EcoHealth 2, 244–257, 2005
DOI: 10.1007/s10393-005-8961-3

ECOHEALTH

Review

Emerging and Reemerging Infectious Diseases: Biocomplexity as an Interdisciplinary Paradigm

Bruce A. Wilcox[1] and Rita R. Colwell[2]

[1]*Division of Ecology and Health, Department of Tropical Medicine, Medical Microbiology, and Pharmacology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96826*
[2]*Institute for Advanced Computer Studies, College of Computer, Mathematical and Physical Sciences, University of Maryland, College Park, MD 20742*

Abstract: Understanding factors responsible for reemergence of diseases believed to have been controlled and outbreaks of previously unknown infectious diseases is one of the most difficult scientific problems facing society today. Significant knowledge gaps exist for even the most studied emerging infectious diseases. Coupled with failures in the response to the resurgence of infectious diseases, this lack of information is embedded in a simplistic view of pathogens and disconnected from a social and ecological context, and assumes a linear response of pathogens to environmental change. In fact, the natural reservoirs and transmission rates of most emerging infectious diseases primarily are affected by environmental factors, such as seasonality or meteorological events, typically producing nonlinear responses that are inherently unpredictable. A more realistic view of emerging infectious diseases requires a holistic perspective that incorporates social as well as physical, chemical, and biological dimensions of our planet's systems. The notion of biocomplexity captures this depth and richness, and most importantly, the interactions of human and natural systems. This article provides a brief review and a synthesis of interdisciplinary approaches and insights employing the biocomplexity paradigm and offers a social–ecological approach for addressing and garnering an improved understanding of emerging infectious diseases. Drawing on findings from studies of cholera and other examples of emerging waterborne, zoonotic, and vectorborne diseases, a ''blueprint'' for the proposed interdisciplinary research framework is offered which integrates biological processes from the molecular level to that of communities and regional systems, incorporating public health infrastructure and climate aspects.

Key words: emerging infectious diseases, complexity, disease ecology, global environmental change, climate variability

INTRODUCTION

Understanding the mechanisms that underlie newly emerging and reemerging infectious diseases (EID) is one of the most difficult scientific problems facing society today. EIDs are diseases that have recently increased in incidence or in geographic or host range (e.g., tuberculosis, cholera, malaria, dengue fever, Japanese encephalitis, West Nile fever, and yellow fever), diseases caused by new variants assigned to known pathogens (e.g., HIV, new strains of influenza virus, SARS, drug resistant strains of bacteria, Nipah virus, Ebola virus, hantavirus pulmonary syndrome, and avian influenza virus), and bacteria newly resistant to

Published online: October 31, 2005
Correspondence to: Bruce A. Wilcox, e-mail: bwilcox@hawaii.edu

antibiotics, notably the multiple resistant strains that render the armamentarium of antibiotics useless (Smolinski et al., 2003).

Fundamental questions persist concerning molecular mechanisms and specific cellular processes involved in pathogenesis, as well as transmission dynamics and epidemiology, of pathogens that cause some of the most studied of the reemerging infectious diseases, such as tuberculosis, malaria, and cholera. Newly emerging diseases caused by entirely novel or previously unrecognized pathogens, such as HIV/AIDS, SARS, and hantavirus, or those whose modes of transmission are currently under study, as in the case of Ebola and Nipah, represent yet another significant challenge. Certainly the mechanisms or processes of disease emergence involve factors in addition to those at molecular and cellular levels. These include climate, rainfall, ocean and air circulation patterns, and extreme weather events, as well as the ecology of the pathogens' reservoirs and vectors, namely those factors associated with larger-scale mechanisms and the dynamic behavior of ecosystems in which parasite (pathogen) and host relationships are embedded (Horwitz and Wilcox, 2005). Still other factors are involved, and must be identified, if a truly holistic framework is to be constructed that incorporates factors related to human and societal mechanisms.

Demographic and social changes, along with associated environmental alterations, and even the efforts to control disease, have contributed to the severity of the problem of EIDs (Wilcox and Gubler, 2005). The use of antimicrobials, pesticides, and biological controls predictably are effecting changes in pathogens, hosts, and ecological systems, and often unwittingly facilitating disease emergence or reemergence (Lederberg et al., 1992; Gubler, 1998; Burroughs et al., 2003; Knobler et al., 2003; Smolinski et al., 2003). Antibiotic resistant Strepococcus A and *E. coli* 0:157 are prime examples. Pathogens and their hosts, including humans, reproduce, grow, and adapt in an environmental context, devastatingly exemplified by the avian influenza threat (chickens, ducks, pigs, and humans in close confines). This context is most accurately captured using a holistic or systems perspective, considering sub-systems at different levels of organization—those at lower levels embedded within those at successively higher levels—including social as well as physical, chemical, and biological components.

This view, applied to the extraordinary depth and richness of living systems, spanning the scale of microbial genomes to the regional ecosystems populated by humans and reservoir species, evoked the term biocomplexity (Colwell, 1998). Several investigators, including social scientists, conceived and elaborated on similar themes using different terminology. Ecological and social scientists working on ecosystem and natural resources management challenges refer to ''social–ecological systems'' (Berkes and Folke, 1998; Berkes et al., 2003) or ''human and natural systems'' (Gunderson and Holling, 2002). The contraction of social–ecological systems, ''socioecological systems,'' has been used to describe this same systems perspective, stressing coupled human–natural systems and complexity theory, in the context of health and emerging infectious diseases (Waltner-Toews, 2001). The hyphenated or contracted terms share with biocomplexity an emphasis on the interaction of humans and nature as a complex system, and arguably embrace what is fundamentally the same paradigm. For convenience in this article, we will refer to ''human–natural systems perspective'' as synonymous with ''biocomplexity.'' We also note these ideas, including those associated with ''eco-epidemiology'' expressing the need for a broadened concept of causality in epidemiology (Kaufman and Poole, 2000), are part of a larger emerging paradigm called ''post-normal science'' by some investigators (Ravetz, 1999).

In this article, we draw from our own research and the results of a recent meeting entitled *Social–Ecological Systems and Emerging Infectious Diseases*, that was part of the National Institutes of Health Roadmap initiative, *Research Teams of the Future*, the purpose of which was to examine EIDs through the lens of this new paradigm. The objective of this meeting was to facilitate interdisciplinary research on the problem of emerging and reemerging infectious diseases. Our aim here is to provide a short review and synthesis of these interdisciplinary approaches and insights emerging from the meeting and reported in the recent literature. We use the case of cholera, the current scientific understanding of which currently provides a basis for the most complete human–natural systems model of any EID, and a complementary model based on zoonotic and vectorborne EIDs in general. Together, with two published EID case studies from this meeting, a framework is developing that has significant potential for explaining the phenomenon of global infectious disease emergence. We believe the approach has significant bearing on the interdisciplinary methodology of emerging infectious disease research, and suggests future research directions, as well as prospects for managing infectious disease emergence.

