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Disease Ecology and the Global Emergence of Zoonotic Pathogens

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Abstract

The incidence and frequency of epidemic transmission of zoonotic diseases, both known and newly recognized, has increased dramatically in the past 30 years. It is thought that this dramatic disease emergence is primarily the result of the social, demographic, and environmental transformation that has occurred globally since World War II. However, the causal linkages have not been elucidated. Investigating emerging zoonotic pathogens as an ecological phenomenon can provide significant insights as to why some of these pathogens have jumped species and caused major epidemics in humans. A review of concepts and theory from biological ecology and of causal factors in disease emergence previously described suggests a general model of global zoonotic disease emergence. The model links demographic and societal factors to land use and land cover change whose associated ecological factors help explain disease emergence. The scale and magnitude of these changes are more significant than those associated with climate change, the effects of which are largely not yet understood. Unfortunately, the complex character and non-linear behavior of the human-natural systems in which host-pathogen systems are embedded makes specific incidences of disease emergence or epidemics inherently difficult to predict. Employing a complex systems analytical approach, however, may show how a few key ecological variables and system properties, including the adaptive capacity of institutions, explains the emergence of infectious diseases and how an integrated, multi-level approach to zoonotic disease control can reduce risk.

Key words: emerging diseases, ecosystem change, ecology, complexity, sustainable development

Introduction

The growing problem of globally emerging infectious diseases (EIDs) has prompted a substantial effort by the biomedical research establishment to identify the causes and recommend action. As reported in the most recent of a series of volumes (1), a main finding is that the current episode of global infectious disease emergence is the result of a convergence of factors involving complex interactions among numerous variables. This includes genetic, biological, social, economic, political, ecological, and physical environmental factors, and calls for an interdisciplinary research agenda. It is also concluded that "human development and large scale social phenomena are closely associated to infectious disease threats

at a global level," which points to the need for research focused on "social and ecological factors affecting infectious disease emergence" (1).

The phenomenon of globally emerging infectious diseases requires understanding biological systems in the broadest sense and dealing with their extraordinary complexity. This includes processes operating at the level of transmission and evolution of a pathogen within and among host species and humans. It extends to and includes processes involving ecosystems and regional environmental change occurring on a global scale (2). In fact the scale and magnitude of anthropogenic activity has reached a point of virtual co-dominance with natural processes of energy and material flows globally (3).

Understanding these kinds of processes traditionally has been the domain of classical ecology, or natural history, plus systems ecology (4, 5). Adding to this are recent ecological perspectives and models applied at the molecular, cellular level, and organismal levels (6), and others addressing the complexity, multiple variables, cross-scale influences, and dynamic behavior at the level of natural ecosystems (7), and social-ecological systems (8).

Along with the research at the organismal level and below,

that aimed at the level of social-ecological (coupled human-natural systems) is critical to the development of the comprehensive scientific framework necessary for understanding zoonotic infectious disease emergence in particular. Not only does this new area address the dynamic behavior of complex, large scale systems, but also bridges theory from the traditionally separate biological and social science disciplines, thus contributing to the interdisciplinary research agenda also called for in the above reports.

The purpose of this paper is to consider how regional and global zoonotic disease emergence trends might be explained on the basis of current thought in biological ecology including the very recent developments new to the field of infectious disease ecology. Here we draw on ecological science as broadly defined as a basis for identifying causal mechanisms of zoonotic disease emergence, the ultimate goal being to enhance disease prevention and control programs.

Disease Ecology and Factors in Emergence

Several authors have categorized causal factors of infectious disease emergence, including explicitly citing 'ecological' ones involving land use change (9–12) or 'land use drivers' (13), human movement (10, 12), encroachment and wildlife translocation (10, 11), rapid transport (9, 10) and climate change (11, 12). Most recently, the Institute of Medicine (1) described these along with others (13 categories of factors in all) and a model stating the major categories of factors have historically converged to bring about the current global emerging infectious disease crisis. Ecological factors are described as one of four major categories of factors that have converged with social, political, and economic factors; genetic and biological factors; and physical environmental factors. We take a different approach to understanding the interaction of the above factors and their causal relationships by focusing on disease emergence as an ecological-evolutionary phenomenon influenced by human factors. Our interest is in how human factors interact with natural processes and, in particular, how mechanisms operating at levels meaningful to understanding pathogen transmission and evolution can result in regional and ultimately global phenomena (i.e., regional endemism, epidemics, or global pandemics).

As a first step we distinguish between the two broad

Table 1 Human factors in disease emergence

Demographic and societal	Disease and intervention policy
Urban-industrially related	Pathogen, vector, or human biology
• unprecedented human population growth	• drug resistance
	• insecticide resistance
• unplanned and uncontrolled urbanization	• pathogenicity and susceptibility
• non-biodegradable packaging	Public health policy
• increasing modern transportation	• emphasis on emergency response
	• de-emphasis on prevention
Rural development related	• complacency
• agricultural practices	• deterioration of the public health
• deforestation	infrastructure

Based on Gubler (1998).

categories of human factors, 'demographic and societal' and 'disease intervention and policy' suggested previously by Gubler (10) (Table 1). This categorization differentiates between factors associated with specific kinds of environments or ecosystems and those involving biological and policy factors not so associated. However, both can be described as part of a single ecological framework involving interaction of systems of essentially natural versus human design, respectively. Our focus is on the first category from the standpoint of how disease emergence is explained by ecological concepts and principles. This includes some relatively new models and theory not previously used to explain the current trend in increasing emerging infectious diseases. We present a general model of zoonotic disease emergence on this basis. We also discuss recent explanations based on complexity theory for how human behavior and ecosystems interact to contribute to disease emergence.

