water systems. Enteric viruses were once thought to be host specific, yet the human *Cyclovirus* is related to the porcine circovirus (PCV1 and PCV2) that infects pigs. New genetic variants and the genetic diversity of the virus are not well understood. Recent global studies have identified the following:

- A fecal-oral *Cyclovirus* causing acute central nervous system infections in humans was sequenced, and 60 percent of the pigs tested positive for this novel virus in Vietnam (Tan et al., 2013).
- Studies of human feces and food products in Minnesota, Nigeria, and Pakistan reported that the viruses in the stools of U.S. adults were porcine circoviruses. They were also found in most U.S. pork products, yet were more diverse compared to Asian and African samples (Li et al., 2010). The *Cyclovirus* is a single-stranded DNA virus, which is smaller than all

[81] See http://www.cdc.gov/parasites/naegleria; http://www.cdc.gov/parasites/naegleria/public-water-systems.html (accessed August 6, 2014).

other known enteric viruses and little is known about its resistance to water treatment. These viruses remain a significant risk as they are excreted in high concentrations, survive in the environment, and can be spread through contaminated manure to people, other animals, and water.

In summary, waterborne disease continues to occur in the United States and throughout the world. Climate variability and increasing intensity of storms could increase outbreaks (Curriero et al., 2001), and aging infrastructure is leading us toward a future of a greater probability of pathogen contamination of water. Emerging pathogens, those associated with chronic diseases, zoonotic transmission, and antibiotic resistance in water, are a threat to human health. Development of molecular-based water diagnostic tools are needed to characterize these risks along recreational, drinking water, and irrigation water exposure pathways. Yet ultimately this characterization of the water pollution biome needs to be put into the context of public health decision frameworks. Both dynamic models of water quality and health linked to management and quantitative microbial risk assessment provide the approaches for understanding and controlling waterborne diseases.

System Dynamics Modeling for Water and Health

Fostering pathways of biohealth associated with water systems requires (i) definition of the goals of a sustainable society in operational terms with respect to human health, water quality, and quantity, and (ii) an understanding of the process by which the various subsystems associated with water interact and affect public health (Mavrommati et al., 2013a). Defining biohealth pathways at an operational level involves not only scientific knowledge but also ethical considerations about how future generations should be treated by the current generation. Protecting earth's key life support systems is a prerequisite for a sustainable society, a goal reiterated during the discussions of the United Nations Rio+20 Summit in 2012 (Griggs et al., 2013). Recent approaches for sustainability at the global level suggest that life support systems related to human health and water quality are at stake of exceeding the planetary boundaries within which humanity is safe (Barnosky et al., 2012; Rockstrom et al., 2009). Thus, there is an urgent need to identify and understand the boundaries (planetary, regional, or local) within which water systems can function and secure biohealth.

Studying the couplings among the elements of water systems transcends the boundaries of one discipline and requires the use of methodologies employing transdisciplinary approaches to include components of socioeconomic, public health, and biophysical systems. Mainstream approaches in which each discipline develops separated models are not sufficient for water system analysis (Simonovic and Davies, 2006). The methodology of system dynamics (SD) has been extensively used for coupling various disciplines into a common framework

of analysis that can be understandable by decision makers and other stakeholders. The methodology of SD is based on systems thinking and recognizes that the inability to capture the structure and dynamics of complex systems stems from the lack of holistic approaches (Sterman, 2000). SD models for water systems can determine the roots of unsustainable water resources management by identifying the source of the problem both in qualitative and quantitative terms (Mirchi et al., 2012; Sterman, 2012). In this way, decision makers and other stakeholders can better evaluate the effects of their actions in relation to the problematic behavior of water systems; hence, they may adopt more informed and efficient policies for sustaining biohealth in water systems (Hopkins et al., 2012; Mavrommati et al., 2013b).

A system dynamics model displays positive and negative feedbacks (reinforcing and counteractive, respectively) between different variables and drivers, and it helps us understand how a system changes over time. Failure to identify the feedback loops related to the problems of the studied system results in misleading models for decision making. SD models can be both qualitative and quantitative. Qualitative models are represented through causal loop diagrams (CLDs), and quantitative models through stock-flow diagrams where parameter values and functions are estimated through various types of data (e.g., mental, numerical, written).

The recreational waterborne disease exposure pathway is shown as an example CLD for the Lake St. Clair (LSC) region, which is part of the Laurentian Great Lakes System, as a case study (Figure A18-4) (Mavrommati et al., 2013a). This CLD includes the analysis of two counteractive and reinforcing loops with respect to water quality, lake visitors, and human health/well-being (Figure A18-5a,b).

Wastewater discharge and beach use create pollutants/exposure pathways, and the impact from these pollutants entering lake waters can be measured by chlorophyll *a*, a proxy for primary production and toxic algal exposure, and concentrations of the fecal indicator bacteria *Escherichia coli* (*E. coli*) that is used to measure pathogen risks. High concentrations of *E. coli* directly affect public health. In addition, when *E. coli* is above a certain level defined through current water quality regulations, then local beaches are closed to protect public health. Beach closures result in the decrease of the number of lake visitors and impact public health policies. Drinking and recreational water pollution associated with sewage and nonpoint sources of pathogens can be examined along with climate factors (precipitation). This example presents specific aspects of biohealth in water systems and the ability of system dynamics modeling to capture their complexity.

In summary, recreational pathways for waterborne disease may be becoming increasingly important, yet lack of data and appropriate models to capture the interactions between society, climate, water quality, ecosystem services, and health make it difficult to address the complexities of what makes a sustainable

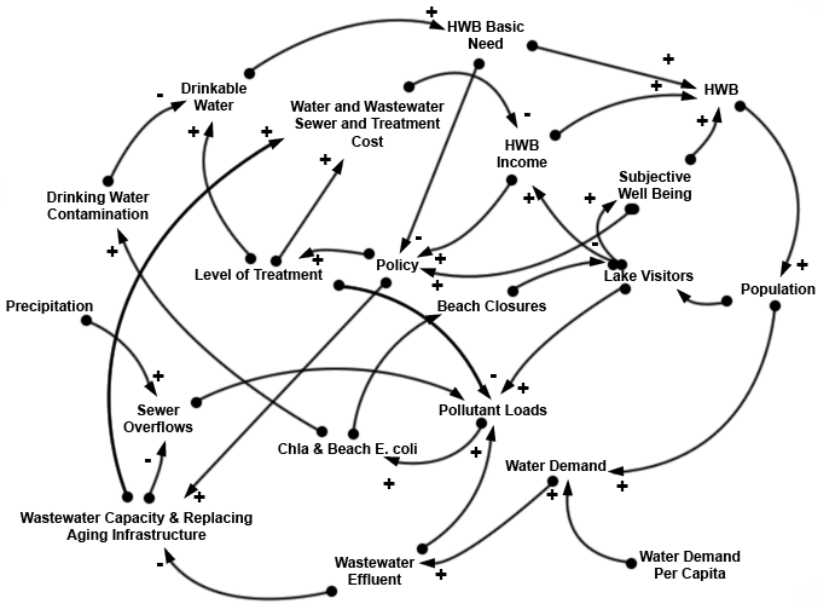

FIGURE A18-4 A causal loop diagram that represents coupled socioeconomic and biophysical systems in Lake St. Clair. Reproduced from Mavrommati et al. (2013a).
NOTE: HWB: Human well-being.

and safe water system. Models allow one to explore changes in pathogen sources associated with various infrastructure; drivers of deteriorating water quality such as human dynamics, climate change, eutrophication, and algal blooms; and the role of policies in protecting health. This will be particularly important for examining future scenarios.

