Interactions between Global Change and Human Health
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OUR CHANGING BIOGEOPHYSICAL AND SOCIOECONOMIC ENVIRONMENTS: INFLUENCE ON INFECTIOUS DISEASES

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1. Introduction

The health of human populations – particularly in the medium-to-longer term – depends, fundamentally, on the conditions of the social and natural environments. This statement represents an ecological perspective. It is pitched at the level of whole communities or populations, and thus differs from the view held by most lay individuals and health professionals who typically think of health as a function of personal circumstances and behaviors, genes and access to the health-care system.

During the latter decades of last century there was a growing awareness of environmentally-based risks to health. Today, we must look to even wider environmental horizons. The increasing scale of human impact on the world's environment is now causing unprecedented changes in Earth's ecological and biogeophysical systems, and these necessarily jeopardize the prospects for human health. Of particular concern is the generalized resurgence in infectious diseases. Historically, changes in social and environmental conditions have often fostered the emergence or spread of infections.

Half a century ago, developed countries assumed that infectious disease, the age-old scourge of humankind (the biblical 'Fourth Horseman'), was at last receding. The antibiotic era had begun successfully in the 1940s; vaccine development was accelerating; pesticides were being used to control mosquito populations; and surveillance and control measures (border controls, quarantine, other social controls, public education) were improving and becoming internationally coordinated. Hence, by the early 1970s, various eminent authorities proclaimed the end of the

infectious disease era. In retrospect this was naïve: by late twentieth century a generalized upturn in emerging and resurgent infectious diseases had become evident.

More than 30 new infectious diseases were identified in the final quarter of the 20th century, including HIV/AIDS, Legionnaire's disease, hepatitis C, Nipah virus disease and many viral haemorrhagic fevers [1]. Since 2000, the story has continued worldwide, particularly with the emergence of SARS and the Avian influenza virus in the Asia-Pacific region. Meanwhile, many long-recognized infectious diseases have increased, including tuberculosis, malaria and dengue fever. Cholera, too, continues to enjoy its largest-ever and longest-ever pandemic (see Box 1) – and a new, eighth, cholera pandemic, entailing a new strain of the cholera bacterium, is currently emerging. Meanwhile, mired in poverty and squalor, diarrhoeal disease and acute respiratory infections continue to kill a total of around seven million infants and children every year.

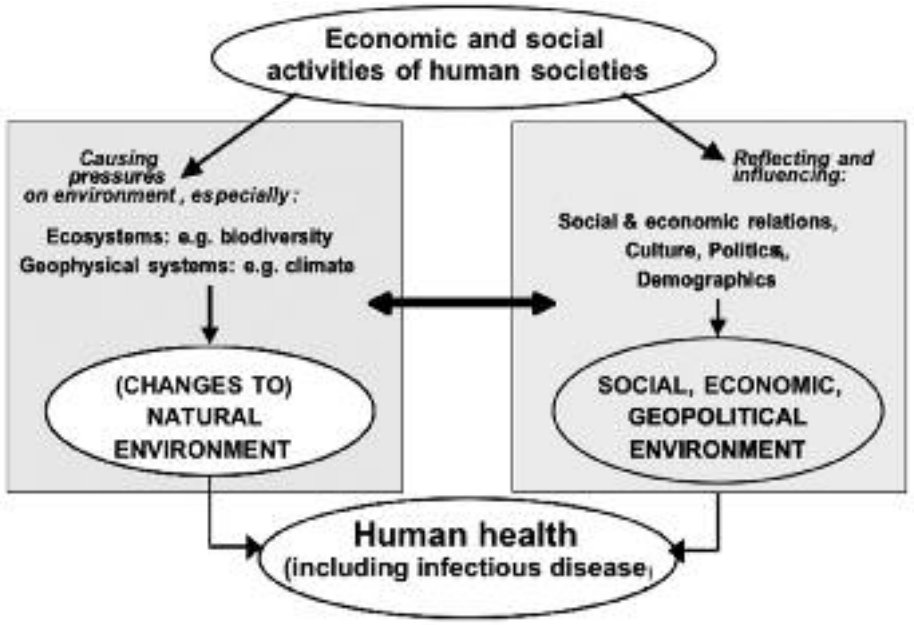

Figure 1. The pathways by which 'social' and 'environmental' changes arise and influence patterns of human health. Note also the interaction between the social and environmental domains.