Classical ecology, or natural history, has been the basis and mainstay of infectious disease research since its origins with 'Koch's Postulates' and subsequent development of microbiology and zoonotic disease epidemiology during the 19th and 20th Centuries (14, 15). Throughout much of its early history, zoonotic disease research involved this descriptive, empirically-based ecology: identifying the life cycle, transmission, incidental and natural hosts of pathogens, along with demographic, life history, dispersal, and habitat attributes of reservoirs and vectors. A substantial theoretical dimension has developed, beginning with Ross's mathematical analysis of malaria transmission (16) and extending to Anderson and May's (17) recent synthesis *Infectious Diseases of Humans*.

Although essential to designing effective prevention and control programs, empirical field based, disease ecology has been neglected in recent years (18). Fortunately, theoretical disease ecology, stimulated largely by the work of Anderson, May and others has flourished and led to a significant syntheses involving application of ecological-evolutionary biology to the study of infectious diseases (19, 20). Parallel to this, systems ecology has begun to extend its domain by applying complexity theory to emerging infections with at least initial suggestions of its implications (6). This development in particular, along with observations from several decades of applications of systems ecology to natural resources and economic development (8, 21–23), have resulted in important insights of significant potential in understanding zoonotic disease emergence as a cross-scale process. This area uses complex systems theory applied to coupled, human-natural systems to explain how processes such as local phenomena can result in a cascade of effects ultimately reaching global proportions. The finding suggests this cross-scale behavior is controlled by relatively few variables, and is mitigated by social and ecological resilience. The loss of this resilience in ecological systems is observed to lead inevitably to unpredictable events or the 'surprise' characteristic of complex systems generally. This combination of social-ecological systems and resilience theory helps explain the unpredictability of disease emergence events. It represents another potentially useful area of application to understanding emerging infectious diseases along with those areas generally considered within the domain of ecology mentioned above:

population ecology and genetics, community ecology, and systems ecology.

Population ecology, genetics and disease emergence

Of particular relevance to disease emergence is the explanation provided by theoretical population biology, already mentioned, of how host (including human) population size determines whether or not a pathogen can persist in a population. The accumulated findings demonstrate thresholds exist, depending on the type of pathogen and host population, below which a pathogen cannot be sustained. Considered in light of the exponentially increasing size of human and domestic host and vector populations in the world, the breaching of thresholds of pathogen persistence can explain much of the increase in emerging infectious diseases.

This can be explained as follows. Although zoonotic disease emergence is not entirely a tropical phenomenon, it is mostly associated with tropical developing regions undergoing the most rapid population growth and ecological changes. Prior to the post-WWII economic era, most regional ecosystems in the tropics consisted of relatively scattered human settlements, and only a few large cities (>500,000) (24). These were separated by large expanses of cropland and pastureland and relatively undisturbed forest. Since then, in what has been the most rapid period of large scale ecological transformation in human history, the pattern has essentially reversed (25). The once scattered settlements and few large cities have coalesced into expansive megacities and surrounding periurban settlements with only remnant patches of undisturbed forest remaining in a sea of cropland, scrub, and ecologically degraded lands. Dacca, Bangladesh, which grew from a population size of 200,000 to 13 million from 1970 to 2003, is one of many examples.

Thus the existence of population density-dependent thresholds for disease emergence is particularly relevant (26, 27). This explains the abrupt transitions of urban diseases between non-persistence to endemic and endemic to epidemic behavior as population densities of susceptible humans, hosts, and vectors reach critical densities. The classic illustration is that of measles which, given its particular transmission rate, requires human settlements with population sizes in excess (>250,000) of what historically existed in most pre-industrial states and geographically isolated populations even today (28). Thus, for example, many infectious diseases endemic on continents have not become established on islands despite their occasional introduction and the occurrence of local outbreaks. The same mathematical ecology that explains why measles and virtually all diseases have threshold densities, explains the much lower thresholds existing for vector-borne diseases such as arboviruses (29). Particularly noteworthy is the theoretical demonstration that the pathogen 'reproductive rate' increases with the square of vector population density. This indicates threshold densities can fast be breached as domestic and peridomestic hosts and vectors expand (or re-expand) their geographic ranges (once they are introduced or re-introduced) and increase their densities. This helps explain the explosive re-emergence of dengue and dengue hemorrhagic fever in the American Tropics as vector populations responded to relaxed

controls and new breeding habitats associated with urbanization (30). This phenomenon can be likened to the gradual build-up of 'dead and down' wood across a forested landscape with a history of fire suppression. The build-up of fuel, like that of host or vector populations, becomes an 'accident waiting to happen' when a single ignition event in one locality, similar to a single infection event, spreads to the entire region.

Another consequence of the dramatically increased densities of humans, host reservoirs, and vectors is the increased number of pathogen genomes. The resulting increased levels of genetic variability can accelerate microbial adaptation, including evolution of pathogenesis, and antimicrobial resistance. Genetic variability increases with population size and density through a variety mechanisms including mutation. The probability of producing more virulent variants not only increases with host population size but also with crowding and co-mingling of different host species (31). In general, parasite (pathogen)-host relations naturally constitute a co-adaptive/evolutionary 'dance' along the pathogenicity threshold, which is likely to be crossed with greater frequency due to unnatural anthropogenic disturbances (32) independent of increasing population sizes and pathogen genetic diversity.