New EID Research Paradigm

Two complementary views or general models of emerging infectious disease have developed, based on the human–natural systems perspective: one centered on and illustrated by the case of cholera and the other which builds on the accumulating cases of mainly reemerging zoonotic and vectorborne diseases. Cholera is historically the most studied infectious disease, since the discovery of its etiology established the theory of communicable diseases and the field of epidemiology (Snow, 1855). The relatively recent discovery (Huq et al., 1983; Colwell, 1996) of the connection of cholera with the natural environment and ecological processes has dramatically broadened the scope of cholera research. With a few exceptions, zoonotic and vectorborne diseases are, in general, readily understood as having links with the natural environment. However, the connection between their epidemiology and ecosystem dynamics or processes, not to mention coupled human–natural system behavior, is only now beginning to be appreciated. Some EIDs like SARS, Ebola, even HIV/AIDS, and the more recent and disturbingly potentially disastrous avian influenza (Aldhous and Tomlin, 2005; Osterholm, 2005) are diseases that effectively originate as zoonotic parasites or pathogens whose transmission cycles can become completely uncoupled from their animal reservoirs.

Biocomplexity and the Case of Cholera

The most significant challenge in what has come to be called sustainability science (Kates et al., 2001), is reaching across and connecting disciplines toward understanding the complex chemical, biological, and social interactions in the systems comprising our planet. In pointing this out, the term ''biocomplexity'' was introduced to capture the depth and richness and interaction of society and natural systems (Colwell, 1998). The coining of this term embraces a wide variety of goals and phenomena that Pickett et al. (2005) summarized to include:

(a) links across the sciences;
(b) the linkage of biological and physical processes;
(c) the wide scope of various methodological approaches;
(d) the inherent complexity of the Earth, including global scales and the human components of systems;
(e) environmental problem solving;
(f) a foundation in systems and chaos theories; and
(g) the creation of order in nature.

The imperative for such a paradigm can be described in terms of the global context that now frames all health issues, and specifically in the case of one infectious disease, namely cholera, and the environment (Colwell, 2004). The world has become so integrated and global (with international arrivals per year in the U.S. alone in the hundreds of millions), that the notion that a disease can be completely eradicated has become simplistic. Infectious disease is a moving target, and as the climate, as well as other sources of natural or anthropogenic environmental variation changes, any disease that has an environmentally sensitive stage, reservoir, or vector will be affected. Thus, the simplistic view must be expanded to recognize that neither ecosystems nor the pathogens that live in them respond linearly to environmental changes. Moreover, many environmental events such as climate change and seasonality, but particularly associated meteorological and oceanographic events, are inherently unpredictable by present models. The expanding field of global climate research must include the human dimension, i.e., infectious diseases. Incorporating a prediction based on signals from climate models into health measures can thereby provide new opportunities for proactive, rather than reactive, approaches to public health.

Cholera provides possibly the best example of how our understanding of an emerging infectious disease has evolved from a linear reductionist model focused on oral–fecal transmission of a waterborne bacterium and a human host, to a vastly more complex, yet accurate ecological model of an infectious disease. This model includes global weather patterns, aquatic reservoirs, bacteriophages, zooplankton, the collective behavior of surface attached cells, an adaptable genome, and the deep sea, together with the bacterium and its host (Huq et al., 1983; Colwell, 1996; Faruque and Nair, 2002; Merrell et al., 2002; Huq et al., 2003; Lipp et al., 2003; Louis et al., 2003; Zampini et al., 2003; Espeland et al., 2004; Gil et al., 2004; Huq et al., 2005).

A study of the coast of Peru has provided new insights in this regard. Here, cholera surfaced in 1991 after a century of absence in Latin America. Cholera has recurred in Peru since then, following a seasonal pattern, with the greatest number of cases in summer (June–March) in Lima and other major cities along the coast. The detection of *V. cholerae* followed both ambient and sea surface temperature increases and coincided with, or preceded, annual outbreaks of cholera in summer (Huq and Colwell, 2003; Lipp et al., 2003). Off the Peruvian coast, there was a sig-

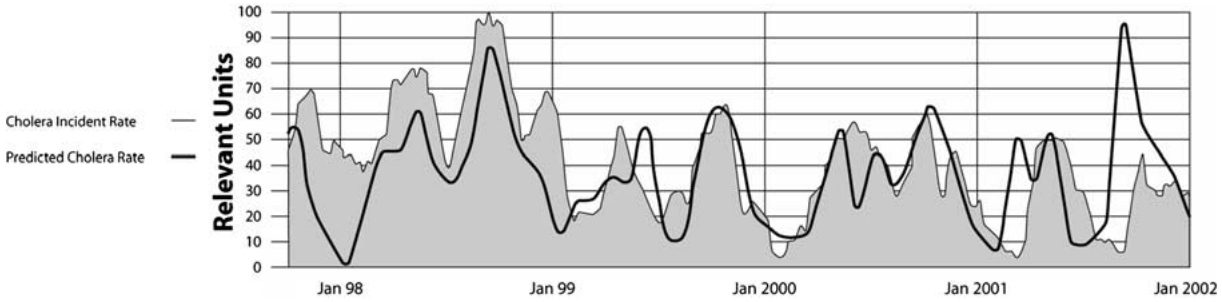

Figure 1. Time series comparison of predicted and observed cholera incidence in Matlab, Bangladesh, 1998–2002. Predicted Cholera Rate is calculated based on sea surface temperature and sea surface height data measured by satellite remote sensing data, and chlorophyll. Cholera Incidence Rate is actual incidence. Based on Calkin and Colwell [unpublished data].

nificant correlation between cholera incidence and elevated sea surface temperature from October 1997–June 2000, which included the 1997–1998 El Niño event (Gil et al., 2004). This link suggests that an early-warning system for cholera risk could be established for Peru and neighboring countries. Although not related directly, both El Niño events and cholera outbreaks have increased since the 1970s. This pattern has emerged in both Peruvian waters and the Bay of Bengal. Sea surface temperature and height, as well as plankton blooms, can be remotely sensed and thus used to forecast outbreaks of cholera (Colwell, 1996).

In addition to laboratory and satellite studies, social science has contributed to our understanding of cholera. Sari cloth, available even in the poorest household, was found to be useful for removing the cholera bacteria attached to particulates and plankton from water for households, including drinking water, in Bangladesh. Laboratory studies showed that old sari cloth folded at least four times filtered out more than 99% of the *V. cholerae* attached to plankton. A 3-year study in 65 villages in Matlab, Bangladesh, demonstrated the incidence of cholera was roughly half among those who used sari filters compared to the control (Colwell et al., 2003).

The full picture of cholera from a human–natural systems perspective has clearly come together recently, based on the sea surface temperature (SST) and sea surface height (SSH) correlations with disease outbreaks (Colwell, 1996; Lobitz et al., 2000; Pascual et al., 2000). The linkage of disease cycles over a four decade time series with regional climate, rainfall, river discharge, and flooding has now been demonstrated (Koelle et al., 2005). This body of research establishes the linkages across time and space scales in the dynamics of the regional system, the pathogen, and nonlinear human susceptibility levels. The picture that has emerged is that of a causal chain involving regional climatic patterns, river basin rainfall variability, river discharge and flooding, and transmission variability. The interannual variability shows a strong correspondence to climate patterns at long periods (for over 7 years for monsoon rains and Brahmaputra river discharge) and at shorter periods (under 7 years for flood extent in Bangladesh, sea surface temperatures in the Bay of Bengal, and the El Niño Southern Oscillation). Calkin and Colwell [unpublished data] have developed a predictive model that has proven uncannily accurate (Fig. 1).