Quantitative Microbial Risk Assessment (QMRA)

One of the missions of the National Institute of Environmental Health Sciences is the investigation of environmental exposures and human disease. However, research has focused on chemical pollutants, whereas exposure to microbial infectious agents through the environment was not considered. This gap has begun to be filled by the field of risk assessment for microbial pathogens using innovative water genomic technology, quantitative data on persistence in the environment, dose-response, and understanding of acute and chronic health outcomes. QMRA was developed through the integration of environmental microbiology, environmental engineering, and infectious disease epidemiology. Clinical experimental data were first examined by Haas (1983) demonstrating

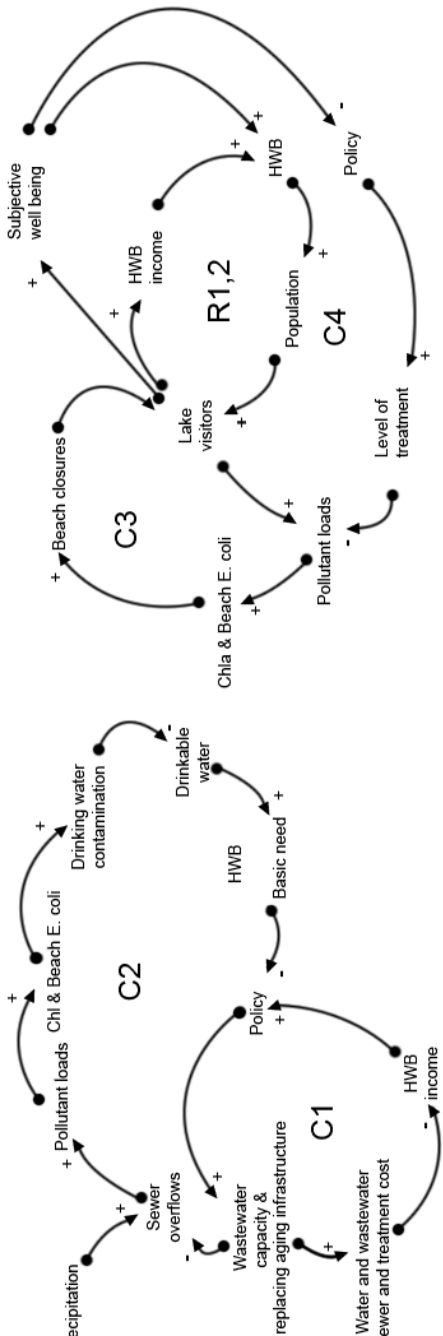

FIGURE A18-5 A causal loop diagram that represents a reinforcing feedback loop (symbolized with *R*) and a counteractive feedback loop (symbolized with *C*). The positive (+) arrows represent a cause-and-effect relationship in which the two parameters change in the same direction, while the negative (-) rows represent two parameters that change in the opposite direction (Ford, 1999). Reproduced from Mavrommati et al. (2013a).
NOTE: HWB: Human well-being.

that dose-response modeling could be used to examine probability of infection. The Center for Advancing Microbial Risk Assessment (CAMRA) funded by the Environmental Protection Agency (EPA) and Department of Homeland Security has now produced a QMRA wiki that houses over 70 dose-response data sets and models for addressing pathogens spread through air, fomites, soil, and water (http://qmrawiki.msu.edu/index.php?title=Dose_Response). QMRA includes four steps:

1. **Hazard identification:** This step includes gathering information regarding the identification of the pathogen(s) and description of the pathogenicity and illness(es). Community-based information on endemic baseline disease levels and attack rates during outbreaks of environmentally transmitted pathogens are also needed. Pathogen discovery is critical, and new genomic tools will be extremely useful. Recent studies on detection and characterization of viruses in community sewage using microarray technology with a total of 780 unique probes targeting 27 different groups revealed a high variety of RNA (astroviruses and enteroviruses) and DNA viruses (adenoviruses, particularly type 41 and BK polyomavirus) (Wong et al., 2013).
2. **Dose-response:** It is now possible to describe the quantitative relationship between doses of the pathogen due to specific exposure pathways and health outcomes as a probability of infection, disease, or in some cases mortality depending on the data sets. Comparative assessments of doses using the ID_{50} or LD_{50} is an approach used to compare the potency of pathogens (Figure A18-6) based on the QMRAwiki (http://qmrawiki.msu.edu/index.php?title=Dose_Response) and illustrates the variability across pathogens.
3. **Exposure assessment:** This is the most challenging part of the QMRA because exposure pathways are complex and data on prevalence, concentrations, distributions (in time and space), and the volume of water consumed are necessary. There are many exposure pathways that require specific parameterization for water. Pathogen persistence under a range of environmental conditions is particularly important. Reductions of the microorganisms during various treatment processes (e.g., disinfection and filtration), and an understanding of the natural history of the pathogen in the built and natural water environment are key to undertaking exposure assessment. Molecular methods are used to improve the pathogen resolution and temporal and spatial distributions for the various polluted water environs. Databases for the water microbiome are needed.
4. **Risk characterization:** The quantitative likelihood of a potential adverse health outcome is based on the above three steps. Risk characterization estimates the magnitude of the public health problem, while also determining the variability and uncertainty of the hazard (Haas et al., 2014).

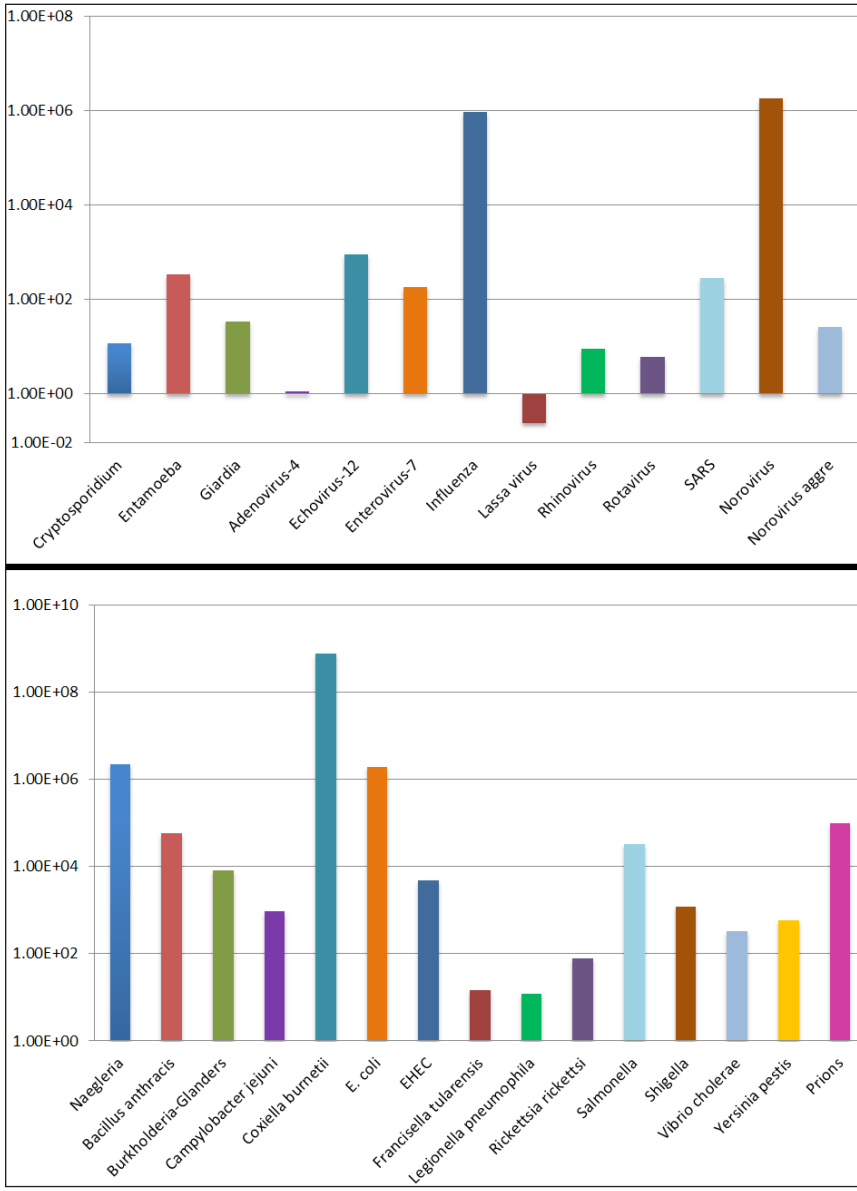

FIGURE A18-6 Comparative assessments of ID_{50} or LD_{50} (Y axis represents the dose in colonies, virons, or cells). The smaller the bar the more potent the organism.
NOTE: EHEC = enterohemorrhagic *E. coli.*

This step is generally pathogen specific and has been used for static estimates focusing on describing the most reasonably exposed individual or describing the distributions of risk with techniques such as Monte Carlo (probabilistic) analysis (Medema et al., 2006; Smeets et al., 2008).

5. **Risk management:** QMRA is used to inform policy and management decisions. Following the new framework suggested by the recent report *Science and Decisions: Advancing Risk Assessment* from the National Academy of Sciences (NRC, 2009), QMRA should integrate the problem identification and risk management strategies into the four-step process. As an example, the effectiveness of household water treatment at reducing diarrheal disease caused by viruses, parasites, and bacteria was evaluated based on treatment efficacy and compliance (Enger et al., 2013) using a QMRA model. The quantitative relationship between compliance and effectiveness is poorly understood; however, this study showed that benefits associated with water treatment were strongly dependent on how many of the households had adequate treatment within the community. Thus policy debates around community water systems and access to safe water and treatment need to include data that protect public health, particularly from emerging contaminants. QMRA methodology has proven invaluable for assisting local, national, and international decision making for protection of health and water quality.