Community ecology and disease emergence

The study of ecological communities and the 'community ecology' theory it has yielded includes a number of principles and mechanisms that describe how human disturbances as well as natural environmental variation can contribute to any of the above population level factors (33). There are a number of implications to zoonotic disease emergence, although most have not yet been described in terms of disease emergence or in the medical, public health, or zoonotic disease literature. Of critical significance from this area of ecology is the general principle of community assembly. Research has demonstrated that communities of arranged predicably in terms of 'assembly rules' (34). This order, in terms of the spatial distribution, composition and the abundance of each species in an ecological community, is affected by interspecific interactions (predation, competition, and parasitism). Density independent factors (e.g., weather, natural catastrophes) play an important, but a more ephemeral role in most ecosystems. The process of community assembly (and disassembly) has been particularly well demonstrated through studies of insular ecosystems, the so-called 'species area relationship,' and the phenomenon of faunal collapse (35–37). A principal outcome and the ecological significance of this body of research first described in terms of the process of 'habitat fragmentation', has been identified as the principal mechanism by which human land and resource use contributes to species extinction (38). Although initially debated, a significant amount of evidence has since accumulated resulting in its general acceptance and applicability, particularly to tropical forest ecosystems (36, 39, 40).

The critical significance of habitat fragmentation and related human disturbances to disease emergence stems from it contribution to the disassembly of orderly natural communities. For example, human activities such deforestation, use of pesticides, and various forms of pollution often result in the loss of predators. In fact, carnivorous mammals typically are the first

species to disappear following forest fragmentation. Their local extinction represents the loss of 'top down' natural control in ecological communities. This can in turn result is an increase in abundance, even 'hyper-abundance' (41), of species such as rodents and biting insects.

Community disassembly and the resulting loss of natural population control mechanisms for such species generally is associated with the conversion of natural landscapes to urban and agriculture landscapes. Broad spectrum pesticide use and habitat simplification, along with habitat fragmentation, are important contributing factors. The reduction in species diversity can contribute to the phenomenon of 'ecological release' in remaining species, whose predators, competitor and parasites are reduced in numbers or eliminated. Some of these may be already serving as zoonotic reservoirs or vectors. If so, ecological release may result in their proliferation. This helps explain why many emerging zoonotic diseases occur in areas where settlement and agricultural expansion recently have encroached into tropical forests. A similar phenomenon, associated with the regrowth of forests in developed regions, can lead to zoonotic disease emergence. The pattern of reforestation in Eastern North America during the past half-century resulted in increased habitat favored by forest edge adapted species such as whitetail deer and white-footed mice. White-tailed deer, the principle host of the adult tick *Ixodes scapulari*, reinvaded the area and with few predators and competitors the population exploded. This pattern of ecological change arguably has been a major factor in the emergence of Lyme disease in this region.

An extension of the concept of 'ecological release' has been suggested to explain the invasive species phenomenon in which super-successful introduced (alien) species have escaped from their natural complement of parasites (42), as well as predators and competitors. This may explain in large part our most successful invasive domestic species, *Rattus* and *Aedes* species, which are hosts and vectors of some of our current and historically most problematic urban zoonotic diseases.

In sum, zoonotic infectious disease emergence can be explained in part as a consequence of the disruption of natural ecological communities, and the breakdown of naturally existing predator-prey, competitive, and host-parasite relationships that tend regulate and stabilize species' abundance. This can occur through the use of non-selective pesticides through changes in land use and land cover that affect the distribution and abundance of species. It should be noted that the disassembly of natural ecological communities that results from habitat fragmentation is a protracted process compared to exponential decay. Depending on the extent of habitat loss and other factors such as the sizes, shapes and spatial relationships of remaining fragments, the process may require decades, centuries or longer as communities 'relax' toward a new equilibrium (36, 43, 44). It follows that the frequency of disease emergence can be expected to follow a similar path: highest rates at first, followed by gradual decline as an ecosystem 'stabilizes'.

Systems ecology and disease emergence

The application of systems thinking to ecological communities centers on the ecosystem concept and has been the basis of significant research activity in ecological science since the 1960's (4). Much of the focus has been on describing and understanding energy and nutrient fluxes across different kinds of ecosystems, and more recently emphasizing the human dimensions of global environmental change (45). Although global scale ecosystem change has been considered in reference to human and infectious diseases (13, 46), no systematic framework has yet been presented in this regard. The evidence presented has been anecdotal.

However, the development and application of systems theory independently of and largely outside the realm of mainstream systems ecology (47) shows significant promise in providing a basis for more systematic interpretation of the role of ecosystem change in disease emergence. Recent thinking draws in particular on the application of the theory of 'complex adaptive systems' to ecological systems in which ecosystems are represented as scaled, self-organizing, far from equilibrium, evolutionary, and non-linear (6). Organization, diversity, and resilience are important 'emerging' properties of complex systems—often equated with a 'healthy' state. 'Surprise', or qualitative disagreements of system behavior with a priori expectations, is another property (48). Their association with loss of system resilience and increased vulnerability applies both to increasing inflexible social systems 'managing' and attempting to 'control' natural variables (i.e., vectors, pathogens) and that of the ecosystems whose component variables (e.g., vector and pathogen populations) are targeted for management or control.

Alteration of natural disturbance regimes (via control of natural variation via flood control projects for example) reduces resilience, while secondary disturbance events (wildfires, storms, floods, and earthquakes) precipitate events caused by cross-scale influences (e.g., a thunderstorm igniting a fire locally that spreads regionally as a result of fuel build-up from years of artificial fire suppression). Regional environmental change such as that associated with population growth development often does not accommodate the need to maintain resilience (21). Such ecosystems have been described as 'over-connected' or 'brittle' and, as stated above, 'accidents waiting to happen' (8, 22). Floods, often associated with waterborne disease outbreaks, occur more frequently and with greater severity as a result of lost resilience in natural systems due to attempts to 'control' (in contrast to manage) natural variation. Conversion of upland forests to plantations or cropping systems for more 'efficient' natural resource production is another, as is agriculture generally. Both result in a reduction of heterogeneity in ecosystems that tend to 'buffer' against disease outbreaks, which can spread more readily across the more uniform landscape including immunologically vulnerable domesticated species. Gunderson et al. (8, 23) describe this as general pattern of institutional behavior. It begins with the targeting of a natural variable for control, followed by increasing institutional efficiency and inflexibility in the control methods used. As the target variable and ecosystem changes and initial signs of failure are ignored, the ultimate result is a crisis. This 'pathology of regional resource and ecosystem management' and is apparently applicable to infectious disease management as well.