Comparison with Leptospirosis and Other Waterborne EIDs

Another globally reemerging waterborne disease, leptospirosis, the subject of one of three methodological case studies during in the recent *Social–Ecological Systems and Emerging Infectious Diseases* meeting (Lewis, 2005; Vinetz et al., 2005), could not be more dissimilar to cholera in its biology and in the epidemiological and basic research attention received. Yet striking similarities with cholera are surfacing that suggest its emergence follows a similar pattern of coupled human–natural system dynamics. Outbreaks commonly are associated with seasonal rainfall and floods, and like cholera, according to local knowledge held by taro farmers (Vinetz et al., 2005), with drought conditions. If confirmed, this would lend further support to a disease emergence model incorporating the effects of anthropogenic environmental change on the hydroecology of natural drainage basins (local watersheds or river basins), contributing to decreased ecological resilience and, thereby, an increased frequency of extreme floods and droughts (Kaneshiro et al., 2005;

[Wilcox et al., unpublished data]). Even without an increase in climate variability predicted to occur with anthropogenic global climate change, the interaction of natural rainfall variability with land use changes (e.g., increasing impervious surface area associated with urbanization) can explain, and is predicted to contribute to, both increased flood and drought conditions. Either appears to promote pathogen spread and survival in the environment, host–host transmission, higher prevalence in host reservoirs, increased environmental contamination by pathogenic bacteria shed by hosts, and the increased risk of human exposure as a causal chain.

This explanation of how climate patterns and rainfall variability interact with land and ocean processes to increase both the pathogen reservoir "pool" and the frequency of human contact with pathogens, may be generally applicable to other emerging infectious diseases caused by waterborne pathogens (*Campylobacter*, *Cryptosporidium*, *Cyclosporidium*, norovirus, rotavirus, and even *Escherichia coli*). Human activity contributes through mechanisms linked across vastly different time and space scales: human behavior and exposure to contaminated water in the household, village, or city; river basin, drainage basin, or catchment management—especially related to agriculture—affecting water quality, pathogen survival, and transport; and global climate change potentially causing more extreme weather conditions, including storm and rainfall variability in general (Curriero et al., 2001). Human mediated transport of these pathogens and their variants can be added as a global-scale mechanism. Expressing these relationships, which produce nonlinear behavior, including the abrupt and as yet unpredictable changes in microorganisms, their ecology, and the infectious diseases they cause, is very difficult. However, a human–natural systems perspective has begun to provide some insights into how to approach the problem of at least predicting the circumstances that facilitate disease emergence. Combining what cholera has taught us with the model of reemerging zoonotic and vectorborne diseases described below may provide the basis for a general theory of infectious disease emergence.

Model of Zoonotic and Vectorborne EIDs

A human–natural systems perspective also has been used to explain zoonotic and vectorborne EIDs (Wilcox and Gubler, 2005). A theoretical framework or "blueprint" depicted in Figure 2, describes disease emergence as involving biological processes operating on the scale of molecules and cells to that of coupled, regional-scale, human–natural systems. Yet it stresses the demographic and social drivers of regional environmental change spreading geographically across the globe, as well as the failure of disease control and public health policy. Urbanization, agricultural intensification, and habitat loss and alteration, in particular, driven by population growth and consumption, characterize the model. In general, this blueprint stresses the role of regional environmental change described by land use transformations and their drivers (population, technological capacity, and sociocultural organization). These transformations have acted in concert with inadequate or inappropriate policies or methods of vector control and disease prevention that have unwittingly promoted disease emergence. The changes taking place (at the second and third levels in Fig. 2) affecting pathogen and host ecology and evolution (e.g., selection for insecticide and antimicrobial resistance) include public health agencies' actions, or inaction. These ecological-evolutionary dynamics are micro-scale in time and space. However, the cumulative effect of these micro-scale processes involving pathogen and host adaptation, and range expansion (or reexpansion), ultimately can produce regional and even global consequences.

This blueprint places more of an equal emphasis on human and natural system behavior. In particular, it emphasizes the interaction of regional environmental change and declining public health infrastructure that has occurred on a dramatic scale in tropical developing regions in recent decades. Thus, in the same period and places in which the most significant human–environmental transformations have been taking place in recent history, divestment in public health infrastructure, including in effective hygiene and disease control measures, has also been occurring. This is an elaboration on the argument that institutional factors, combined with dramatic changes in demographic and social conditions, including an exponential increase in global transport, are responsible for much of the global emerging infectious disease problem (Gubler, 1989; 1998; 2002a,b). In fact, this view is complementary with that described for cholera and leptospirosis above. But it emphasizes more strongly the role of regional environmental change largely associated with urbanization, agricultural intensification, and natural habitat alteration, rather than the role of climate variability (presently observed or that predicted due to anthropogenic