In summary, hundreds of human pathogens can be found in water, and while dose-response models exist for many, there is very little information on exposure including the concentrations, fate, and transport of microbial hazards in the environment. Exposure pathways for emerging and recalcitrant pathogens are not well described. QMRA frameworks now allow data to be systematically evaluated so disease can be better understood. These approaches are just now being further expanded to animal and plant diseases. Through such analyses, critical information that is needed for decision making to address water security and safety can now be identified, gathered, synthesized, and communicated.

Research Recommendations for Addressing Biohealth in Urban Water Systems

There are a tremendous number of scientific, technological, and societal questions that need to be answered as we attempt to address health and water quality in the Anthropocene. Several key questions are:

- What is the risk of waterborne disease?
- Will it change with changes in animal populations?
- Will it change with population growth?
- Will it change with new emerging pathogens?

- What is the risk of an outbreak occurring?
- Will it change with precipitation?
- Will it change with the failure of our infrastructure and treatment?

Global water quality is deteriorating and threatens public health. Human wastewater and animal wastes remain some of the most important sources of pathogens. Preparing for a future where climate, water infrastructure, and emerging pathogens are colliding and impacting the components of human well-being (e.g., human health, subjective well-being derived from recreation) and ecosystem services (e.g., drinking water and recreation) necessitates research on the essential elements for sustainable water and biohealth of the planet. The research recommendations that should be considered include the following:

- Fill key knowledge gaps necessary for using the QMRA framework:
  - Critical water quality diagnostic tools should be used to address exposure assessment for recalcitrant and emerging pathogens, which includes exploration of the water microbiome along the human exposure pathway.
  - Health risks should be calculated and known for all waters in the United States.
- Develop a framework for transdisciplinary research with respect to biohealth linked to water systems. The systems dynamics methodology should be used to:
  - Create and explore the theoretical couplings between the various components of water systems (including the socioeconomic [health] and biophysical [water quality]).
  - Develop and operationalize indicators for assessing and managing key linkages among various components of human and natural systems.

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Appendix B

Agenda

The Influence of Global Environmental Change on Infectious Disease Dynamics

September 24–25, 2013
500 Fifth Street, NW
Washington, DC

DAY ONE: TUESDAY, SEPTEMBER 24, 2013

8:30 – 9:00: Registration and Continental Breakfast

9:00 – 9:15: Welcoming Remarks: David A. Relman, James M. Hughes, and Lonnie King

9:15 – 10:00: **KEYNOTE:** Global environmental change, biodiversity, and infectious disease: Misperceptions and challenges
Andrew Dobson, Princeton University

10:00 – 10:30: DISCUSSION

10:30 – 10:45: BREAK

SESSION I: ANTHROPOGENIC FACTORS DRIVING INFECTIOUS DISEASE ESTABLISHMENT, ADAPTATION, AND SPREAD

Moderator: Peter Daszak

10:45 – 11:15: Migration, civil conflict, mass gathering events, and disease
Chris Beyrer, Johns Hopkins University

11:15 – 11:45: Urbanization, climate change, infrastructure: Impacts on water quality, accessibility, and disease emergence
Joan Rose, Michigan State University

11:45 – 12:15: Circumpolar populations and changing disease patterns
Alan Parkinson, Centers for Disease Control and Prevention

12:15 – 12:45: DISCUSSION

12:45 – 1:30: LUNCH

SESSION II: TRANSPORTATION, MIGRATION, AND INFECTIOUS DISEASE DYNAMICS

Moderator: Lonnie King

1:30 – 2:00: Wildlife–disease interactions in response to climate shifts and animal migration
Sonia Altizer, University of Georgia

2:00 – 2:30: International travel and tourism, mass migration events, refugees, and infectious disease dynamics
Martin Cetron, Centers for Disease Control and Prevention

2:30 – 3:00: Rapid urbanization and social inequity as drivers of infectious disease emergence: Example of leptospirosis in urban slums
Albert Ko, Yale University/School of Public Health

3:00 – 3:30: BREAK

3:30 – 4:00: Road construction as a driver of infectious disease movement in remote locations
Joseph Eisenberg, University of Michigan

4:00 – 4:30: Public health impacts of travel and trade-related zoonotic and communicable diseases
Nina Marano, Centers for Disease Control and Prevention

4:30 – 5:00: Plant diseases: How they affect global food security, and how they are affected by anthropogenic global change
Caitilyn Allen, University of Wisconsin

5:00 – 5:45: DISCUSSION

5:45 – 6:00: CONCLUDING REMARKS

6:00: ADJOURN DAY ONE

DAY TWO: WEDNESDAY, SEPTEMBER 25, 2013

8:00 – 8:30: Registration and Continental Breakfast

8:30 – 8:45: Welcoming Remarks and Summary of Day One:
David A. Relman

8:45 – 9:30: **KEYNOTE:** Global climate and ecological change: Impacts on health
Jonathan Patz, University of Wisconsin

9:30 – 10:00: DISCUSSION

10:00 – 10:15: BREAK

SESSION III: THE IMPACT OF ENVIRONMENTAL AND ECOLOGICAL FACTORS ON DISEASE DYNAMICS AND HOST–MICROBE INTERACTIONS

Moderator: James M. Hughes

10:15 – 10:45: Climate change, dust storms, and the risk of valley fever: Coccidioidomycosis
John Galgiani, University of Arizona

10:45 – 11:15: Emergence and spread of vector-borne diseases in the face of climate change, population shifts, urbanization, and economic factors
Janey Messina, University of Oxford

11:15 – 11:45: Persistence of infectious disease transmission in the face of environmental change and intensive interventions
Uriel Kitron, Emory University

11:45 – 12:15: Impacts of climate change on plant diseases: New scenarios for the future
Marco Pautasso, Centre d'Ecologie Fonctionnelle et Evolutive (CNRS)

12:15 – 12:45: DISCUSSION

12:45 – 1:30: LUNCH

SESSION IV: NEW APPROACHES TO DETERMINING THE FACTORS CONTRIBUTING TO DISEASE EMERGENCE—IMPLICATIONS FOR SURVEILLANCE, PREVENTION, INTERVENTION, AND RESPONSE

Moderator: Jeffrey S. Duchin

1:30 – 2:00: Developing and evaluating interventions to reduce pandemic risk: The case of influenza and henipaviruses
Steve Luby, Stanford University

2:00 – 2:30: Strategies to predict and anticipate the emergence of novel pathogens
Peter Daszak, EcoHealth Alliance

2:30 – 3:00: The application of statistical and mathematical models to investigate and predict emerging infectious disease dynamics
Neil Ferguson, Imperial College London

3:00 – 3:15: BREAK

3:15 – 3:45: Mapping at-risk populations: Improving spatial demographic data for infectious disease modeling
Nita Bharti, Penn State University, Research Associate; Stanford University, Visiting Scholar

3:45 – 4:15: BioMosaic: Mapping the intersection of migration, demography, and emerging infectious diseases
Martin Cetron, Centers for Disease Control and Prevention

4:15 – 5:00: DISCUSSION

5:00 – 5:15: CONCLUDING REMARKS

5:15: ADJOURN DAY TWO

Appendix C

Acronyms

ACAP	Arctic Contaminants Action Program
ACS	American Community Service
ADHS	Arizona Department of Health Services
AHO	African Health Observatory
AIDS	acquired immunodeficiency syndrome
AIV	avian influenza virus
AMAP	Arctic Monitoring and Assessment Program
ANOVA	analysis of variance
APHIS	Animal and Plant Health Inspection Service
AR	antibiotic resistant
BBC	British Broadcasting Corporation
BRT	boosted regression tree
BXW	banana *Xanthomonas* wilt
CAFF	Conservation of Arctic Flora and Fauna
CAMRA	Center for Advancing Microbial Risk Assessment
CDC	U.S. Centers for Disease Control and Prevention
CHANS	coupled human and natural systems
CI	confidence interval
CLD	causal loop diagram
CSIRO	Commonwealth Scientific and Industrial Research Organisation
CSO	combined sewer overflow
DALY	disability-adjusted life year