Causal Schema of Zoonotic Disease Emergence

The above body of ecological theory and observations involving specific emerging infectious disease cases suggests a causal schema that links ecological phenomena on the scale of pathogen transmission and evolution to regional and global transformations. This is represented by Figure 1, focusing on the role of demographic and societal factors in disease emergence (shown in Table 1). This schema is constructed using the generally adopted view of human-environment interaction in which the impact of human population and technology is taken as the driving force, or ultimate cause. Clark et al. (25) elaborate on this in their seminal treatment on global and regional change. Here, the combination of population, technological capacity, and sociocultural organization act as the system drivers of regional environmental change. These and 'mitigating' forces are in turn influenced by 'human behavior', referring to patterns of actions and the rationales giving rise to them. Broadly speaking, these forces and their affects on ecosystems represent the 'ecological factors' in social-ecological systems, while human behavior represents the 'social factors' for the purposes of discussion.

This schema represents zoonotic disease emergence from the perspective of the ecosystems within a regional environment, the large scale processes involved, and the associated ecological effects and processes involved in disease emergence. Thus, referring to Table 1, the factors under 'Demographic and Societal Changes' can be identified in reference to particular ecosystems and processes (i.e., urban and urbanization, agriculture and agricultural intensification, forest and forest alteration), and associated factors operating on regional and global scales. These are unprecedented population growth, unplanned and uncontrolled urbanization, non-biodegradable packaging of consumer goods, and modern transportation, all contributing to conditions that promote pathogen transmission and persistence.

For zoonotic diseases, which by definition involve the jumping of a pathogen from its natural host to humans, and in some instances extension of its host cycle to include humans, conditions can be described for this simple schema as follows. The likelihood or frequency of transmission events change when the natural host or pathogen changes, humans change, or the ecosystem supporting both changes. Thus, fundamentally the processes influencing transmission of zoonotic pathogens can be described as a consequence of one or a combination of three possible kinds of change: expansion of the habitat or geographic range of a host, of a pathogen or both; expansion of human's habitat or geographic range; or change in the habitat or ecosystem occupied by both humans and the natural host. Evolutionary adaptation of pathogens is omitted from the figure. However, it can be assumed any factor contributing to increased likelihood of transmission, as well as increased population size of hosts and pathogens will contribute to the potential that new, increasingly pathogenic, infectious, antimicrobial resistant variants will emerge. Anthropogenic climate change, while not incorporated in the diagram, can be considered to potentially contribute to disease emergence through its contribution to habitat alteration.

Our review of ecological theory and the resulting complex

model described here demonstrates the limitation of classical disease ecology and natural history. For example, without incorporation of population genetic theory in ecology as 'evolutionary ecology', along with the concepts of pathogen spillover and cross-scale ecosystem dynamics, classical disease ecology cannot explain recent emergence events like those involving HIV/AIDS, SARS, avian influenza, E. coli 0:157, dengue, malaria, West Nile virus, and Nipah virus, among others. The resurgence of vector populations, having acquired pesticide resistance and lost predators and competitors as natural controls after a regimen of inappropriate pesticide use, similarly is explained by modern ecology and evolutionary biology. This has direct application to control and intervention policies and practices. For example, it points to the need to adopt control strategies that integrate landscape and habitat management with careful rotation of targeted chemical and biological agents (30). Developing such strategies requires detailed field studies, built on traditional natural history and classical disease ecology, but supplemented with advanced molecular techniques, as well as ecological research that takes into account the community and systems level dimensions of a particular pathogen-host complex.

Discussion

The continual expansion of human populations since prehistoric times, and particularly since the advent of settled agriculture with its associated domesticated animals exposing humans to their pathogens as well as those spilling over from wild animal populations, has incrementally added to the pathogen load through successive invasions by different organisms over time (49, 50). Well established principles of population ecology, applied via mathematical epidemiology as Anderson and May and others so aptly have done, readily explain why, *ceteris paribus*, infectious disease incidence should generally be increasing with human population size, as it has in the world's poorest and most populous regions. Yet in spite of what are in general commonly understood principles, and warning signs that went unheeded in the 1970's and 1980's (10, 30), biomedical and public health institutions were unprepared for the recent surge in emerging infectious diseases (1, 9, 10, 51). Not until the 1990's, prompted in part by the HIV/AIDS pandemic and the failure of 'quick-fix' solutions based on drugs, vaccines, and pesticides (18), did the biomedical science and public health communities begin to launch a significant response.

In light of the complexity of the factors involved, this lack of preparedness should perhaps not be surprising. As explained by the infectious disease ecology described here, zoonotic disease emergence involves biological processes operating on the scale of molecules and cells to that of coupled, regional scale human-natural systems. The latter involve political economic factors and policies driving regional environmental change, spreading geographically across the globe. It is this process of globalization—its ecological underpinnings and consequences—to which the current EID global trend of zoonotic disease emergance can be largely attributed.