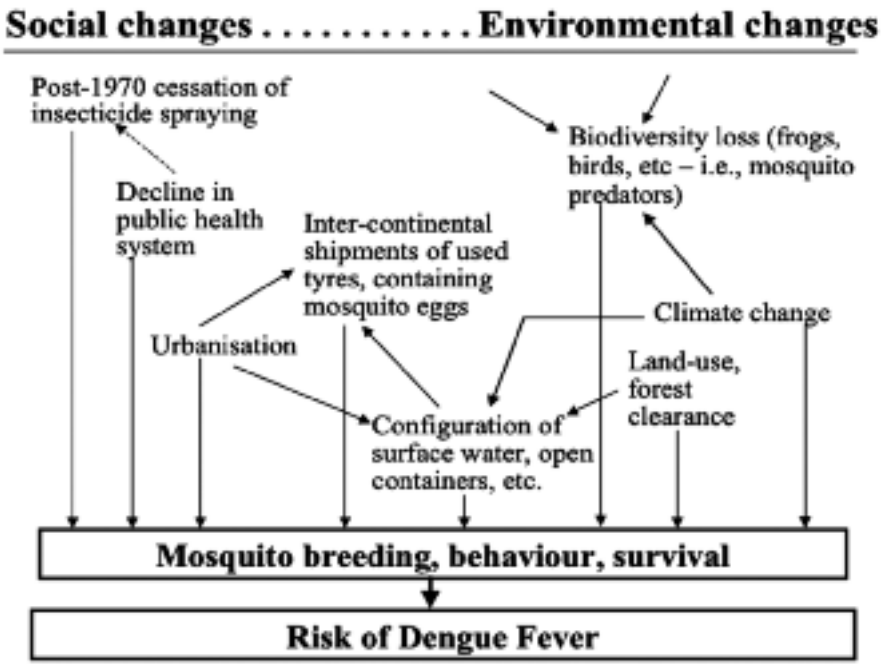

Figure 2. Illustration of the multiple social-cultural changes (e.g., pesticide spraying policy, urbanization) and environmental changes (e.g. land-use, biodiversity loss, climate change) that coexist and interact as influences on the risk of dengue fever occurrence.

Broadly, this upturn reflects a diverse range of distinctive conditions of the modern globalizing world: the growth in population size and density, urbanization, human mobility, long-distance trade, persistent poverty, conflict and warfare, and, increasingly, the advent of human-induced global environmental changes that entail large-scale disturbance and destabilization of ecosystems and biophysical processes (such as the world's climate system) [2].

Figures 1 and 2 show how this mix of (often coexisting) 'social' and 'environmental' factors influences the dynamics of infectious disease emergence, transmission and dissemination.

Figure 1 shows schematically how both 'social' and 'environmental' changes arise as manifestations of human economic and social activity. However, the depiction of the two separate causal pathways is somewhat

misleading, since, as shown with the two-way arrow, there is a variety of interactions between the left and right sides of the schema.

For example, poverty is often associated with over-use of, and damage to, local forests and marginal farmland; and, obversely, local environmental deterioration will often tend to exacerbate poverty and resource deprivation. Further, the levels of material resources, social and human capital, and governmental stability and capacity will influence the extent of vulnerability of local populations to the stressors of environmental change. (In general, poor populations in tropical regions are much more likely to experience an actual increase in vector-borne infectious disease in response to the warming and altered rainfall patterns of climate change than are richer temperate-zone countries with strong public health defenses).

A more specific example of this constellation of large-scale social and environmental influences, as coexistent and interacting determinants of the probability of dengue fever outbreaks, is shown in Figure 2.