DGMQ	Division of Global Migration and Quarantine
DHS	U.S. Department of Homeland Security
DNA	deoxyribonucleic acid
DRC	Democratic Republic of Congo
EIA	enzyme immunoassay
EID	emerging infectious disease
EIEC	enteroinvasive *E. coli*
EIP	extrinsic incubation period
EPA	U.S. Environmental Protection Agency
EPEC	enteropathogenic *E. coli*
EPPR	Emergency Prevention Preparedness and Response
ETEC	enterotoxigenic *E. coli*
FAO	Food and Agriculture Organization
FDA	U.S. Food and Drug Administration
FWS	U.S. Fish and Wildlife Service
GDP	gross domestic product
GEE	general estimating equation
GIDEON	Global Infectious Disease and Epidemiology Network
HAB	harmful algal bloom
HHS	U.S. Department of Health and Human Services
HIA	health impact assessment
HIV	human immunodeficiency virus
HP	highly pathogenic
HPS	hantavirus pulmonary syndrome
ICS	International Circumpolar Surveillance
IHR	International Health Regulations
IOM	Institute of Medicine
IPCC	Intergovernmental Panel on Climate Change
ITDS	International Trade Data System
IUCN	International Union for the Conservation of Nature
LEMIS	law enforcement management information system
LEO	local environmental observer
LPAI	low-pathogenic avian influenza
MBG	model-based geostatistics
MDG	Millennium Development Goal
MERS	Middle East respiratory syndrome

MERS-CoV	Middle East respiratory syndrome coronavirus
MRSA	methicillin-resistant *Staphylococcus aureus*
MSX	multinucleated sphere X
MTE	metabolic theory of ecology
NHP	nonhuman primate
NIH	National Institutes of Health
OIE	World Organisation for Animal Health
OR	odds ratio
OTIS	online tuberculosis information system
PAHO	Pan American Health Organization
PCR	polymerase chain reaction
PRISM	Parameter-Elevation Regressions on Independent Slopes Model
QMRA	quantitative microbial risk assessment
RELU	rural economy and land use
RF	radiative forcing
RNA	ribonucleic acid
RSV	respiratory syncytial virus
SAD	sudden aspen decline
SARS	severe acute respiratory syndrome
SCLB	Southern corn leaf blight
SD	standard deviation
SDWG	Sustainable Development Working Group
SFV	simian foamy virus
SIV	simian immunodeficiency virus
SNV	sin nombre virus
SPDC	State Peace and Development Council
STD	sexually transmitted disease
STI	sexually transmitted infection
TB	tuberculosis
TBE	tick-borne encephalitis
TDR	training in tropical diseases
UAE	United Arab Emirates
UN	United Nations
USDA	U.S. Department of Agriculture

VBD	vector-borne disease
WHO	World Health Organization
WMO	World Meteorological Organization
WNV	West Nile virus

Appendix D

Glossary

Acquired immune deficiency syndrome (AIDS): An infectious disease caused by the human immunodeficiency virus (HIV). There are two variants of the HIV virus, HIV-1 and HIV-2, both of which ultimately cause AIDS.

Agent (of disease): Factor such as a microorganism whose presence is essential for the occurrence of a disease.

***Anophelines*:** A genus of mosquitoes that includes all mosquitoes that transmit malaria to humans.

Anthropogenic: Caused or produced by humans.

Anthroponotic: Transmission from human to human and potentially from human to animal.

Antibiotic: Class of substances that can kill or inhibit the growth of some groups of microorganisms. Used in this report to refer to chemicals active against bacteria. Originally antibiotics were derived from natural sources (e.g., penicillin from molds), but many currently used antibiotics are semisynthetic and modified with additions of man-made chemical components. See *antimicrobials*.

Antibiotic resistance: Property of bacteria that confers the capacity to inactivate or exclude antibiotics or a mechanism that blocks the inhibitory or killing effects of antibiotics.

Antimicrobials: Class of substances that can destroy or inhibit the growth of pathogenic groups of microorganisms, including bacteria, viruses, parasites, and fungi.

Arboviral diseases: Shortened form of arthropod-borne virus. Any of a group of viruses that are transmitted to man and animals by mosquitoes, ticks, and sand flies; they include such agents as yellow fever and eastern, western, and Venezuelan equine encephalitis viruses.

Arthropod: Any of a phylum (Arthropoda) of invertebrate animals (as insects, arachnids, and crustaceans) that have a segmented body and jointed appendages, a usually chitinous exoskeleton molted at intervals, and a dorsal anterior brain connected to a ventral chain of ganglia.

Asymptomatic: Presenting no symptoms of disease.

Bacteria: Microscopic, single-celled organisms that have some biochemical and structural features different from those of animal and plant cells.

Biological weapon: A harmful biological agent (such as a pathogenic microorganism or a neurotoxin) used as a weapon to cause death or disease usually on a large scale.

Biota: The animal and plant life of a given region.

Bioterrorism: Terrorism involving use of biological warfare agents (as disease-causing viruses or herbicides).

Botulism: A rare but serious paralytic illness caused by a nerve toxin. Symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. The illness can cause paralysis, respiratory failure, and death.

Bushmeat: Wildlife species that are hunted in the "bush" or forests.

Chemoprophylaxis: The use of drugs or biologics taken by asymptomatic persons to reduce the risk of developing a disease.

Circumpolar region: The region that extends above 60° north latitude, borders the Arctic Ocean, and includes all, or the northern parts, of eight nations: the United States (Alaska), Canada, Greenland, Iceland, Norway, Finland, Sweden, and the Russian Federation.

Climate: Average meteorological conditions over a specified time period, usually at least 1 month, resulting from interactions among the atmosphere, oceans, and land surface. Climate variations occur over a wide range of spatial and temporal scales.

Climate change: A change of climate that is attributed directly or indirectly to human activity that alters the composition of the global atmosphere and that is in addition to natural climate variability observed over comparable time periods.

Climate extremes: Used to represent weather extremes, but viewed over seasons (e.g., droughts) or longer periods. See *extreme weather*.

Climate variability: Refers to variations or deviations from the mean state of the climate or temporal variations of the atmosphere–ocean system around a mean state measure over a long period of time. Typically, this term is used for time scales longer than those associated with synoptic weather events (i.e., months to millennia and longer). The term *natural climate variability* is further used to identify climate variations that are not attributable to or influenced by any activity related to humans. However, it is recognized that such "internal or natural variability" could be affected by external factors driving climate change such as changes in the atmospheric concentration of greenhouse gases. The El Niño-Southern Oscillation (ENSO) phenomena is a good example of the variability in the coupled oceanic and atmosphere system that is a central factor in short-term climate variability and the interannual time scale (http://www.cpc.noaa.gov/products/analysis_monitoring/ensostuff/prelude_to_ensofaq.shtml; http://www.ncdc.noaa.gov/paleo/outreach/coral/coralenso.html; http://www.sws.uiuc.edu/atmos/statecli/Climate_change/glossary.htm).

Communicable disease: An infectious disease transmissible (as from person to person) by direct contact with an infected individual or the individual's discharges or by indirect means (as by a vector).

Disease: As used in this report, refers to a situation in which infection has elicited signs and symptoms in the infected individual; the infection has become clinically apparent.

DNA (deoxyribonucleic acid): Any of various nucleic acids that are usually the molecular basis of heredity and are constructed of a double helix held together by hydrogen bonds between purine and pyrimidine bases that project inward from two chains containing alternate links of deoxyribose and phosphate, and that in eukaryotes are localized chiefly in cell nuclei.

Ecology: The scientific study of the relationship between living things and their environments.

Ecosystem: Mutually interrelated communities of species and abiotic components, existing as a system with specific interactions and exchange of matter, energy, and information.

Ectoparasite: A parasite that lives on the exterior of its host.

El Niño: A warming of the surface waters of the tropical Pacific that occurs every 3 to 5 years, temporarily affecting weather worldwide.

Emerging infection: Either a newly recognized, clinically distinct infectious disease or a known infectious disease whose reported incidence is increasing in a given place or among a specific population.

Emerging infections: Any infectious disease that has come to medical attention within the last two decades or for which there is a threat that its prevalence will increase in the near future. Many times, such diseases exist in nature as zoonoses and emerge as human pathogens only when humans come into contact with a formerly isolated animal population, such as monkeys in a rain forest that are no longer isolated because of deforestation. Drug-resistant organisms could also be included as the cause of emerging infections since they exist because of human influence. Some recent examples of agents responsible for emerging infections include human immunodeficiency virus, Ebola virus, multidrug-resistant *Mycobacterium tuberculosis*, and influenza A(H1N1).

Emerging infectious diseases: Infections that are rapidly increasing in incidence or geographic range.

Emigration: To leave one's usual country of residence to settle in another.

Endemic: Present in a community or common among a group of people; said of a disease prevailing continually in a region.

Enteric: Of, relating to, or affecting the intestines.

Enzootic: A disease of low morbidity that is constantly present in an animal community.

Epidemic: The condition in which a disease spreads rapidly through a community in which that disease is normally not present or is present at a low level.

Epidemiology: Study of the distribution and determinants of health-related states or events in specified populations. Epidemiology is the basic quantitative science of public health.