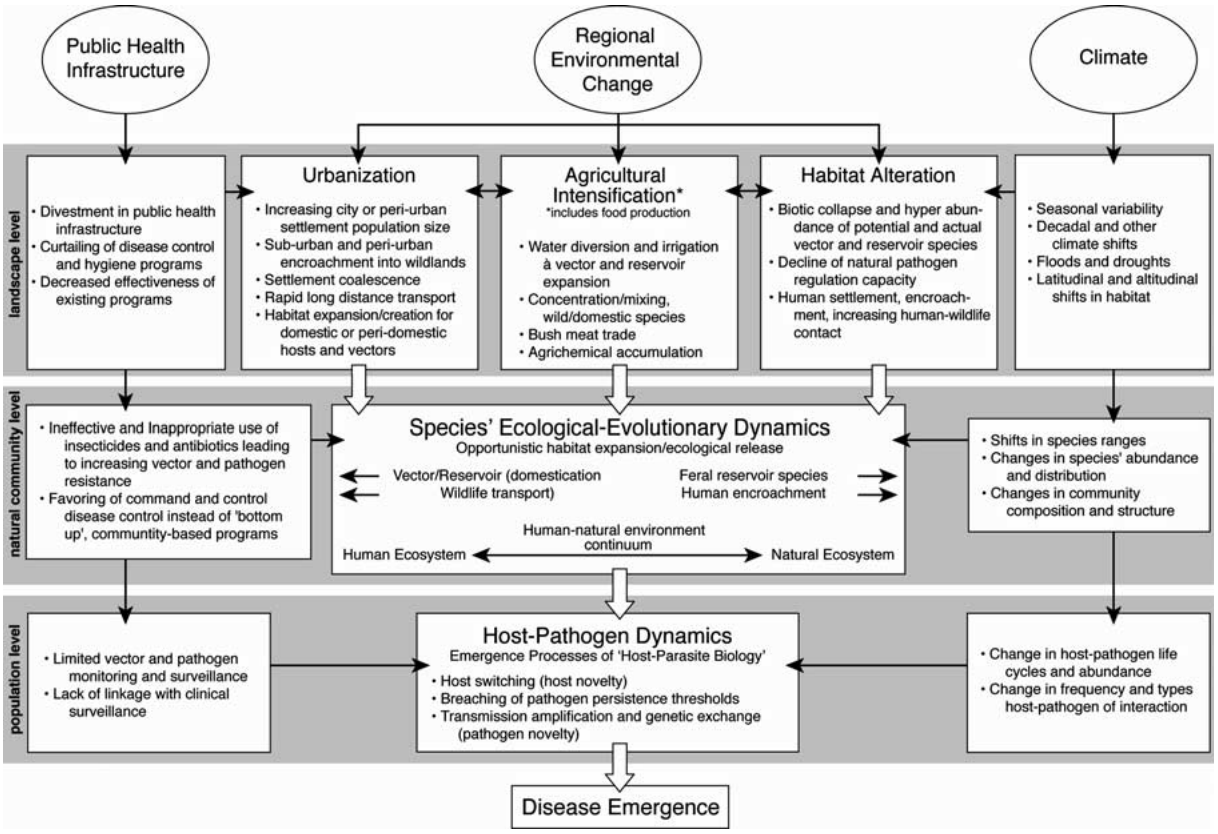

Figure 2. Blueprint illustrating environmental factors associated with emergence of disease. Regional environmental change, which is influenced significantly by population growth, resource consumption, and waste generation, plays an important role in the emergence of infectious disease, especially in tropical developing regions. Associated land use and transformation of resource production (urbanization, agricultural expansion and intensification, and natural habitat alteration), have produced changes in ecological systems, notably in landscapes and, in turn, their natural communities and ultimately in their pathogen, animal host, and human populations. Thus, the altered "host-pathogen" dynamics facilitate novelty, including exchange of genetic material among pathogens, resulting in rapid adaptations by the pathogens and more frequent generation of novel pathogen variants. Some will be more virulent, infective, and/or capable of enhanced transmission, contributing to disease reemergence or emergence. Factors related to public health infrastructure and climate variability, and their interactions with regional environmental change, also contribute significantly to disease emergence. In addition to natural climate variability and climate shifts, the climate change contribution of global warming may well contribute further to disease emergence.

global climate change). Geographic shifts in vectors, effects of temperature change on pathogens and transmission rates, and other factors predicted by global climate change models (including increased climate variability) potentially will magnify disease emergence already caused by these human–natural system dynamics, again an argument for the holistic perspective.

Pathology of Disease Control

The emphasis on inadequate or inappropriate institutional actions (or inactions) coupled with the response of vectors, pathogens, and ecological systems (which in many cases are believed to provide natural control mechanisms), is particularly well suited to the application of the body of theory derived from the social–ecological systems and resilience literature, developed mainly to explain failures in natural resource management systems. This theory, centered on the so-called adaptive cycle has been used to help explain why, in most cases, such management efforts have failed (e.g., most managed fisheries have either collapsed or have been over-fished, and efforts to control floods or pests frequently have resulted in worse floods or pest outbreaks). It also has been applied, in a very limited but promising degree, to the

Table 1. Key Concepts Associated with the Recent Synthesis of Coupled Human–Natural Systems and Complexity Theory and Their Relevance to Emerging Infectious Diseases, Employed at the Meeting ''Social –Ecological System and Emerging Infectious Diseases''

Concept	Description/Definition	Relevance to EIDs
SES	The integrated concept of humans-in-nature recognizing the delineation of social and ecological systems is artificial and arbitrary (Berkes et al., 2003). Draws from the accumulated empirical evidence concerning the behavior of ecosystems and their sustainability (Berkes and Folke, 1998).	The collective body of theory and concepts associated with the SES framework provides interdisciplinary approaches and methods with significant potential for understanding EIDs. Sustainability, broadly and operationally defined in terms of human health, is integral to managing infectious disease emergence.
Resilience	Defined in the SES context as ''ecosystem resilience,'' a nonequilibrium concept. It is the magnitude of a disturbance that can be absorbed or buffered by a system without the system undergoing a fundamental change or reconfiguration. (Holling and Gunderson, 2002).	Both social and ecological systems can exhibit resilience, in terms of organizational flexibility and adaptive management to learning and the capacity of ecosystems absorb disturbance. Decreased resilience (increased vulnerability) tends to encourage disease emergence.
Surprise	The cognitive disagreement between system behavior and a priori expectations inherent in complex adaptive systems (Gunderson, 2003). Different types of *surprise* have been recognized in social–ecological systems: local surprise, cross-scale surprise, and true novelty.	EIDs generally fit this definition of *surprise* in that the appearance of the current global EID trend was generally unexpected, though the warning signs appear obvious retrospectively. This typology shows possible applicability to understanding EIDs.
Barriers and bridges	*Barriers* are represented by the impediments to values and knowledge exchange that result from institutional constructions and create dysfunctionality in a system. *Bridges* are the links between agencies and disciplines that become possible through an integrated understanding of systems (Gunderson et al., 1995).	Understanding EIDs requires collaboration of people from a wide range of disciplines, within and outside biomedicine. Managing EIDs in general, and controlling specific diseases, requires similar collaboration among many sectors in addition to public health. An integrated vision of ''disease systems'' is required to provide the ''blueprint'' for action.
Adaptive cycle	A metaphor describing the repeated cycles of change apparently exhibited by ecological, economic, institutional systems—and linked human–natural systems—through four distinct phases: exploitation, conservation, release, and organization (Holling and Gunderson, 2002).	The first two phases of the adaptive cycle correspond to a ''pathology of disease control'' in which institutions become increasingly inflexible (conservative) after initial success in controlling a disease, followed by a period of denial as warning signs go unheeded until a crisis develops.

EIDs, emerging infectious diseases; SES, social–ecological systems.

problem of infectious disease emergence (Holling, 1986; Holling et al., 2002). Other investigators (Waltner-Toews, 2001) have also described the imperative to consider EIDs from a complex, coupled human–natural systems perspective.

In fact, a ''syndrome'' has been described, called the ''pathology of regional development and ecosystem management,'' in which a causal chain of events is precipitated by human action, followed by natural system reaction, etc. (Gunderson et al., 1995). This could be extended to emerging infectious diseases and be termed ''the pathology of infectious disease control.'' The basic features of the new synthesis by Holling (2001) and Holling et al. (2002) are most readily explained in terms of the definitions of the core concepts involved (Table 1). A remarkable feature of this ''model'' is its demonstration of how disease emergence results from the interaction of variables on vastly different time and space scales, as alluded to above (Fig. 2).

While pathogen life cycles and human infection events, for example, act as ''fast variables'' with periodicities on the scale of days, weeks, or less, regional environmental and global climate change represent ''slow variables'' with periodicities on the scale of decades or longer. These variables interact through the mediation of cross-scale influences, for example, floods or drought, and their increased severity because of the loss of ecological resilience arising from anthropogenic land use change. The regional environmental change model of disease emergence and the ecological resilience model noted above, that incorporates the role of extreme weather events, readily integrate into a single general model that largely explains the current global EID phenomenon. It may provide a basis for developing future scenarios, including those incorporating an increased frequency of extreme meteorological events predictable from anthropogenic global temperature increase.

Holling (1986), and subsequently Holling et al. (2002), used this theoretical framework to explain the resurgence of malaria in Africa. Janssen and Martens (1997) took a similar approach, developing a model simulating malaria prevalence, taking into account adaptation of the vector and parasite and adaptive management in the application of insecticide according to mosquito abundance. However, the ''adaptive cycle'' of Holling et al. (2002) reflects the lack of adaptive management. It metaphorically describes a chain of events characteristic of coupled human–natural systems whereby the social and economic environment changed (more development became possible in areas protected from malaria by vector control programs), followed by a narrowing of the agencies' goal (socioeconomic initially), from the agencies' objective to spray insects and reduce mosquito populations and treat the human population, to that of distributing insecticide or antimalarial drugs. However, the persistent reduction in mosquitoes led to gradual increases in the number of people susceptible to malaria and mosquitoes resistant to insecticide. The objective to control the vector and disease succeeded, until the system itself evolved to a less resilient state producing, paradoxically, less control of the vector and disease, ending up with a return of episodic outbreaks of malaria.