The underlying determinants of infectious disease emergence and occurrence can be better understood within both an ecological frame and against an historical background. Since we must continue to live in a microbially-dominated world, we should think in ecological terms, not adversarial militaristic terms, about our relations with bacteria, viruses, protozoa and other tiny parasites. Having learnt that we cannot definitively conquer the disease-inducing microbes, we should now develop a better capacity to anticipate the risks of new or resurgent infectious diseases, while we continue to coexist with an ever-changing microbial world.

In historical terms, there are many recorded episodes and processes in history that can teach us more about the consequences of human actions, of changes in human ecology, for the patterns of occurrence of infectious diseases in human populations.

BOX 1. CHOLERA – THE SEVENTH PANDEMIC

Cholera illustrates how modern social, economic and environmental conditions, having undergone various recent changes at large scale, can affect the pattern of occurrence of infectious diseases.

Cholera originated in the Ganges delta, in India, where epidemics of a cholera-like disease have been described over the past four centuries [3]. Since 1961, a major pandemic of cholera has occurred. This is the seventh pandemic since cholera (apparently reinforced with a newly acquired toxin-producing gene) first extended outside South Asia in 1817. That initial spread followed the Great Kumbh annual religious festival in the Upper Ganges, in which pilgrims from all over India came to bathe in the sacred waters. Their subsequent dispersal, and contacts with British troops mobilizing in the northwest frontier region, caused a cholera epidemic that spread from India to the Arabian Peninsula and along the trade routes to Africa and the Mediterranean coast. In the early 1830s, the faster-traveling steamboats enabled cholera to cross the Atlantic. The disease reached North America in 1832, and spread rapidly around the coastline and inland via major rivers.

This seventh pandemic has reached further than ever before, affecting Asia, Europe, Africa, North America and Latin America. It is by far the longest lasting pandemic to date [4]. This pandemic entails the El Tor strain of the vibrio, which, in mid-twentieth century, replaced the more lethal classical biotype of the nineteenth century pandemics. The scale of this pandemic is likely to reflect the confluence of greatly amplified human mobility between continents, the rapidity and distance of modern shipping-based trade, coincident increases in nutrient enrichment of coastal and estuarine waters by phosphates and nitrates in run-off water (enhancing proliferation of vibrio-harboring phytoplankton and zooplankton), and the growth of urban slums with unsafe drinking water.

2. ECOLOGICAL PERSPECTIVES, WITHIN AN HISTORICAL FRAME

The worldwide dispersal of the human species over the past 50,000-100,000 years, along with cultural evolution and inter-population contacts, has profoundly transformed the relationship between *Homo sapiens* and the microbiological world [5]. During this grand odyssey, there have been several major transitions at key historical junctures, each entailing the emergence of various new or unfamiliar infectious diseases, and occurring at increasingly large scale.

The co-evolution of humans and infectious agents has, of course, a long history. In human prehistory two profound transitions in this relationship occurred: the first when early humans became serious meat-eaters, thereby exposing themselves to various animal parasites, and the second when *Homo sapiens* spread out of Africa into new environments and climates where they encountered unfamiliar microbes. Since the advent of agriculture and animal husbandry, and the dawn of 'history' via written records, three other great transitions have occurred in the human-microbe relationship [2]. First, early agrarian-based settlements enabled enzootic microbes to cross the species barrier and make contact with *Homo sapiens*. Hence, the early city-states of the Middle East, Egypt, South Asia, East Asia and Central and South America each acquired their own distinct repertoire of locally evolving 'crowd' infectious diseases. Second, later, over the course of a thousand years or so the ancient civilizations of greater Eurasia (Egypt, India, Rome, China) made contact, swapped their dominant microbes and painfully equilibrated. (Perhaps a similar process occurred within some other continents, but, if so, the historical record is not available. Eurasia, the largest continent, and with a predominant east-west axis, afforded a particularly auspicious opportunity for inter-civilization contacts.) Third, from the fifteenth century onwards, expansionist sea-faring Europe, technologically pre-eminent in the world, inadvertently exported its lethal, empire-winning, germs to the Americas and later to the south Pacific, Australia and Africa.