Epizootic: A disease of high morbidity that is only occasionally present in an animal community.

Eradication: Reduction of the worldwide incidence of a disease to zero as a result of deliberate efforts.

***Escherichia coli*:** A straight rod-shaped gram-negative bacterium that is used in public health as an indicator of fecal pollution (as of water or food) and in medicine and genetics as a research organism and that occurs in various strains that may live as harmless inhabitants of the human lower intestine or may produce a toxin causing intestinal illness.

Etiology: Science and study of the causes of diseases and their mode of operation.

Extreme weather: Refers to weather phenomena that are at the extremes of the historical distribution and are rare for a particular place and/or time, especially severe or unseasonal weather. Such extremes include severe thunderstorms, sever snowstorms, ice storms, blizzards, flooding, hurricanes, and high winds, and heat waves. For example, although flooding is common in the United States, the impacts of flooding are not consistent from year to year through time. Many years of small floods with little impact may be followed by a single large flood with a sizable loss (e.g., the June 2008 flooding in the Midwestern United States) (http://www.greenhouse.gov.au/impacts/resources/glossary.html; http://en.wikipedia.org/wiki/Extreme_weather; http://www.sws.uiuc.edu/atmos/statecli/General/Illinois-climate-narrative.htm).

Extrinsic incubation period: Time required for the development of a disease agent in a vector from the time of uptake of the agent to the time the vector is infective.

Food-borne diseases: Disease caused by consuming contaminated foods or beverages. Many different disease-causing microbes, or pathogens, can contaminate foods, so there are many different food-borne infections. In addition, poisonous chemicals, or other harmful substances can cause food-borne diseases if they are present in food (http://www.cdc.gov/ncidod/dbmd/diseaseinfo/foodborneinfections_g.htm).

Genome: The complete set of genetic information in an organism. In bacteria, this includes the chromosome(s) and plasmids (extra-chromosomal DNA molecules that can replicate autonomously within a bacterial cell).

Genomics: The study of all the genes in a person, as well as interactions of those genes with each other and with that person's environment (http://www.cdc.gov/genomics/faq.htm).

Global warming: The gradual increase, observed or projected, in global surface temperature, as one of the consequences of radiative forcing caused by anthropogenic emissions.

Globalization: The increased interconnectedness and interdependence of peoples and countries is generally understood to include two interrelated elements: the opening of borders to increasingly fast flows of goods, services, finance, people, and ideas across international borders; and the changes in institutional and policy regimes at the international and national levels that facilitate or promote such flows (http://www.who.int/trade/glossary/story043/en/index.html).

Host (disease): Person or other living animal that affords subsistence or lodgment to an infectious agent under natural conditions.

Human immunodeficiency virus (HIV): A retrovirus that causes AIDS by infecting helper T cells of the immune system. The most common serotype, HIV-1, is distributed worldwide, while HIV-2 is primarily confined to West Africa.

Immigration: To arrive and take up permanent residence in a country other than one's usual county of residence.

Immune-competence: The ability of the immune system to respond appropriately to an antigenic stimulation.

Incidence: Number of cases of a disease commencing, or of persons falling ill, during a given period of time in a specified population. Incidence rate is the number of new cases of a specific disease diagnosed or reported during a defined interval of time divided by the number of all persons in a defined population during the same time.

Infection: The invasion of the body or a part of the body by a pathogenic agent, such as a microorganism or virus. Under favorable conditions the agent develops or multiplies, the results of which may produce injurious effects. Infection should not be confused with disease.

Intermediate host: A host that is normally used by a parasite in the course of its life cycle and in which it may multiply asexually but not sexually.

International Health Regulations (IHR): An international legal instrument that is binding on 194 countries across the globe, including all the member states of WHO. Their aim is to help the international community prevent and respond to acute public health risks that have the potential to cross borders and threaten people worldwide. The IHR, which entered into force on June 15, 2007, requires countries to report certain disease outbreaks and public health events to WHO. Building on the unique experience of WHO in global disease surveillance, alert, and response, the IHR defines the rights and obligations of countries to report public health events, and establishes a number of procedures that WHO must follow in its work to uphold global public health security.

La Niña: Cooler than normal sea surface temperatures in the central and eastern tropical Pacific ocean that impact global weather patterns. La Niña conditions recur every few years and can persist for as long as 2 years.

Microbe: A microorganism or biologic agent that can replicate in humans (including bacteria, viruses, protozoa, fungi, and prions).

Microbial threat: Microbes that lead to disease in humans.

Microbiology: A branch of biology dealing especially with microscopic forms of life.

Middle East respiratory syndrome: A viral respiratory illness first reported in Saudi Arabia in 2012. It is caused by a coronavirus called MERS-CoV. This particular strain of coronavirus has not been previously identified in humans. There is very limited information on transmission, severity, and clinical impact with only a small number of cases reported thus far.

Migration: The regular, usually seasonal, movement of all or part of an animal population to and from a given area.

Millennium Development Goals: Eight international development goals that were established following the Millennium Summit of the United Nations in 2000, following the adoption of the United Nations Millennium Declaration.

Mitigation: Initiatives that reduce the risk from natural and man-made hazards. With respect to climate change, mitigation usually refers to actions taken to reduce the emissions or enhance the sinks of greenhouse gases.

Monoculture: The cultivation or growth of a single crop or organism especially on agricultural or forest land.

Morbidity: Diseased condition or state.

Mortality: The number of deaths in a given time or place; the proportion of deaths to population.

Outbreak: Localized occurrence as opposed to a generalized epidemic.

Pandemic: Epidemic occurring over a wide geographic area and affecting an exceptionally high proportion of the population.

Pathogen: Organism capable of causing disease.

Pathogenic: Capable of causing disease.

Pathology: The branch of medicine concerned with disease, especially its structure and its functional effects on the body.

Permafrost: Permanently frozen land.

Phenology: The study of periodic plant and animal life cycle events and how these are influenced by seasonal and interannual variations in climate, as well as habitat factors (such as elevation). Because many such phenomena are very sensitive to small variations in climate, especially to temperature, phenological records can be a useful proxy for temperature in historical climatology, especially in the study of climate change and global warming. For example, viticultural records of grape harvests in Europe have been used to reconstruct a record of summer growing season temperatures going back more than 500 years. In addition to providing a longer historical baseline than instrumental measurements, phenological observations provide high temporal resolution of ongoing changes related to global warming.

Phylogeny: The connections between all groups of organisms as understood by ancestor/descendant relationships.

Polymerase chain reaction (PCR): A scientific technique in molecular biology to amplify a single or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.

Prevalence: Proportion of persons in a population currently affected by a particular disease. Prevalence rate is the number of cases of a specific disease at a particular time divided by the population at that time living in the same region.

Prophylaxis: Measures designed to preserve health (as of an individual or of society) and prevent the spread of disease.

Quarantine: The enforced isolation or restriction of free movement imposed to prevent the spread of disease.

Reservoir: Any person, animal, arthropod, plant, soil, or substance (or combination thereof), that harbors disease-causing organisms and serves as a potential source of disease outbreaks.

Resistance: See *antibiotic resistance*.

Risk: Probability that an event will occur; a measure of the degree of loss expected by the occurrence of a loss.

RNA (ribonucleic acid): Any of various nucleic acids that contain ribose and uracil as structural components and are associated with the control of cellular chemical activities.

***Salmonella*:** A genus of bacteria that cause typhoid fever, food poisoning, and enteric fever from food poisoning.

Salmonellosis: An infection by *Salmonella* bacteria. Most persons infected with *Salmonella* develop diarrhea, fever, and abdominal cramps 12 to 72 hours after infection. The illness usually lasts 4 to 7 days, and most persons recover without treatment.

Severe acute respiratory syndrome (SARS): A contagious and sometimes fatal respiratory illness caused by a coronavirus, transmitted especially by contact with infectious material and characterized by fever, headache, body aches, dry cough, hypoxia, and usually pneumonia. SARS first appeared in China in November 2002.

Southern Oscillation: A large-scale atmospheric and hydrospheric fluctuation centered in the equatorial Pacific Ocean; it exhibits a nearly annual pressure anomaly, alternatively high over the Indian Ocean and high over the South Pacific; the variation in pressure is accompanied by variations in wind strengths, ocean currents, sea surface temperatures, and precipitation in the surrounding areas.

Species barrier: Difficulty or impossibility for an infectious agent to pass from one species to another (due to differences between species).

***Staphylococcus aureus*:** A facultatively anaerobic, gram-positive coccus that is the most common cause of staph infections. It is frequently part of the skin flora found in the nose and on skin.

Surveillance: Used in this workshop summary to refer to data collection and record-keeping to track the emergence and spread of disease-causing organisms such as antibiotic-resistant bacteria.