Reemergence of Dengue as a Human–Natural System Phenomenon

The subject of case study during the recent *Social–Ecological Systems and Emerging Infectious Diseases* meeting, dengue is a classic reemerging infectious disease from which much can be learned by using a human–natural systems perspective. Although new infections are reported annually on a lesser scale (approximately 50 million) than cholera and malaria, dengue has become one of the most troubling global infectious diseases, because it is reemerging at a faster rate, with a more severe form (dengue hemorrhagic fever), than perhaps any other. As summarized by Spiegel et al. (2005) and described previously (Gubler, 1997; Pinheiro and Corber, 1997), dengue fever and dengue hemorrhagic fever (DF/DHF) has gone from being an insignificant health problem 20 years ago to one of the world's most important global public health problems today. Clearly, the interaction of key policy changes in vector control strategy with dramatic changes in demographic and social conditions accompanying unplanned urbanization can be concluded to be responsible for reemergence of DF/DHF in the Americas (Gubler, 2002a).

An arboviral (arthropod transmitted) virus, transmission of dengue is dependent entirely on the mosquito *Aedes egypti;* herein lies the fundamental biological factor contributing to this pathogen's success. Outside its native range in Africa from which it spread (and ultimately the dengue virus with it) centuries ago, *A. egypti*'s adaptability to domestic environments, including its capability of readily breeding inside dwellings, makes the disease difficult to control in the absence of integrated ''top-down'' and ''bottom-up'' vector control programs, beginning virtually at the neighborhood level. *A. egypti* had been, in fact, all but eliminated from Latin America by the 1970s, but its geographic distribution has since reexpanded and now extends from Paraguay to the U.S.–Mexico border. While many governments and agencies carried out ineffective, if any, vector control programs, the mosquito's habitat (human settlements) and the virus' host population (humans) grew exponentially. Ironically, reducing dengue to its pre-1970's level will require a vastly greater effort than before. This time, not only will it require a much higher level of planning and coordination of vector control efforts, but many of the same challenges facing global sustainability: increased rates of human migration, driven by poverty and political instability, and sprawling and overcrowded cities, where unscreened housing, dense residential areas with large numbers of household breeding sites (e.g., nonbiodegradable containers), and absence of waste management, sewer and water systems, produce ideal conditions for mosquito breeding.

Examining the history of DF/DHF and a number of country-level programs in the Americas and Asia and using

a social–ecological system perspective, Spiegel et al. (2005) identified a number of important elements of successful control programs. Without going into detail, but relevant to this discussion, is the fact that the elements identified, using this approach, largely reflect what would have been required to avoid the system failure that is suggested by ''pathology of disease control.'' That is, adaptability, both of programs to control the mosquito vector's changing behavior and to educate the public, addressing local to regional scale in the control efforts and the capacity to learn from experience, were found to be critical elements absent from the failed programs and key in the successful programs. Barriers (defined in Table 1) to their development and sustainable implementation include lack of interdisciplinary cooperation, reinforced by differences in values held by the different players and the failure to take into account the complexities of coupled ecological and social systems.

Toward a General Theory

The case of cholera, along with the preliminary studies of the disease ecology of leptospirosis, and the cases of malaria and dengue fever, all share a number of features. First, their resurgence generally was not predicted, and can be characterized by what social–ecological systems theory calls ''surprise,'' the unexpected result (Table 1) of the abrupt, nonlinear or discontinuous behavior characteristic of ecosystems arising, for example, from interaction between key variables that operate at distinctly different scales—a faster variable interacting with slower variables. Spatially contagious processes, such as epidemics that spread geographically, occur only when there is an interaction among a trigger, a pathogen jumping to a new intermediate host, or a human infection event (a fast variable), and a sufficiently large and connected population of susceptible hosts or humans (a slow variable). Thus, demographic, social, and landscape transformations occurring on the scale of a regional system over a period of decades or more, interact with changes in host–parasite/pathogen dynamics that occur on the scale of a single watershed or catchment area, with a periodicity of days or months.

How these cross-scale mechanisms produce regional- or global-scale disease emergence patterns is outside the realm of conventional epidemiology or analytical approaches generally. Such cross-scale processes are, however, characteristic of ecosystems (Holling, 1992) and coupled human–natural systems (Gunderson and Holling, 2002; Berkes et al., 2003), whose dynamics are influenced by the interaction of variables and dynamics operating on vastly different time and space scales that involve natural processes discontinuously distributed, as shown in Figure 3. An essential component of this dynamic, not easily conveyed visually (at least within the graphical representation of time and space scales), is that of resilience as a variable, both in the human and natural sub-systems comprising the human–natural environment (or social–ecological system) as a whole. This can be envisioned as the increased or diminished capacity of the system to absorb impacts of periodic events, whose timing and location is inherently unpredictable, at least at the level of current scientific understanding and available models. For example, deforestation lessens the capacity of a watershed or river basin to absorb storm events and prevent excessive runoff that is laden with nutrients and/or pathogens contributing to disease emergence. Similarly, narrowly focused and inflexible bureaucracies are unable to detect and learn from such events, so as to be able to respond with appropriate measures that either address the problem of lost resilience in the natural environment or increased vulnerability of human populations to infections, outbreaks, or epidemics—as the pathogen expands from a local toward a global scale, via cross-scale influences. The spread of waterborne pathogens by flooding and other pathogens by human migration, transport, or other spreading modalities, is illustrated by the widening plume in the center of the space-time graph (Fig. 3).

Connecting Climate Change and the Effects on Human Health

The complexity and uncertainty associated with global climate change and its effect on disease incidence and distribution have proven challenging from both the research and policy standpoints. As a public health issue this can, unfortunately, be misconstrued as suggesting a lack of consensus among experts that the potential human health consequences—though as yet not clearly demonstrated—are of significant concern (Colwell et al., 1998). Uncertainty, due both to an incomplete picture of how climate and pathogens interact as well as the complexity inherent in human–natural systems, has been a major factor. Moreover, few longitudinal disease databases are long enough in time to study long-term trends required to monitor health effects