Today, we are living through the fourth great transition, which, for the first time, extends globally. The generalized increase in lability in occurrence, spread and biological behavior of infectious diseases largely reflects the combined and increasingly widespread impacts of demographic, commercial, environmental, behavioral, technological and other rapid changes in human ecology. The main characteristics that underlie this contemporary global transition, foreshadowed in the introduction, are summarized in Box 2.

BOX 2. THE MAIN DRIVERS OF THE CONTEMPORARY GLOBAL TRANSITION IN HUMAN-MICROBE RELATIONS

- Increased human mobility: travel, migration (including refugees)
- Long-distance trade
- Ever-larger cities and urban populations:
  - Large, dense populations
  - Freer, non-traditional, sexual contacts
  - IV drug injecting
  - Unsanitary shanty towns and slums
- Intensified food production practices (especially livestock)
- Various modern medical/hospital procedures (injection, transfusion, transplantation)
- Global environmental changes: climate change, land-use change, dam-building and irrigation, ecosystem disruption (including biodiversity loss), etc.

3. FOOD SOURCES; FOOD PRODUCTION

The spectacular outbreak of 'mad cow disease' (bovine spongiform encephalopathy, BSE) in the UK in the mid-1980s underscored the infectious disease risks inherent in changes in food production methods. Within many cultures, the predilection for eating meat of various exotic species exacerbates the risk of exposure to infectious agents not previously encountered. Indeed, this situation probably triggered the 2003 epidemic of Severe Acute Respiratory Syndrome, SARS, in the Guangzhong region of southern China [6]. Recent studies have implicated bats as the natural reservoir species for the SARS coronavirus. Other wild mammals, including civet cats, have been reported to be infected with SARS-related viruses, and surveys in live markets and restaurants in Guangzhong, southern China, identified various small carnivore species that had been captured in rural China, Laos, Vietnam and Thailand and that were then brought into close proximity with one another [7].

The consumption of bushmeat in Africa poses a serious risk of emerging infectious diseases (as well as a risk for species conservation) [8]. Indeed, it is the sick, infected, animals that are often more easily captured. Molecular genetic studies indicate that the HIV virus has crossed from chimpanzees into humans at least three times [9], and it is plausible that one or more of these cross-over events arose from butchering the animals.

Southern China, with its traditional close-contact animal husbandry, has long been implicated in the origin of epidemic influenza virus strains via the juxtaposition of ducks, chickens, pigs and humans. The generation of novel zoonotic viral strains occurs readily in this environment. Over recent decades, the human population and the animal populations needed to support them have rapidly increased. The numbers of poultry and pigs are now at record levels and, as wealth increases and dietary preferences 'modernize', those numbers are set to double approximately every 10 years [10].

4. Social, Economic and Associated Influences

Each year 17 million people, mostly young children, die from infectious diseases. Worldwide, infectious diseases account for almost one in three of all deaths. However, the discrepancy between rich and very poor countries is huge: infections cause 1-2% of all deaths in the former, but more than 50% in the latter. Diseases such as tuberculosis, leprosy, cholera, typhoid and diphtheria are known to be pre-eminently diseases of poverty. Malaria, tuberculosis and dengue fever have all increased their compass over the past 20 years, particularly within poorer communities or groups, [11], [12]. Similarly, urbanization, long-distance travel and freer sexual relations have all amplified the spread of various such diseases. As happened historically with tuberculosis, HIV infection seems now to be entrenching itself among the world's poor and disempowered, especially in sub-Saharan Africa and South Asia. Much of the spread of HIV has been along international 'fault lines', tracking the inequality and vulnerability that accompany migrant labor, educational deprivation and sexual commerce [12].