Syndrome: A group or recognizable pattern of symptoms or abnormalities that indicate a particular trait or disease (http://www.genome.gov/glossary.cfm?key=syndrome).

Temporal barrier: A barrier that blocks the movement of the entire population of an organism some of the time.

Transmission: Process by which a pathogen passes from a source of infection to a new host.

Vaccine: A preparation of living, attenuated, or killed bacteria or viruses, fractions thereof, or synthesized or recombinant antigens identical or similar to those found in the disease-causing organisms, that is administered to raise immunity to a particular microorganism.

Vector: An organism, such as an insect, that transmits a pathogen from one host to another.

Vector-borne: Transmitted from one host to another by a vector.

Vector-borne disease: (1) *Mechanical*: This includes simple mechanical carriage by a crawling or flying insect through soiling of its feet or proboscis or by passage of organisms through its gastrointestinal tract. This does not require multiplication or development of the organism. (2) *Biological*: Propagation (multiplication), cyclic development, or a combination of these (cyclopropagative) is required before the arthropod can transmit the infective form of the agent to humans. An incubation period (extrinsic) is required following infection before the arthropod becomes infective. The infectious agent may be passed vertically to succeeding generations (transovarian transmission); transstadial transmission indicates its passage from one stage of the life cycle to another, as nymph to adult. Transmission may be by injection of salivary gland fluid during biting, or by regurgitation or deposition on the skin of feces or other material capable of penetrating the bite

wound or an area of trauma from scratching or rubbing. This transmission is by an infected nonvertebrate host and not simple mechanical carriage by a vector or vehicle. However, an arthropod in either role is termed a vector.

Virome: The sum of all viruses living in the tissues of the host or infecting organisms in the microbiome.

Virulence: The ability of any infectious agent to produce disease. The virulence of a microorganism (such as a bacterium or virus) is a measure of the severity of the disease it is capable of causing.

Virus: A small infectious agent that can only replicate inside the cells of another organism. Viruses are too small to be seen directly with a light microscope. Viruses infect all types of organisms, from animals and plants to bacteria and archaea.

Weather: Condition of the atmosphere at a particular place and time measured in terms of wind, temperature, humidity, atmospheric pressure, cloudiness, and precipitation. In most places, weather can change from hour to hour, from day to day, and from season to season.

Weather extremes (extreme weather events): Signifies individual weather events that are unusual in their occurrence (minimally, the event must lie in the upper or lower 10 percentile of the distribution) or have destructive potential, such as hurricanes and tornadoes.

West Nile virus: A flavivirus that causes an illness marked by fever, headache, muscle ache, skin rash, and sometimes encephalitis or meningitis and that is spread especially from birds to humans by mosquitoes.

Zoonotic infection: Infection that causes disease in human populations but can be perpetuated solely in nonhuman host animals (e.g., bubonic plague); may be enzootic.

Appendix E

Speaker Biographies

Caitilyn Allen, Ph.D., is Professor and Chair of Plant Pathology at the University of Wisconsin-Madison. She earned a Ph.D. in plant pathology from Virginia Tech and did postdoctoral study in Lyon, France. Her lab studies the mechanisms of virulence and fitness in plant pathogenic bacteria, with a particular focus on the select agent pathogen *Ralstonia solanacearum*. Her second area of expertise is tropical plant pathology, especially current and historical epidemic crop diseases in the tropics. Dr. Allen has research collaborations in France, Germany, Guatemala, Uganda, and China. Her teaching on molecular plant–microbe interactions and on tropical plant pathology has garnered national awards. She is a Chevalier de l'Ordre des Palmes Académiques, a Fellow of the American Association for the Advancement of Science, and a Fellow of the American Phytopathological Society.

Sonia Altizer, Ph.D., is an associate professor and Associate Dean of Academic Affairs in the Odum School of Ecology at the University of Georgia. She received her B.S. in biology from Duke University in 1992, and completed her Ph.D. in ecology at the University of Minnesota in 1998, followed by postdoctoral work at Princeton and Cornell University. Dr. Altizer has been at the University of Georgia since 2005. Her research interests center on infectious disease ecology and its interface with animal behavior, anthropogenic change, and evolution. In her work, Dr. Altizer uses a combination of field studies, experiments, comparative analyses, and modeling to study the ecological and evolutionary interactions between hosts and pathogens in natural populations. A major focus has been to understand the consequences of long-distance migration for animal–pathogen interactions, using monarch butterflies and a protozoan parasite as a global case

study. She also collaborates on studies looking at how factors such as seasonality, anthropogenic change, and contact behavior influence the dynamics of pathogens affecting passerine birds, bats, primates, and rodents.

Chris Beyrer, M.D., M.P.H., is Professor in the Departments of Epidemiology, International Health, and Health, Behavior and Society at the Johns Hopkins Bloomberg School of Public Health. He serves as director of the University's Center for Public Health and Human Rights, associate director of the Centers for AIDS Research and of Global Health, and as Director of the Johns Hopkins Fogarty AIDS International Training and Research Program. He is the President-Elect of the International AIDS Society, the largest body of HIV professionals worldwide. Dr. Beyrer's research interests focus on the burden of HIV and other infectious diseases and the association with human rights, with specific interests in epidemiology among high-risk or marginalized populations, prevention research, and molecular epidemiology. He currently has research and/or training activities in Thailand, China, Burma, Malawi, Uganda, Ethiopia, South Africa, Brazil, Russia, Kazakhstan, and the United States. He is the co-editor of the books *Public Health and Human Rights: Evidence-Based Approaches* as well as *Public Health Aspects of HIV/AIDS in Low- and Middle-Income Countries: Epidemiology, Prevention and Care* and is the author of the 1998 book *War in the Blood: Sex, Politics and AIDS in Southeast Asia*. Dr. Beyrer has published extensively on HIV/AIDS epidemiology and prevention research, HIV vaccine research, and public health and human rights and is the author of numerous articles and scientific papers. Currently, he is a consultant to the World Bank Institute, a member of the Technical Advisory Group of the Independent Commission on AIDS & the Law, and a Scientific Advisor of the International Centre for Science in Drug Policy, and has served as a consultant for the World Bank Thailand Office, The Office for AIDS Research of the U.S. National Institutes of Health, The Levi Strauss Foundation, The U.S. Military HIV Research Program, the Henry M. Jackson Foundation for the Advancement of Military Medicine, The Open Society Institute, The Royal Thai Army, and numerous other organizations.

Nita Bharti, Ph.D., is a Research Associate at Penn State and a Visiting Scholar at Stanford University. Dr. Bharti's research focuses on the interactions between social and biological processes as underlying determinants of human health. She is interested in detecting and measuring movement and mobility of populations and how they influence the transmission and spread of infectious diseases in humans. She is also working on linking behavior and health by using remote measures for estimating changes in settlements and land use, and the potential impact these could have on species interactions and the risk of disease transmission. She received her Ph.D. in biology and M.A. in anthropology from Penn State University.

Martin Cetron, M.D., is currently the Director for the Division of Global Migration and Quarantine (DGMQ) at the U.S. Centers for Disease Control and Prevention (CDC). The DGMQ mission is to prevent introduction and spread of infectious diseases in the United States and to prevent morbidity and mortality among immigrants, refugees, migrant workers, and international travelers. Dr. Cetron's program is responsible for providing medical screening and disease prevention programs to 1.2 million immigrants and 80,000 refugees prior to U.S. resettlement each year. Dr. Cetron has authored or co-authored more than 150 publications and received numerous awards for his work. In 2009, Dr. Cetron was honored with the Public Health Hero Award by Research America. In 2010, Dr. Cetron received the Dean's Award by the Tufts Medical Alumni Association for Distinguished Contributions to Medicine 25 years post-graduation. In 2014, Dr. Cetron was honored by Dartmouth College with the Lester B. Granger Lifetime Achievement Award as part of the Martin Luther King Awards for a lifetime of work dedicated to social justice and combating health disparities.

Dr. Cetron holds faculty appointments in the Division of Infectious Disease at the Emory University School of Medicine and the Department of Epidemiology at Rollins School of Public Health. His primary research interests are global health and migration with a focus on health disparities, emerging infections, tropical diseases, and vaccine-preventable diseases particularly in mobile populations. Dr. Cetron teaches and lectures worldwide and is frequently quoted in the media. Dr. Cetron serves as an expert on several intergovernmental and international committees. He is a graduate and adviser to the National Preparedness Leadership Institute at the Harvard School of Public Health and the Kennedy School of Government.