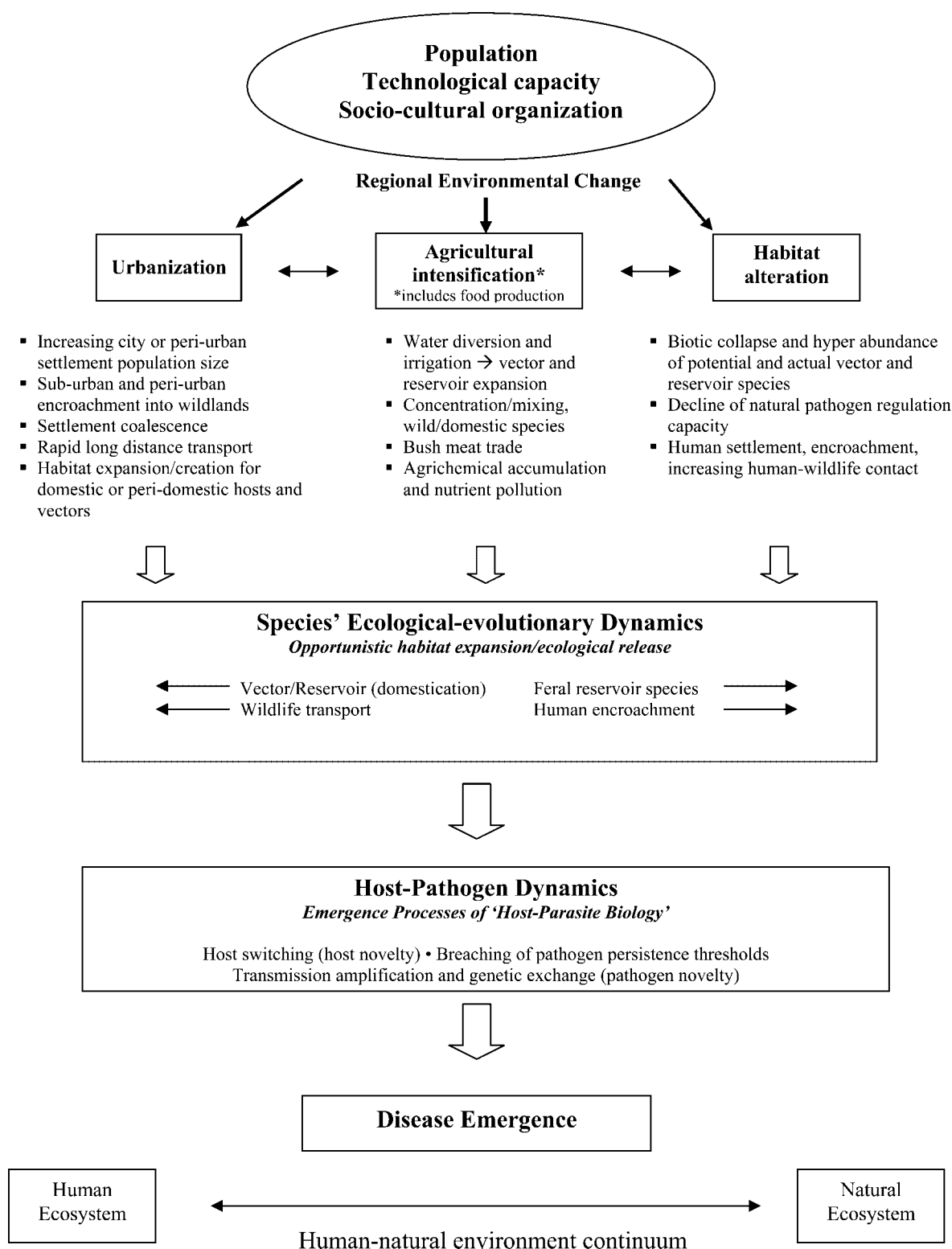Lack of awareness of the ecological implications of

Fig. 1   Diagram depicting infectious disease ecology causal schema. The aggregate variable at the top of the diagram, representing population and consumption, along with mitigating socio-cultural attributes, is the driver or 'forcing function' responsible for land use and land cover change characteristic of a particular region. The result is varying degrees (and types) of urbanization, agricultural intensification (including food production and distribution), and alteration of natural habitat. These changes at the level of landscapes and habitat produce conditions influencing the ecological and evolutionary dynamics of vector and host species and vector/host-pathogen dynamics. In turn, these conditions facilitate the geographic expansion, novel appearance, or increased epidemic activity of a disease.

regional environmental transformations, and of their synergy with the ecological and evolutionary consequences of inadequate or inappropriate policies or methods of vector control and disease prevention, have unwittingly promoted disease emergence. The 'ecological' changes taking place as a result of public health agencies' actions (or inaction) involve pathogen biology and are small scale in time and space: selection for vector pesticide and antimicrobial resistance. However, the cumulative effect of micro-scale processes involving pathogen adaptation and host range expansion (or re-expanding) can ultimately produce regional and even global consequences.