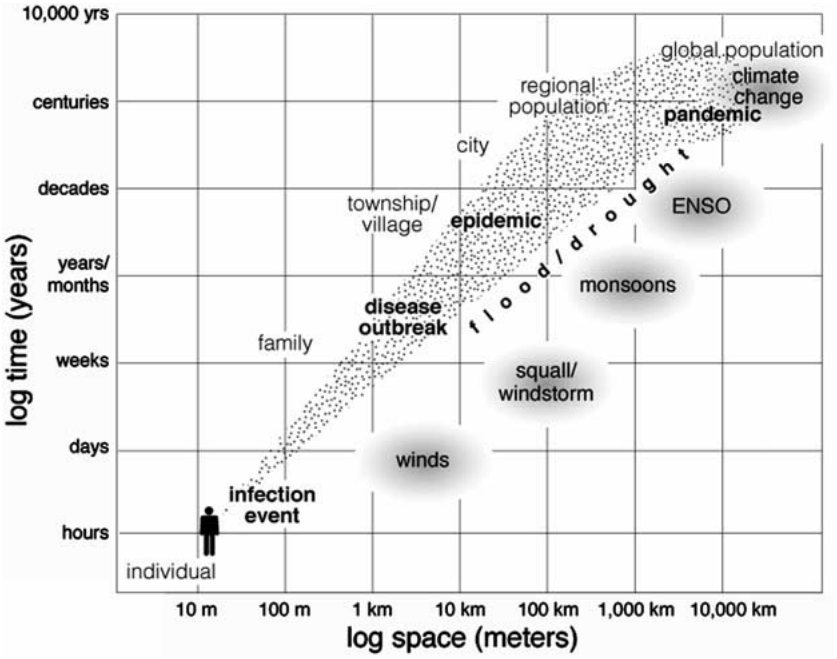

Figure 3. Time and space scales of demographic units, disease processes, and environmental events. Climate variability and meteorological events, with distinct periodicities and occurring on specific geographic scales, interact with the dynamics of the pathogen–host (human populations in this example) that occur on similar scales. For example, a local windstorm or rainstorm can disperse mosquitoes or waterborne pathogens within a locality. Factors, such as social behavior and specific environmental conditions that are characteristic for a given human population, can determine whether or not a disease agent will flourish in an environment and be transmitted among hosts, including humans, in a particular settlement. Meteorological events that affect the environment, such as seasonal monsoon rains or the El Niño Southern Oscillation (ENSO), which occur on a larger scale in time and space, can induce drought or flood conditions. The result can be the spread of a disease agent(s), setting the stage for epidemics, the occurrence of which will, in turn, depend on human population factors, such as human behavior and the level of herd immunity. Additional variables can facilitate disease emergence, i.e., increased connectivity created by urbanization, increased rate of regional migration, and global transport; and/or decreased social and ecological system resilience, resulting, for example, in more severe and larger scale impacts of the meteorological event.

of climate change. However, the progress made in understanding cholera's reemergence and that of zoonotic and vectorborne EIDs generally, has been significant and has, to some extent, begun to reduce uncertainty.

Most modeling of the effects of climate change have been done with the focus on malaria (e.g., Martens et al., 1999; Rogers and Randolf, 2000), the only zoonotic and vectorborne EID for which adequate climate change or variability models and surveillance data of sufficient resolution were available (van Lieshout et al., 2004), at least until recently (e.g., Hales et al., 2002; Brownstein et al., 2005). Though at first considered too simplistic (Rogers and Randolph, 2000), the malaria models have attempted to incorporate an increasing realism, taking into account altitudinal instead of latitudinal shifts alone, and the adaptive capacity of public health infrastructure, in addition to socioeconomic conditions (Haines and Patz, 2004; van Lieshout et al., 2004). The MARA (Mapping Malaria Risk in Africa) project is one such example. Derived maps of malaria suitability (based on climate) were compared with previously collected, independent data including surveys, site visits, parasite rates, and spleen rates gathered in several East African countries and providing a more thorough validation than past climate-malaria modeling (MARA/AMRA, 1998). Excluding any increase in population, an increase of 16%–28% in person-month exposure to malaria risk by year 2100 was determined (Tanser et al., 2003). In spite of these improvements and the availability of increasingly high resolution geographic data, the reliability of projections for vectorborne diseases, in general, has been hampered by the complex and nonlinear dynamics of the relationship between the vector population

and disease prevalence. This is a result of the interactions between transmission rates, the rate of development and duration of temporary acquired immunity, and the age structure of the population, for which the field data are too limited to resolve (Rogers et al., 2002).

However, even with such data, the inability of present modeling approaches to capture the uncertainty, nonlinearity, and the cross-scale nature of pathogen–vector–human host relationships—and the ecosystems in which they are embedded—represents a major challenge. Nor can current modeling approaches account for locally or regionally abrupt climatic shifts that have proven societally disruptive in the past (Alley et al., 2003). Predicting the timing, spatial scale, and intensity of such shifts and their effects on transmission rates, host susceptibility, socioeconomic conditions, and public health infrastructure defies conventional analytical modeling. However, some projections for malaria have incorporated measures of ''adapative capacity'' based on expert opinion (van Lieshout et al., 2004). This notion has received recent attention, due to the coastal disasters in South Asia and the U.S., producing qualitative indicators of resilience (Adger et al., 2005). These potentially are quantifiable and could at least provide a basis for assessment and predictions of local- and regional-scale social–ecological resilience in response to the effects of abrupt change.

Although progress awaits better and more field surveillance data and modeling methods that combine the power of multivariate statistical analysis with the realism of complex systems thinking, a significant amount of ecological theory and empirical data exists that link anthropogenic environmental change and pathogen emergence. Moreover, the validity and robustness of some of the key relationships, including the quantitative expressions describing them, are beyond dispute. For example, the mechanisms involved and the relationship of species extinction to habitat loss, in general (Rosenzweig, 1995), and the case of tropical forest, in particular (Laurence and Bierregaard, 1997), are relatively well understood, empirically demonstrated, and follow quantitative rules that are among the most thoroughly documented in ecology. The effect of climate change on habitat in terms of latitudinal and altitudinal shifts resulting in the contraction in the areal extent of many types of habitat is virtually certain. So, too, is the corresponding reduction in the sizes of local and regional populations of vulnerable wildlife species. These direct impacts on natural ecological communities, along with the effects of urbanization and agricultural intensification shown in Figure 2, undoubtedly will affect pathogen emergence in ecosystems through multiple feedback loops linking ecosystem disturbance, local extinction, and disease (Harvell et al., 2002). Ecosystem-focused infectious disease research will require monitoring and surveillance that integrate wildlife and human disease (Deem et al., 2005).

The decline or local extinction of species also diminishes ecosystem resilience (Chapin et al., 1997; 2005; Elmqvist et al., 2003), thus adding to their vulnerability to climate variability. A causal link between the present global warming trend and more extreme meteorological events remains to be established statistically. However, the interaction of the increased number and intensity of tropical storms that has been recently demonstrated (Webster et al., 2005), with the increased vulnerability of developed landscapes to floods and drought, has undeniably contributed to disease emergence.

Conclusions: The Challenge of Forging a New Paradigm

The metaphor of biocomplexity was inspired by the interdisciplinary imperative, not only to integrate more completely the natural sciences, but also to understand the role that natural and social system interactions play in the dynamics of our planet's systems and how these influence sustainability. The coupled human–natural systems perspective embodied in these ideas is fundamental to the development of a science of sustainability. As described by Kates et al. (2001), it requires addressing core questions, such as how these interactions can be incorporated into emerging models and conceptualizations of long-term trends in environment and development. What determines the vulnerability or resilience for particular types of ecosystems and human livelihoods? How can meaningful ''limits'' or ''boundaries'' be defined to provide effective warning of conditions beyond which nature–society systems incur significantly increased risk?

No issue could be a more fundamental measure of sustainability than public health, and the increasing emergence and reemergence of infectious diseases globally is possibly the world's most challenging public health problem today. Yet this problem is incomprehensible without a vastly broadened research perspective, if not an entirely new paradigm—one that is encompassed by biocomplexity and new conceptual frameworks provoking new theories and models. The body of theory associated with new

literature on social–ecological systems and resilience, as well as other schools of thought employing a human–natural system perspective show promise for advancing interdisciplinary agenda for research and practice aimed at controlling infectious diseases.