The health ramifications of economic disadvantage have been further highlighted by some recent infectious disease outbreaks attributed, in part, to the impacts of free trade agreements. For example, in the 1990s several outbreaks of hepatitis A and cyclosporiasis (a protozoal infection) occurred in the United States from fecally-contaminated strawberries and raspberries imported from Central America. Such contamination is likely to have occurred because of the introduction of the North American Free Trade Agreement. This, like other such agreements, tends to subordinate environmental and labor standards (including worker access to toilet facilities) to the primacy of profitability.

Socially disordered populations living in circumstances of privation, unhygienic conditions and close contact, are susceptible to infectious dis-

ease. History abounds with examples. The severity of the bubonic plague (Black Death) in mid-fourteenth century Europe appears to have reflected, in part, the malnutrition and impoverishment caused by several preceding decades of unusually cold and wet weather with crop failures. This, in conjunction with the incipient destabilization of the hierarchical feudal system, would have heightened the vulnerability of the European populations to epidemic disease.

In modern times, the urban environment and associated ways of life has become an increasingly important influence on infectious disease patterns around the world. Cities are now the dominant human habitat. Urbanism typically leads to a breakdown in traditional family and social structures, and entails greater personal mobility and extended and changeable social networks. These features along with access to modern contraception have facilitated a diversity of sexual contacts and, hence, the spread of STDs. This risk is further amplified by the growth in sex tourism in today's internationally mobile world, which capitalizes on the desperation and ignorance of poverty, combined with exploitative behaviors, in developing countries. More generally, cities act as highways for 'microbial traffic' [13].

Rural-urban migration is fuelled by the primary drive to enter the cash economy, allied with the burgeoning international demand for skilled and unskilled workers in a globalizing marketplace. Rapid, unplanned, urbanization exacerbates old infectious diseases such as childhood pneumonia, diarrhea, tuberculosis and dengue. It also facilitates the spread of various 'emerging' diseases; for example, high-rise housing can create new infectious disease risks, as was recently observed for SARS in Hong Kong. Such housing also increases risks of infection via the consequences of family breakdown and social instability, intravenous drug abuse and sexual transmission of infections [14].

4.1. *Travel and Trade*

Microbes are no respecters of political and administrative borders. The mobility of humans, animals and birds is a constant stimulus to changes in the pattern of infectious disease occurrence. HIV/AIDS has spread quickly around the world in the past twenty years. SARS spread readily from Hong Kong to Vietnam, across to Germany and Toronto [6]. Vector mosquito species can travel with trade and transport – as apparently did the bubonic plague-infected black rat, traveling westwards across the Silk Road towards the Black Sea and Europe in the fourteenth century.

Dengue fever, numerically the most important vector-borne viral disease of humans, illustrates well how patterns of trade, travel and settlement can influence various infectious diseases. Although dengue is primarily a tropical disease, its extension in recent decades into various temperate countries reflects both the introduction of the disease's main mosquito vector species, *Aedes aegypti* (which is behaviorally adaptable to a cold climate), and the increase in imported cases resulting from increased air travel [15]. It also reflects the rapid evolutionary adjustment of this mosquito species to coexistence with urban-dwelling humans, having originated in forest Africa. Indeed, *Aedes aegypti* has followed humankind on its travels and migrations around the world [16]. A major alternate mosquito vector for the dengue virus, *Aedes albopictus* (the 'Asian tiger mosquito'), has been disseminated widely in recent years via the unwitting intercontinental exportation of mosquito eggs in used car tires from Asia into Africa and the Americas [17].

Neisseria meningitidis, a global bacterial pathogen, causes seasonal epidemics of meningitis in the 'meningitis belt' of Sahelian Africa. Molecular marker studies have revealed that, in recent decades, Muslim pilgrims brought an epidemic strain of *N. meningitidis* from southern Asia to Mecca. In Mecca they passed it on to pilgrims from sub-Saharan Africa who, after returning home, initiated strain-specific epidemic outbreaks in several locations [18].

The globalization of the food market has potentiated the movement of pathogens between regions. As examples, first, an outbreak of cholera in Maryland, USA, was traced to imported contaminated frozen coconut milk [19], and, second, alfalfa sprouts grown from contaminated seed sent to a Dutch shipper caused outbreaks of infections with *Salmonella* species in both the USA and Finland [20].