However, policy action and inaction outside the domain of biomedical or public health agencies has produced ecological changes at a historically unprecedented rate and scale. Urbanization, agricultural and food production intensification, alteration of natural habitat, along with concomitant loss of ecosystem functions, have transformed entire regional ecosystems during the past 50 years. The role of urbanization cannot be underestimated. The direct land use changes associated with urbanization effectively concentrate human, animal reservoir and vector populations at unprecedented densities. But urbanization also is strongly tied to socio-economic and cultural factors, along with human migration dynamics, affecting agricultural and food production intensification, as well as rural and natural ecosystems. In the case of food production and distribution, dramatically increased contact with and transport of wildlife (e.g., bush meat trade in Africa), and increased rural-urban transport and concentration of wild species for the exotic food market (e.g., civet cats in Guangdong, China), is another contributor to increasing disease emergence. It can be assumed these impacts on wildlife populations also contribute to changes in the composition of ecological communities on a regional scale (52), and often result in a hyper-abundance of small mammal species low in the food chain, which are likely to serve as human disease reservoirs. Similar effects of ecological disruption appear to generally apply to invertebrate commu-
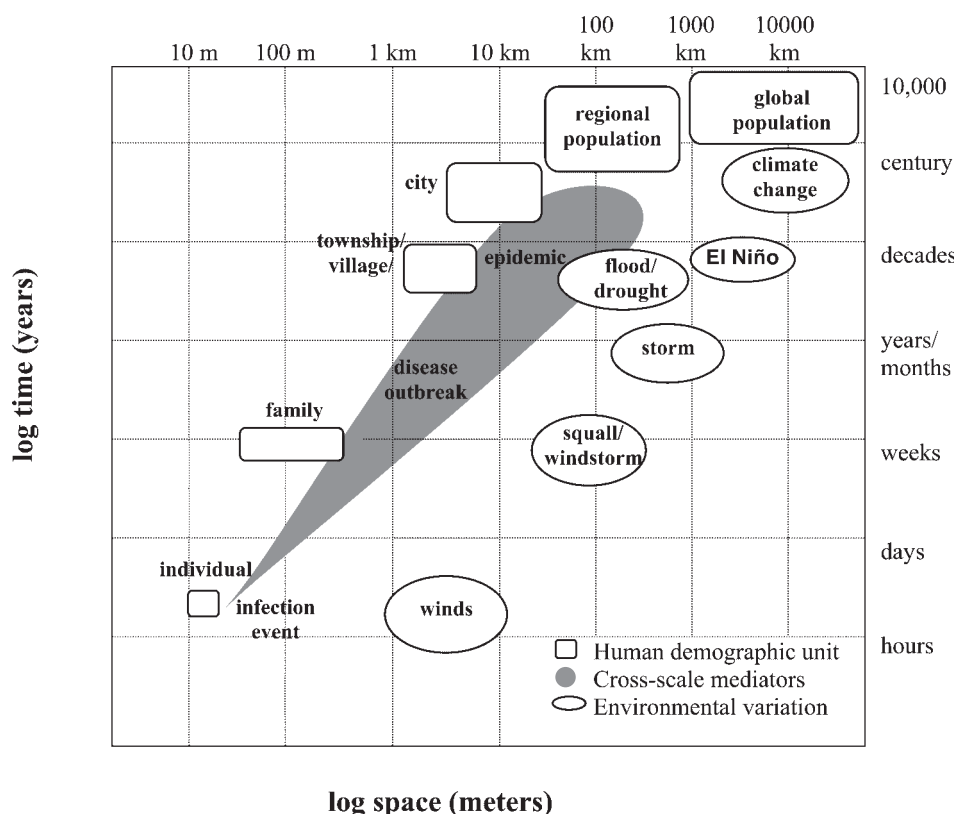

Fig. 2 Time and space hierarchy of interacting human, disease, and ecological systems. This figure illustrates the hierarchical character of human demographic units and environmental disturbances, and how these interact through cross-scale flowing and spreading processes. The boxes illustrate the hierarchically-scaled structure of human population, in which demographic units (individual, family, town, etc.) form a nested hierarchy. These units exhibit characteristic behaviors and dynamics occurring in distinct time and space scales, beginning with the infection of one person. Whether a disease 'jumps' to the regional population and the global human population scale is determined by quite different processes. These depend on demographic and transport patterns related to processes, like urbanization, influencing pathogen transmission and behavior operating on the regional and global scales. Physical environmental processes such as climate variability (on the right side of the figure), which are episodic by nature, include short term and small scale variations in the form of seasonal storms (e.g., monsoons), for example, as well as larger time and space scale variations. These include, for example, decadal and regional scale changes in weather patterns such as El Niño. These climate changes and weather events can precipitate floods and droughts. These act as cross-scale mediators that directly affect disease reservoir and vector populations, or pathogens (e.g, dispersal via flood waters). They cause the disease to jump from a smaller demographic unit to a larger one (e.g., from a single village to a district). Human Factors such as land use and land cover changes (Table 1 and Fig. 1) produce ecosystem changes contributing or magnifying the cross-scale processes. For example, urbanization and deforestation increase the magnitude of floods and droughts resulting from natural or anthropogenic climate variation.

nities (53), the kinds of organisms most commonly serving as human disease vectors. The estimated acceleration of natural species extinction rates by orders of magnitude over non-anthropogenic extinction rates (54) gives an indication of the scale and magnitude of change in natural communities, particularly in the tropics. In these regional ecosystems, the original extent of tropical forest has declined to a fraction of its original area with concomitant affects on biodiversity (38).

Large scale agricultural expansion (a common proximate cause of tropical deforestation) has decelerated and all but ended in many regions. This suggests that further contributions from what historically has been a main factor in natural habitat alteration, ecosystem disturbance and biodiversity loss, will decline. Yet agricultural intensification has replaced expansion with technologies that further impact native biodiversity (55). The reduction in plant species richness that accompanies agricultural intensification leads to changes in the community composition of the pest complex—herbivorous insects, their natural enemies (predators and parasites), and the microbial community attacking crops (56).

Cross-scale influences and coupled human-natural systems

The schema described here demonstrates how regional environmental change, involving ecological dynamics such as demographic or landscape transformations on the scale of decades, interact with change on the scale of host-parasite/pathogen dynamics. How these cross-scale mechanisms produce regional or global scale disease emergence patterns is beyond the realm of conventional epidemiology, or analytical approaches generally. This may explain why such changes either are not apparent or their implications in terms of disease emergence are a low priority to biomedical and public health agencies. Such cross-scale processes are however characteristic of ecosystems, whose dynamics involve interaction of variables and operate on vastly different time and space scales, involving natural processes that are discontinuously distributed as shown in Figure 2.