Dr. Cetron has worked at the CDC since 1992 where he has led several domestic and international outbreak investigations, conducted epidemiologic research, and been involved in domestic and international emergency responses. He has played a leadership role in the CDC responses to intentional and naturally-acquired emerging infectious disease outbreaks, including the Anthrax Bioterrorism (2001), Global SARS epidemic (2003), U.S. Monkeypox Outbreak (2003), Pandemic Influenza H1N1 (2009), Haiti Earthquake and Cholera (2010), Japan Tsunami and Radiation Response (2011), and Middle Eastern Respiratory Syndrome (MERS) Coronavirus Response (2013).

Dr. Cetron is part of the CDC Pandemic Influenza Planning and Preparedness Team. He leads the CDC's preparedness for international border responses and community mitigation strategies. Dr. Cetron is also part of the World Health Organization (WHO) Influenza Pandemic Task Force, WHO Director General's International Health Regulations Emergency Committee of Experts for Influenza and MERS Coronavirus.

Dr. Cetron received his B.A. in biochemistry *summa cum laude* from Dartmouth College in 1981 and his M.D. from Tufts University School of Medicine in 1985. He trained in internal medicine at the University of Virginia (1985–1988)

and infectious diseases at the University of Washington (1989–1992) before joining the CDC's Epidemic Intelligence Service and becoming a Commissioned Officer in the U.S. Public Health Service (1992–present).

Peter Daszak, Ph.D., is President of EcoHealth Alliance, a U.S.-based organization that conducts research and outreach programs on global health, conservation, and international development. Dr. Daszak's research has been instrumental in identifying and predicting the impact of emerging diseases across the globe. His achievements include identifying the bat origin of SARS, identifying the causes of Nipah and Hendra virus emergence, producing the first ever global emerging disease "hot spots" map, identifying the first case of a species extinction due to disease, coining the term *pathogen pollution*, and the discovery of the disease chytridiomycosis as the cause global amphibian declines. Dr. Daszak is a member of the Institute of Medicine's (IOM's) Forum on Microbial Threats, and served on the IOM Committee on global surveillance for emerging zoonoses, the National Reserch Committee committee on the future of veterinary research, the International Standing Advisory Board of the Australian Biosecurity Cooperative Research Centre, and he has advised the Director for Medical Preparedness Policy on the White House National Security Staff on global health issues. Dr. Daszak won the 2000 CSIRO medal for collaborative research on the discovery of amphibian chytridiomycosis and is Editor-in-Chief of the journal *EcoHealth*. He has authored more than 200 scientific papers, and his work has been the focus of extensive media coverage, ranging from popular press articles to television appearances.

Andrew Dobson, D.Phil., is a professor in the Department of Ecology and Evolutionary Biology at Princeton University. He first developed a fascination with natural history during childhood afternoons roaming the Scottish hillside. Those rambles led him to study zoology and applied entomology at Imperial College London as an undergraduate. He then spent 2 years researching parasites at King's College London. Dobson marvels at parasites' domination of the natural world—"at least half of the biodiversity on the planet is parasitic on the other half," he says. "The more we look the more parasitic diversity we see." His next stop was the University of Oxford where he earned a D.Phil. for developing mathematical models of climate change's impact on bird populations. Enthralled with the power of modeling, he explored the dynamics of parasite infections of wild animal populations at Imperial College, Princeton, and the University of Rochester, before finally landing at Princeton University, where he has remained since 1990 as a professor in the Department of Ecology and Evolutionary Biology. Dobson has written and edited 4 books and around 200 scientific papers; his current research focuses on understanding the multiple roles that pathogens play in natural ecosystems, the population ecology of infectious disease, and the double-edged role that pathogens play in conservation biology. His research is

sponsored by NIH, National Science Foundation, and the McDonnell Foundation. He's been involved in projects to conserve elephants in East Africa, carnivores in the Serengeti and Yellowstone, and finches in the backyards of New England. He's particularly interested in parasites and food webs, climate change and disease dynamics in the Arctic, and how pathogens rapidly evolve in order to increase, or in some cases, decrease their virulence. He served as Chair of the U.S. National Academy of Sciences "Diversitas" Committee and is an Elected Fellows of AAAS.

Joseph Eisenberg, M.P.H., Ph.D., is an Associate Professor of Epidemiology in the School of Public Health at the University of Michigan. Dr. Eisenberg received his Ph.D. in bioengineering in the joint University of California, Berkeley/University of California, San Francisco, program, and an M.P.H. from the School of Public Health at the University of California, Berkeley. He is an expert in water- and vector-borne transmission modeling, infectious disease epidemiology, and microbial risk assessment. A continual theme in Dr. Eisenberg's work is the use of a systems-level perspective to understand dynamic infection and disease processes across scales, as they interact through the molecular, individual, community, and regional scales. To inform processes at each of these scales he initiated a systems platform in Ecuador (funded by NIH and NSF) that enables primary data collection at multiple scales over time. Methodologically, Dr. Eisenberg has made substantial contributions to transmission modeling, explicitly incorporating environmental processes into the model structure. This work has influenced agencies such as the U.S. Environmental Protection Agency to consider these environmentally mediated transmission models in their regulatory process. Substantively, Dr. Eisenberg's research has focused on water, sanitation, and hygiene (WASH) where he has made major contributions to our understanding of the interdependency of transmission pathways.

Neil Ferguson, Ph.D., is founding director of the Medical Research Council Centre for Outbreak Analysis and Modelling at Imperial College London. He uses mathematical and statistical models to investigate the processes shaping infectious disease pathogenesis, evolution, and transmission. In addition to basic theoretical work, Professor Ferguson has applied models to study the transmission and control of influenza, SARS, BSE/vCJD, HIV, dengue, foot-and-mouth disease, and bioterrorist threats. He was educated at Oxford University where he also undertook postdoctoral research, then held a readership at the University of Nottingham before moving to Imperial College. Professor Ferguson is a Senior Investigator of the National Institute for Health Research, a Fellow of the U.K. Academy of Medical Sciences, and received the U.K. honour of Officer of the Most Excellent Order of the British Empire for his work on the 2001 U.K. foot-and-mouth disease epidemic. His recent work has focused on the use of models as contingency planning tools for emerging human infections (notably pandemic

influenza), bioterrorist threats, and livestock outbreaks, though he also undertakes research on the dynamics and control of vector-borne diseases (dengue, yellow fever, and malaria) and pathogen evolution. Professor Ferguson advises the U.K. and U.S. governments, the World Health Organization, and the European Union on emerging infections and infectious disease modelling.

John Galgiani, M.D., joined the faculty of the University of Arizona in 1978, and currently he is Professor of Medicine. He received his B.A. from Stanford University, his M.D. from Northwestern University, and a fellowship in infectious diseases from Stanford. Dr. Galgiani has focused his career primarily on the special problems of coccidioidomycosis (valley fever) and its impact on the general population and special groups such as organ transplant recipients and patients with AIDS. For 19 years, he was project director of an NIH-sponsored coccidioidomycosis clinical trials group. Dr. Galgiani's laboratory has collaborated in efforts to develop vaccines to prevent valley fever. For the past 9 years, Dr. Galgiani has led a development program for nikkomycin Z, a possible cure for valley fever, now in clinical trials. In 1996, Dr. Galgiani founded the Valley Fever Center for Excellence to disseminate information about valley fever, help patients with the severest complications of this disease, and to encourage research into the biology and diseases of its etiologic agent.

Uriel Kitron, Ph.D., M.P.H., is the Goodrich C. White Professor and Chair of the Environmental Sciences department at Emory University. Dr. Kitron's research and teaching programs center around the eco-epidemiology of infectious diseases, with an emphasis on tropical and emerging diseases and their environmental risk factors. In his global health research he emphasizes anthropogenic changes, including issues of climate, urbanization, agricultural practices, and conservation. For diseases such as dengue, malaria, schistosomiasis, Chagas disease, and West Nile virus, Dr. Kitron's group studies transmission dynamics and the ecology of insect vectors and mammalian or avian reservoir hosts, incorporating a strong field component (trapping vertebrates, collecting insects, identifying environmental features), spatial analysis, and laboratory work. Dr. Kitron applies geographic information systems (GIS) and remote sensing to gather and manage environmental data that can help explain the spatial distribution of disease and vectors, and assess transmission risk. Following quantitative spatial analysis, Dr. Kitron's group produces maps and models to target further research efforts, and help support surveillance and control efforts by public health agencies. Current research efforts funded by NIH, NSF, and the CDC include large-scale collaborative international studies of malaria and schistosomiasis in Kenya; Chagas disease in Argentina; dengue in Peru, Brazil, and Australia; and West Nile virus and eco-epidemiology of disease emergence in urban areas of the United States.