4.2. *Land Use and Environmental Change*

Like other very large mammals, we humans are 'patch disturbers'. This we do via tropical deforestation, irrigation, dam building, urban sprawl, road building, intensified food production systems, and pollution of coastal zones. The increasing scale of this encroachment on the natural environment accelerates the emergence of new infectious diseases. As we spread into the last corners of Earth's tropical forests, new contacts occur between wild fauna and humans (and their livestock), increasing the risk of cross-species infection.

Habitat fragmentation and biodiversity changes alter the risks of infectious disease. This is well illustrated by deforestation that results in habitat fragmentation – and an increase in the 'edge effect' that promotes pathogen-vector-host interaction. This process has contributed, in recent decades, to the emergence of a number of viral haemorrhagic fevers in South America. Various such viral infections have been caused by arenaviruses. Major examples, mostly in rural populations, have been described in Argentina (Junin virus), Bolivia (Machupo virus) and Venezuela (Guanarito virus) [21], [22], [23]. The Machupo virus is an example. Forest clearance in Bolivia in the 1960s, accompanied by blanket spraying of DDT to control mosquitoes, led, respectively, to infestation of cropland by *Calomys* mice and to the poisoning of the rodents' usual predators (village cats). The consequent proliferation of mice and their viruses resulted in the appearance of a new viral fever, the Bolivian (Machupo) haemorrhagic fever, which killed around one seventh of the local population.

More generally, rodents, responding to environmental disturbances, are a prime source of new and re-emerging infections. Consider the emergence of Hanta viruses as a source of human disease in the USA in the 1990s. In mid-1993, an unexpected outbreak of acute, sometimes fatal,

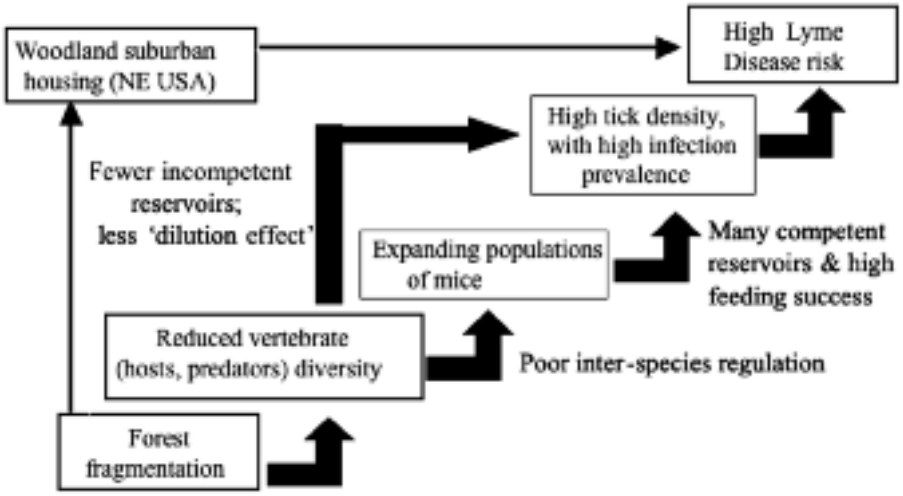

Figure 3. Schematic representation of the sequence of environmental and ecological changes that, along with social-residential changes, increase the probability of Lyme Disease transmission in northeast USA (based on the work of R. Ostfeld).

respiratory disease occurred in southwest USA [24]. This 'hantavirus pulmonary syndrome' was caused by a previously unrecognized virus, maintained in the natural environment primarily within native deer-mice and transmitted via rodent excreta. The 1991-92 El Niño event, causing unseasonally heavy summer rains and a proliferation of piñon nuts within southwest USA, hugely amplified local rodent populations, leading to the 1993 outbreak of 'hantavirus pulmonary syndrome' [24], [25].