Change in such systems is difficult to understand employing conventional analytic approaches alone, but require new thinking and analytical methods drawn from complex systems theory. The discontinuous character of the processes or variables makes their interaction intuitively improbable except for the mediating effect of 'cross-scale influences' as illustrated in Figure 2. Examples include the eruption of Hantavirus in the American Southwest, thought be associated with weather events precipitated by El Nino Southern Oscillation. Storms events are similarly episodic, and represent a discontinuous form of variation transporting pathogens via flood waters in domestic and natural environments. On the other hand, massive environmental events, like the recent Southeast Asian tsunami, are potentially capable of producing epidemics across an entire region, and may episodically extinguish some zoonotic diseases by temporarily destroying reservoir and vector populations and habitat. The roles of resilience and vulnerability in determining the severity of such events, both in terms of social systems and ecological systems is another critical aspect of social-ecological systems behavior (8).

Conclusion

The recent worldwide upsurge of zoonotic infectious diseases, involving the resurgence of a growing number of diseases previously believed under control or the emergence of newly recognized diseases, has been attributed to a list of global factors characterized in terms ranging from microbial adaptation and land use to changing ecosystems, breakdown of public health, and poverty (1, 57). The categorization provided by Gubler (10), elaborated here based on an expanded view of infectious disease ecology, provides the basis for a schema describing the causal relations involving factors previously identified, along with hypothesized mechanisms.

The complicated nature of this problem, which obviously entails numerous interacting variables operating on different time and space scales pose a significant challenge to biomedical science and epidemiological research as well as public health intervention. However, the current trend of increasing global emerging infectious diseases is linked with another issue of 'global governance', sustainable development, with which disease control and prevent strategies must be integrated. Here too, the problems of politically stability, population growth, unplanned urbanization and economic development, income disparity, and environmental degradation, are all integral to the solution.

This interdisciplinary imperative challenges what historically has been an increasing disciplinarily focus in infectious disease research. Greater investment in research has succeeded in revealing more detail about diseases within specific disciplines. Yet this arguably has been at the cost of greater disintegration rather than integration among disciplines. The division is widest between the genetic and biological aspects of disease and health on the one hand and the social, economic, political, and physical environmental factors on the other. The disciplinary distinctions within infectious disease research of course belie the true transdisciplinary nature of this and most problems in the global heath and environment arena (59). The above disciplinary divisions largely reflect the gap between disciplines focusing on systems at or below and above the level of the organism or species. The former involve disciplines addressing the genetics, pathogenesis, or immune response within particular organisms (humans, vectors of pathogens), for example, or disease as a statistical phenomena at the species population level (the mainstay of epidemiology). The latter deal with social or ecological phenomena, essentially representing higher levels of biological organization, within which the organism-level processes operate but that also involve many other variables or processes operating on a wide range of biological scales (from genes to the biosphere) characterized by cross-scale influences, and interactions at multiple societal and ecological levels.

It follows that for intervention to be globally effective, in addition to rebuilding public health infrastructure based on the comprehensive view of infectious disease ecology presented here, at least three elements are required:

1. a multilevel ecosystem approach, involving cross-scale integration.
2. incorporated ecological theory and data for the specific disease system,

3. local scale intervention using a participatory approach that matches pathogen management with sustainable development across ecosystem and institutional scales.

Acknowledgments

References

(1) Institute of Medicine. Microbial threats to health: emergence, detection, and response. Smolinski MS, Hamburg MA, Lederberg J editors. Washington, DC: National Academy Press; 2003.

(2) Meyer WB, Turner BL. Changes in Land Use and Land Cover: A Global Perspective. Cambridge University Press; 1994.

(3) Vitousek PM, Mooney HA, et al. Human domination of earth's ecosystems. Science. 1997;277:494–499.

(4) Golley F. A History of the Ecosystem Concept in Ecology. New Haven, CT: Yale University Press; 1993.

(5) Keller DB, Golley FB. The Philosophy of Ecology, from Science to Synthesis. Athens: University of Georgia Press; 2000.

(6) Levin SA. Fragile Dominion: Complexity and the Commons. Perseus Books Group; 1999.

(7) Levin BR, Lipsitch M, et al. Population biology, evolution, and infectious disease: convergence and synthesis. Science. 1999;283:806–809.

(8) Gunderson LH, Holling CS editors. Panarchy: Understanding Transformations in Systems of Humans and Nature. Washington DC: Island Press; 2002.

(9) Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis. 1995;1:7–15.

(10) Gubler DJ. Resurgent vector-borne diseases as a global health problem. Emerg Infect Dis. 1998;4:442–450.

(11) Daszak P, Cunningham AA, Hyatt AD. Emerging infectious diseases of wildlife—threats to biodiversity and human health. Science. 2000;287:443–449.

(12) Patz J, Graczyk TK, Geller N, Yittor AY. Effects of environmental change on emerging parasitic diseases. Int J Parasitol. 2000;30:1395–1405.

(13) Patz J, Daszak P, Tabor GM, Aguirre AA, Pearl M, Epstein J, et al. Unhealthy landscapes: policy recommendations on land use change and infectious disease emergence. Env Health Persp. 2004;112:1092–1097.

(14) De Kruif P. Microbe Hunters. Harcourt, Brace and Co.; 1926.

(15) Oldstone MBA. Viruses, Plagues & History. Oxford University Press; 1998.

(16) Ross R. An application of theory of probabilities to the study of an a priori pathometry, number I. Proc R Soc A. 1916;92: 204–230.

(17) Anderson RM, May RM. Infectious Diseases of Humans. Dynamics and Control. Oxford: Oxford University Press; 1991.

(18) Gubler DJ. Prevention and control of tropical diseases in the 21st century: back to the field. Am J Tr Med Hygiene. 2001;65:1.

(19) Stearns SC editor. Evolution in Health and Disease. Oxford University Press; 1999.