This noble goal will not be reached easily and will require science and education initiatives that cross disciplinary as well as institutional, societal, and cultural boundaries (e.g. Kaneshiro et al., 2005), much like the case of HIV/AIDS. Clearly, without appreciating the complex dynamic between social and ecological processes so readily apparent for the diseases discussed here, and employing the related frameworks and perspectives, we will forego the ability to gain insights into the underlying causes of the recent historical upsurge in emerging infectious diseases.

Acknowledgments

This work was supported by conference grants from the U.S. Public Health Service, R13TW007300—NIH Roadmap initiative ''Research Teams of the Future'' and the Henry M. Jackson Foundation for the Advancement of Military Medicine Telemedicine and Advanced Technology Research Center (TATRC) (USAMRAA Emerging Infectious Disease Conference—05357001) (Principal Investigator, B.A.W.).

References

Adger WN, Hughes TP, Folke C, Carpenter SR, Rockstrom J (2005) Social-ecological resilience to coastal disasters. *Science* 309:1036–1039

Aldhous P, Tomlin S (2005) Avian flu special: avian flu: are we ready? *Nature* 435:399

Alley RB, Marotzke J, Nordhaus WD, Overpeck JT, Peteet DM, Pielke RA Jr, et al. (2003) Abrupt climate change. *Science* 299:2005–2010

Berkes F, Colding J, Folke C (2003) *Navigating through Social-ecological Systems: Building Resilience for Complexity and Change,* Cambridge, UK: Cambridge University Press

Berkes F, Folke C (1998) Linking social and ecological systems for resilience and sustainability. In: *Linking Social and Ecological Systems: Management Practices and Social Mechanisms for Building Resilience*, Berkes F, Colding J, Folke C (editors), Cambridge, UK: Cambridge University Press, pp 1–24

Brownstein JS, Holford TR, Fish D (2005) Effect of climate change on Lyme disease risk in North America. *EcoHealth* 2:38–46

Burroughs T, Knobler SL, Lederberg J (editors) (2002) *The Emergence of Zoonotic Diseases: Understanding the Impact on Animal and Human Health,* Washington, DC: Institute of Medicine The National Academy Press

Chapin FS, Walker B, Hobbs RJ, Hooper DU, Lawton JH, Sala OE, et al. (1997) Biotic control over the functioning of ecosystems. *Science* 277:500–504

Chapin FS, Eviner VT, Talbot LM, Wilcox BA, Magness DR, Brewer CA, et al. (2005) Disease effects on landscape and regional systems: a resilience framework. In: *Infectious Disease Ecology: Effects of Ecosystems on Diseases and of Diseases on Ecosystems*, Ostfeld R, Keesing F, Eviner VT (editors), in press

Colwell RR (1996) Global climate and infectious disease: the cholera paradigm. *Science* 274:2025–2031

Colwell RR (1998) Balancing the complexity of planet's living systems: a twenty-first century task for science. *BioScience* 48:786–787

Colwell RR (2004) Infectious disease and environment: cholera as a paradigm for waterborne disease. *International Microbiology* 7:285–289

Colwell RR, Epstein PR, Gubler D, Maynard N, McMichael AJ, Patz JA, et al. (1998) Climate change and human health. *Science* 279:963

Colwell RR, Huq A, Islam MS, Aziz KMA, Yunus M, Huda Khan N, et al. (2003) Reduction of cholera in Bangladeshi villages by simple filtration. *Proceedings of the National Academy of Sciences USA* 100:1051–1055

Curriero FC, Patz JA, Rose JB, Lele S (2001) Analysis of the association between extreme precipitation and waterborne disease outbreaks in the United States, 1948–1994. *American Journal of Public Health* 91:1194–1199

Deem SL, Eviner VO, Ward JR, Wilcox BA (2005) Research frontiers in infectious disease ecology: an interdisciplinary agenda for a changing world. In: *Infectious Disease Ecology: Effects of Ecosystems on Diseases and of Diseases on Ecosystems*, Ostfeld R, Keesing F, Eviner VT (editors), in press

Elmqvist T, Folke C, Nyström M, Peterson G, Bengtsson J, Walker B, et al. (2003) Response diversity, ecosystem change, and resilience. *Frontiers of Ecology and Environment* 1:488–494

Espeland EM, Lipp EK, Huq A, Colwell R (2004) Polylysogeny and prophage induction in secondary infection in *Vibrio cholerae*. *Environmental Microbiology* 6:760–763

Faruque SM, Nair GB (2002) Molecular ecology of toxigenic *Vibrio cholerae*. *Microbiology and Immunology* 46:59–66

Gil AI, Louis VR, Rivera IN, Lipp E, Huq A, Lanata CF, et al. (2004) Occurrence and distribution of *Vibrio cholerae* in the coastal environment of Peru. *Environmental Microbiology* 6:699–706

Gubler DJ (1989) *Aedes aegypti* and *Aedes aegypti*-borne disease control in the 1990's: top down or bottom up. *American Journal of Tropical Medicine and Hygiene* 40:571–578

Gubler D (1997) Dengue and dengue hemorrhagic fever: its history and resurgence as a global public health problem. In: *Dengue and Dengue Hemorrhagic Fever*, Gubler D, Kuno G (editors), Wallingford, UK: CAB International, pp 1–21

Gubler DJ (1998) Resurgent vector-borne diseases as a global health problem. *Emerging Infectious Diseases* 4:442–450

Gubler DJ (2002a) Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem in the 21st century. *Trends in Microbiology* 10:100–103

Gubler DJ (2002b) The global emergence/resurgence of arboviral diseases as public health problems. *Archives of Medical Research* 33:330–342

Gubler DJ (2004) The changing epidemiology of yellow fever and dengue, 1900 to 2003: full circle? *Comparative Immunology and Microbiology of Infectious Diseases* 27:319–330

Gunderson LH (2003) Adaptive dancing: interactions between social resilience and ecological crises. In: *Navigating Social-ecological Systems: Building Resilience for Complexity and Change*, Berkes F, Colding J, Folke C (editors), Cambridge, UK: Cambridge University Press, pp 33–52

Gunderson LH, Holling CS (2002) *Panarchy: Understanding Transformations in Human and Natural Systems,* Washington, DC: Island Press

Gunderson LH, Holling CS, Light SS (1995) *Barriers and Bridges to the Renewal of Ecosystems and Institutions,* New York: Columbia University Press

Haines A, Patz JA (2004) Health effects of climate change. *JAMA* 291:99–103

Hales S, de Wet N, Maindonald J, Woodward A (2002) Potential effect of population and climate changes on global distribution of dengue fever: an empirical model. *The Lancet* 360:830–834

Harvell CD, Mitchell CE, Ward JR, Altizer S, Dobson AP, Ostfeld RS, et al. (2002) Climate warming and disease risks for terrestrial and marine biota. *Science* 296:2158–2162

Holling CS (1986) The resilience of terrestrial ecosystems: local surprise and global change. In: *Sustainable Development of the Biosphere*, Clark WC, Munn RE (editors), Cambridge, UK: Press Syndicate of the University of Cambridge, pp 292–320

Holling CS (1992) Cross-scale morphology, geometry, and dynamics of ecosystems. *Ecological Monographs* 62:447–502

Holling CS (2001) Understanding the complexity of economic, ecological, and social systems. *Ecosystems* 4:390–405