Albert Ko, M.D., is an infectious disease physician, Professor and Chair of the Department of Epidemiology of Microbial Diseases at Yale School of Public Health, and Collaborating Researcher at the Oswaldo Cruz Foundation, Brazilian Ministry of Health. His research focuses on the health problems that have emerged as a consequence of rapid urbanization and social inequity. Dr. Ko coordinates an NIH-supported research and training program on urban slum health in Brazil, where his group is conducting long-term prospective studies on urban health problems, which include dengue, meningitis, and respiratory infections, as well as noncommunicable diseases such as hypertension and violence. His work is particularly interested in understanding the natural history of leptospirosis, which is a model for an infectious disease that has emerged in slum settlements due to the interaction of climate, urban ecology, and social marginalization. His research combines field epidemiology and translational research approaches to identify prevention and control strategies that can be implemented in slum communities.

Stephen Luby, M.D., is Professor of Medicine with the Division of Infectious Diseases and Geographic Medicine; Deputy Director for Research at the Center for Global Health Innovation; Senior Fellow at the Woods Institute; and Senior Fellow at the Freeman Spogli Institute for International Studies at Stanford University. Prior to his current appointment, Dr. Luby served for 8 years at the International Center for Diarrheal Diseases Research, Bangladesh (ICDDR,B), where he directed the Centre for Communicable Diseases. Dr. Luby was secunded from the CDC and was the Country Director for CDC in Bangladesh. From 1993 to 1998, Dr. Luby directed the Epidemiology Unit of the Community Health Sciences Department at the Aga Khan University in Karachi, Pakistan; and from 1998 to 2004 worked as a medical epidemiologist in the Foodborne and Diarrheal Diseases Branch of the CDC in Atlanta. Dr. Luby's research has addressed a number of public health issues. In Bangladesh he led a research group that explored the epidemiology of Nipah virus including studies of villagers' perspective on and response to the outbreaks and studies of virus circulation in its bat reservoir and spillover into domestic animals and humans. He has authored more than 200 scientific manuscripts.

Nina Marano, D.V.M., M.P.H., Dipl.ACVPM, is a native New Yorker trained in veterinary medicine at the University of Georgia and in public health at Emory University. Since 1998, Dr. Marano has been a medical epidemiologist at the CDC where she has worked on antimicrobial resistance of food-borne pathogens, anthrax bioterrorism, and SARS investigations, and forged new partnerships with the veterinary medical community to prevent zoonotic diseases. In 2006, Dr. Marano joined the CDC Division of Global Migration and Quarantine as the Branch Chief for the Travelers' Health and Animal Importation Branch. In 2009 she became the Branch Chief for the Quarantine and Border Health Services

Branch where she worked on national policy, regulations, and research to mitigate translocation of pathogens via travel and transportation. Under her leadership, the Branch responded to the 2009 influenza A H1N1, earthquake and cholera in Haiti, and nuclear radiation leakage in Japan. In June 2012, Dr. Marano was appointed Director of the Africa Refugee Health Program at the CDC Kenya office in Nairobi. As Director of the program, she and her team are responsible for overseeing the implementation of guidelines for disease screening and treatment, tracking and reporting disease, responding to disease outbreaks, and advising partners on health care for refugees and immigrants from Africa.

Jane Messina, Ph.D., is a medical geographer whose interests lie primarily in the spatial epidemiology of infectious diseases. She concentrates particularly on the application of GISs and spatial statistical analysis to public health questions, having completed her undergraduate and graduate degrees in geography. She received her Ph.D. from the University of North Carolina at Chapel Hill in 2011, where she conducted spatial epidemiological research about HIV, malaria, and anemia in the Democratic Republic of Congo. Now a Senior Postdoctoral Epidemiologist in the Department of Zoology at the University of Oxford, Dr. Messina works as part of the Spatial Ecology & Epidemiology Group, coordinating their contribution to the International Research Consortium on Dengue Risk Assessment, Management and Surveillance. Her work focuses on the changes in the landscape and epidemiology of dengue resulting from factors such as urbanization, climate change, and economic shifts. Dr. Messina also studies the spatial ecology and risk of other vector-borne diseases such as Crimean-Congo hemorrhagic fever and Japanese encephalitis, underlining the importance of cartography in understanding the current distribution and future spread of these and other infectious diseases.

Alan Parkinson, Ph.D., is currently Deputy Director of the CDC's Arctic Investigations Program, a field station within the Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, located in Anchorage, Alaska. Dr. Parkinson earned his Ph.D. degree in microbiology in 1976 from Otago University, Dunedin, New Zealand, and undertook a postdoctoral fellowship at the Oklahoma University Health Sciences Center. He joined the CDC in 1984. Dr. Parkinson has been instrumental in establishing the International Circumpolar Surveillance system, a U.S.-led Arctic Council, Sustainable Development Working Group project for monitoring emerging infectious diseases in the Arctic.

Jonathan Patz, M.D., M.P.H., is professor and Director of the Global Health Institute at the University of Wisconsin in Madison. He co-chaired the health expert panel of the *U.S. National Assessment on Climate Change* and was a convening lead author for the *United Nations/World Bank Millennium Ecosystem*

Assessment. For the past 15 years, Dr. Patz has been a lead author for the United Nations Intergovernmental Panel on Climate Change (or IPCC)—the organization that shared the 2007 Nobel Peace Prize with Al Gore.

Dr. Patz has written more than 90 peer-reviewed scientific papers, a textbook addressing the health effects of global environmental change, and most recently, co-edited the five-volume *Encyclopedia of Environmental Health* (2011). He has been invited to brief both houses of Congress, served on several scientific committees of the National Academy of Sciences, and federal agency science advisory boards for both the CDC and EPA. From 2006 to 2010, Dr. Patz served as Founding President of the International Association for Ecology and Health. In addition to sharing the 2007 Nobel Peace Prize, Dr. Patz received an Aldo Leopold Leadership Fellows Award in 2005, shared the Zayed International Prize for the Environment in 2006, and earned the distinction of becoming a University of Wisconsin (UW)-Madison Romnes Faculty Fellow in 2009.

Aside from directing the university-wide UW Global Health Institute, Professor Patz has faculty appointments in the Nelson Institute, Center for Sustainability & the Global Environment, and the Department of Population Health Sciences. He also directs the NSF-sponsored Certificate on Humans and the Global Environment.

Dr. Patz earned medical board certification in both occupational/environmental medicine and family medicine and received his medical degree from Case Western Reserve University (1987) and his master of public health degree (1992) from Johns Hopkins University.

Marco Pautasso, Ph.D., is working at the European Food Safety Authority in the plant health team. He was previously a postdoctoral researcher at ETH Zurich, the Centre for Evolutionary and Functional Ecology of the French National Centre for Scientific Research in Montpellier, France (2011–2013), the University of Cambridge (2011), the London Metropolitan University (2010), Imperial College London (2006–2009), and the Swiss Federal Institute of Technology (2002–2005, 2013–2014). His Ph.D. (2005) was in macroecology at the University of Sheffield (United Kingdom). His interests are in network epidemiology, landscape pathology, conservation biogeography, and scientometrics. He has peer-reviewed manuscripts for about 60 journals and published about 25 literature reviews on topics such as networks in plant epidemiology; European ash dieback as a conservation biology challenge; the geographical genetics of forest trees; plant health and global change; and peer-reviewing interdisciplinary papers. His research has dealt with epidemic development in small-size directed networks; the scale dependence of the spatial correlation between human population and biodiversity; geographical patterns of the species richness of the living collections of the world's botanic gardens; and the temporal development of the file-drawer problem. He was selected by the European Commission in 2012 to participate in

"Voice of Researchers," a network of 25 researchers that aims to act as a bridge between European Union policy makers and researchers.

Joan Rose, Ph.D., is currently a professor at Michigan State University in the Departments of Fisheries & Wildlife and Plant, Soil, and Microbiological Science, holds the Homer Nowlin Chair in Water Research, and serves as the Co-Director of the Center for Advancing Microbial Risk Assessment. Dr. Rose earned her B.Sc. and Ph.D. in microbiology from the University of Arizona, Tucson. She is a member of the National Academy of Engineering and a Fellow of the American Academy of Microbiology. Dr. Rose is a recipient of the Clarke Water Prize, the Singapore Public Service Medal, and the International Water Association Hei-jin Woo Award for Achievements of Women in the Water Profession. Dr. Rose is an international expert in water microbiology, water quality, and public health safety, and has published more than 300 manuscripts. She has been involved in the investigation of numerous waterborne outbreaks worldwide. Her work addresses the use of new molecular tools for surveying and mapping water pollution for recreational and drinking water; assessment of innovative water treatment technology for the developed and developing world; and use of quantitative microbial risk assessment.