(20) Frank SA. The immunology and evolution of infectious disease. Princeton University Press; 2002.

(21) Holling CS. The resilience of terrestrial ecosystems: Local surprise and global change. In: Clark WC, Munn RE editors. Sustainable Development of the Biosphere. Cambridge Press, Syndicate of the University of Cambridge; 1986. p. 292–397.

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

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

(24) Berry BLJ. Urbanization. In: Turner BL II, Clark WC, Kates RW, Richards JF, Mathews JT, Meyer WB editors. The Earth as Transformed by Human Action: Global and Regional Changes in the Biosphere over the Past 300 Years. Cambridge, University Press; 1990. p. 103–119.

(25) Clark WC, Kates RW, et al. editors. The Earth as Transformed by Human Action. Cambridge: Cambridge University Press; 1990.

(26) Anderson RM, May RM. Population biology of infectious diseases: part I. Nature. 1979;280:361–367.

(27) May RM, Anderson RM. Population biology of infectious diseases: part II. Nature. 1979;280:455–461.

(28) Black FL. Measles endemicity in insular populations: critical community size and its evolutionary implication. J Theor Biol. 1966;11:207–211.

(29) Anderson RM. Population Ecology of Infection Disease Agents. Theoretical Ecology: Principles and Applications. 1981. p. 318–355.

(30) Gubler DJ. Aedes egypti and Aedes egypti-borne disease control in the 1990s: top down or bottom up. Am J Trop Med Hygiene. 1989;40:571–578.

(31) Schrag, SJ, Wiener P. Emerging infectious disease: what are the relative roles of ecology and evolution. Trends Ecol Evol. 1995;10:319–324.

(32) Horwitz P, Wilcox BA. Parasites, ecosystems and sustainability: some notes on nested interdependencies. Intl J Parasitol. 2005;35:725–732.

(33) May RM. Theoretical Ecology: Principles and Applications. Sinauer Associates. 1981.

(34) Diamond JM. Assembly of species communities. In: Cody ML, Diamond JM editors. Ecology and Evolution of Communities. 1975. p. 342–344.

(35) Diamond JM, May RM. Island biogeography and the design of nature reserves. In: May RM editor. Theoretical Ecology: Principles and Applications. Sinauer Associates; 1981. p. 228–252.

(36) Rosenzwieg ML. Species Diversity in Space and Time. Cambridge University Press; 1995.

(37) Wilcox BA. Insular ecology and conservation. In: Soulé ME, Wilcox BA editors. Conservation Biology: An Evolutionary-Ecological Perspective. 1980. p. 95–117.

(38) Wilcox BA, Murphy DD. Conservation strategy: The effects of fragmentation on extinction. Am Nat. 1985;125:879–887.

(39) Ferraz G, Russell GJ, et al. Rates of species loss from Amazonian forest fragments. PNAS. 2003;100:14069–14073.

(40) Laurance WF, Laurance SG, et al. Biomass collapse in Amazonian forest fragments. Science. 1997;278:1117–1118.

(41) Terborgh J, Lopez L, et al. Ecological meltdown in predator-free forest fragments. Science. 2001;294:1923–1926.

(42) Prenter J, MacNeil C, Dick JTA, Dunn AM. Roles of parasites in animal invasions. Tr Ecol Evol. 2004;19:385–390.

(43) Diamond JM. Normal extinctions of isolated populations. In: Nitecki MH editor. Extinctions. University of Chicago Press; 1984.

(44) Wilcox BA. Supersaturated island faunas: A species-age relationship for lizards on post-Pleistocene land bridge Islands in the Gulf of California. Science. 1978;199:996–998.

(45) National Research Council. Committee on the Human Dimensions of Global Change and Committee on Global Change Research. Human dimensions of global environmental change: research pathways for the next decade. Washington, DC: National Academy Press; 1999.

(46) Aron JL, Patz JA. Ecosystem Change and Public Health: A Global Perspective. Johns Hopkins University Press; 2001.

(47) Checkland P. Systems Thinking, Systems Practice. Wiley; 1981.

(48) Gunderson LH. Adaptive dancing: Interactions between social resilience and ecological crises. In: Berkes F, Colding J, Folke C editors. Navigating Social-Ecological Systems: Building Resilience for Complexity and Change. Cambridge University Press; 2002. p. 33–52.

(49) McNeil WH. Plagues and Peoples. New York: Anchor Press/ Doubleday; 1976.

(50) McMichael T. Human Frontiers, Environments and Disease. Cambridge University Press; 2001.

(51) Hughes JM. Emerging infectious diseases: a CDC perspective. Emerg Infect Dis. 2001;7(3 Suppl):494–496.

(52) Cuaron AD. A global perspective on habitat disturbance and tropical rainforest mammals. Con Biol. 2000;14:1574–1579.

(53) Dangles O, Malmqvist B. Species richness-decomposition relationships depend on species dominance. Eco Let. 2004; 7:395–402.

(54) Lawton JH, May RM editors. Extinction Rates. Oxford: Oxford Univ. Press; 1995.

(55) Matson PA, Parton WJ, Power AG, Swift MJ. Agricultural intensification and ecosystem properties. Science. 1997;277: 504–509.

(56) Power AG, Flecker AS. In: Orians GH, Dirzo R, Cushman JH editors. Biodiversity and Ecosystem Processes in Tropical Forests. New York: Springer-Verlag; 1996. p. 173–194.

(57) Institute of Medicine. Emerging infections: Microbial threats to health in the United States. Lederberg J, Shope RE, Oaks SC Jr editors. Washington, DC: National Academy Press; 1992.

(58) Somerville MA, Rapport DJ. Transdisciplinarity: Recreating Integrated Knowledge. McGill-Queen's University Press; 2003.