Holling CS, Gunderson LH (2002) Resilience and adaptive cycles. In: *Panarchy: Understanding Transformations in Human and Natural System*, Gunderson LH, Holling CS (editors), Washington, DC: Island Press, pp 25–62

Holling CS, Gunderson LH, Peterson GD (2002) Sustainability and panarchies. In: *Panarchy: Understanding Transformations in Human and Natural System*, Gunderson LH, Holling CS (editors), Washington, DC: Island Press, pp 63–102

Horwitz P, Wilcox BA (2005) Parasites, ecosystems and sustainability: an ecological and complex systems perspective. *International Journal for Parasitology* 35:725–732

Huq A, Colwell RR (2003) Direct detection of *Vibrio cholerae* and *ctxA* in Peruvian coastal water and plankton by PCR. *Applied Environmental Microbiology* 69:3676–3680

Huq A, Small EB, West PA, Huq MI, Rahman R, Colwell RR (1983) Ecological relationships between *Vibrio cholerae* and planktonic crustacean copepods. *Applied and Environmental Microbiology* 45:275–283

Huq A, Sack RB, Nizam A, Longini IM, Nair GB, Ali A, et al. (2005) Critical factors influencing the occurrence of *Vibrio cholerae* in the environment of Bangladesh. *Applied and Environmental Microbiology* 71:4645–4654

Kaneshiro KY, Chinn P, Duin KN, Hood AP, Maly K, Wilcox BA (2005) Hawai'i's mountain-to-sea ecosystems: social–ecological microcosms for sustainability science and practice. *EcoHealth* 2 (DOI: 10.1007/s10393-005-8779-z, this issue)

Kates RW, Clark WC, Corell R, Hall JM, Jaeger CC, Lowe I, et al. (2001) Sustainability science. *Science* 292:641–642

Kaufman JS, Poole C (2000) Looking back on ''Causal Thinking in the Health Sciences.'' *Annual Review of Public Health* 21:101–119

Knobler SL, Lemon SM, Najafi M, Burroughs T (editors) (2003) *The Resistance Phenomenon in Microbes and Infectious Disease Vectors: Implications for Human Health and Strategies for Containment. Workshop Summary, Institute of Medicine,* Washington, DC: The National Academy Press

Koelle K, Rodo X, Pascual M, Yunus M, Mostafa G (2005) Refractory periods and climate forcing in cholera dynamics. *Nature* 436:696–700

Janssen MA, Martens WJM (1997) Modeling malaria as a complex adaptive system. *Artificial Life* 3:213–237

Laurence WF, Bierregaard RO Jr (editors) (1997) *Tropical Forest Remnants: Ecology, Management, and Conservation of Fragmented Communities,* Chicago: University of Chicago Press

Lederberg J, Shope R, Oaks SC (editors) (1992) *Emerging Infections: Microbial Threats to Health in the United States, Institute of Medicine,* Washington, DC: The National Academy Press

Lewis ND (2005) Is the social–ecological framework useful in understanding infectious diseases? The case of HIV/AIDS. *EcoHealth* 2 (DOI: 10.1007/s10393-005-8477-x, this issue)

Lipp EK, Rivera ING, Gil AI, Espeland EM, Choopun N, Louis VR, et al. (2003) Detection of *Vibrio cholerae* and *ctxA* in Peruvian coastal waters and plankton by PCP. *Applied and Environmental Microbiology* 69:3676–3680

Louis VR, Russek-Cohen E, Choopun N, Rivera ING, Gangle B, Jiang SC, et al. (2003) Predictability of *Vibrio cholerae* in Chesapeake Bay. *Applied and Environmental Microbiology* 69:2773–2785

Lobitz B, Beck L, Huq A, Wood B, Fuchs G, Faruque ASG, et al. (2000) Climate and infectious disease: use of remote sensing for detection of *Vibrio cholerae* by indirect measurement. *Proceedings of the National Academy of Sciences USA* 97:1438–1443

MARA/AMRA (1998) *Towards an Atlas of Malaria Risk in Africa: First Technical Report of the Collaboration*, Durban, South Africa: MARA/AMRA

Martens P, Kovats RS, Nijhof S, de Vries P, Livermore MTJ, Bradley DJ, et al. (1999) Climate change and future populations at risk of malaria. *Global Environmental Change* 9:S89–S107

Merrell DS, Butler SM, Qadri F, Dolganov NA, Alam A, Cohen MB, et al. (2002) Host-induced epidemic spread of the cholera bacterium. *Nature* 417:642–645

Osterholm MT (2005) Preparing for the next pandemic. *Foreign Affairs* 84:24–37

Pascual M, Rodó X, Ellner SP, Colwell RR, Bouma MJ (2000) Cholera dynamics and El Niño-Southern Oscillation. *Science* 289:1766–1769

Pinheiro FP, Corber SJ (1997) Global situation of dengue and dengue hemorrhagic fever and its emergence in the Americas. *World Health Statistics Quarterly* 50:161

Ravetz JR (1999) What is post-normal science? *Futures* 31:647–653

Rogers DJ, Randolph SE (2000) The global spread of malaria in a future, warmer world. *Science* 289:1763–1766

Rogers DJ, Randolph SE, Snow RW, Hay SI (2002) Satellite imagery in the study and forecast of malaria. *Nature* 415:710–715

Rosenzweig ML (1995) *Species Diversity in Space and Time,* Cambridge, UK: Cambridge University Press

Smolinski M, Hamburg MA, Lederberg J (2003) *Microbial Threats to Health: Emergence, Detection, and Response, Institute of Medicine,* Washington, DC: The National Academy Press

Snow J (1855) *On the Mode of Communication of Cholera,* London: John Churchill

Spiegel J, Bennett S, Hattersley L, Hayden MH, Kittayapong P, Nalim S, et al. (2005) Barriers and bridges to prevention and control of dengue: the need for a social–ecological approach. *EcoHealth* 2 (DOI: 10.1007/s10393-005-8388-x, this issue)

Tanser FC, Sharp B, le Sueur D (2003) Potential effect of climate change on malaria transmission in Africa. *The Lancet* 362:1792–1798

van Lieshout M, Kovats RS, Livermore MTJ, Martens P (2004) Climate change and malaria: analysis of the SRES climate and socio-economic scenarios. *Global Environmental Change* 14:87–99

Vinetz JM, Wilcox BA, Aguirre A, Gollin LX, Katz AR, Fujioka RS, et al. (2005) Beyond disciplinary boundaries: leptospirosis as a model of incorporating transdisciplinary approaches to understand infectious disease emergence. *EcoHealth* 2 (DOI: 10.1007/s10393-005-8638-y, this issue)

Waltner-Toews D (2001) An ecosystem approach to health and its applications to tropical and emerging diseases. *Cad Saude Publica* 17(Suppl):7–22; discussion 23–36

Webster PJ, Holland GJ, Curry JA, Chang H-R (2005) Changes in tropical cyclone number, duration, and intensity in a warming environment. *Science* 309:1844–1846

Wilcox BA, Gubler DJ (2005) Disease ecology and the global emergence of zoonotic pathogens. *Environmental Health and Preventive Medicine* 10:263–272

Zampini M, Canesi L, Betti M, Ciacci C, Tarsi R, Gallo G, et al. (2003) Role for mannose-sensitive hemagglutinin in promoting interactions between *Vibrio cholerae* El Tor and mussel hemolymph. *Applied and Environmental Microbiology* 69:5711–5715