In the USA, nature conservation and increased contact with woodland in the Eastern states has led to the emergence of Lyme disease (borreliosis) – summarized in Figure 3. The ticks that transmit the spirochaete *Borrelia burgdorferi* normally feed on deer and white-footed mice. The latter are the more competent host species. However, forest fragmentation has caused the loss of various predator species – wolves, raptors, and others – with a resultant shift of ticks from the less competent to the more competent host species (i.e., from deer to white-footed mice). These changes, along with suburban sprawl into woodlands, have interacted in the emergence of this disease [26], [27].

5. Global Environmental Changes and Infectious Disease Risk

The large-scale environmental changes that humans are now imposing on the biosphere have great implications for the future pattern of infectious disease. Much research in this emerging topic area has been done specifically in relation to global climate change – although it is now well understood that there will be widespread interactions between the impacts of these environmental changes. A further consideration is that the disease impact of changes in environmental conditions will usually be modulated by the level of susceptibility of the human population – reflecting population density, immune status, nutritional status, extent of mobility, level of social organization/disorganization, flexibility of political systems and of governance, and various other such social-environmental factors.

5.1. *Global Climate Change*

The now-certain prospect of human-induced global climate change raises long-term questions about how infectious diseases will respond over the coming century (and beyond). Many infectious agents, their vector organisms and their reservoir non-human species, are sensitive to cli-

matic conditions and to resultant environmental changes. The example of hantavirus pulmonary syndrome has been discussed above.

Salmonella food-poisoning is known to be very temperature-sensitive, and diarrhoeal diseases peak in summer. In the Asia-Pacific region, El Niño fluctuations appear to affect the occurrence of dengue fever, the world's most prevalent vector-borne viral disease, spread primarily by the *Aedes aegypti* mosquito. Similarly, interannual variations in climatic conditions in Australia, especially those due to the El Niño cycle, influence the pattern of outbreaks of Ross River virus disease [28], [29].

Climate change, via both a shift in background climate conditions and changes in regional climatic variability, will affect the spatial and seasonal patterns of the potential transmission of various vector-borne infectious diseases. These would include: malaria, dengue fever, various types of viral encephalitis, schistosomiasis (spread by water-snails), leishmaniasis (spread by sand-flies in South America and around the Mediterranean coast), onchocerciasis (West African 'river blindness', spread by black flies) and yellow fever (also spread by the *Aedes aegypti* mosquito). The key phrase here is *potential transmission*. It is relevant to estimate how the intrinsic infectious disease transmission properties of the world would alter in response to climate change. Indeed, such research is in the classic tradition of experimental science, which seeks to hold everything else constant while estimating the effect of varying just one key factor. Nevertheless, we know that the *actual* transmission of diseases such as malaria is, and will be, much affected by economic and social conditions and by the robustness of public health defenses. Hence, we also need to develop methods of modeling that can incorporate other reasonably foreseeable contextual changes.

Both statistical and biologically-based ('process-based') models have been used, to assess how shifts in ranges of temperature and patterns of rainfall would affect the transmission potential of various vector-borne diseases [30], [31]. However, this type of scenario-based modeling of future risks has not yet attempted to address all aspects of the 'scenario'. For example, how will domestic and urban water use (particularly relevant to dengue fever occurrence) change in a warmer world with altered patterns of precipitation? How would an increase in the tempo of extreme weather events and natural disasters affect infectious disease occurrence? We still have many things to learn about how the impending shift into unfamiliar climatic conditions will affect the complex processes of infectious disease transmission, especially the vector-borne diseases.

Meanwhile, there is now appearing suggestive evidence that the climate change that has occurred over the past 30 years has influenced cholera outbreaks in Bangladesh [32], the extension of tick-borne encephalitis in Sweden [33] and, more debatably, the range and seasonality of malaria in some parts of eastern Africa [34].

6. The Modern World: Too Hygienic?

There is, finally, one other aspect of modernity that we should note. It, too, reflects a shift in human ecology. The pattern of exposure to infectious agents in childhood can perturb the human immune system in two ways: by influencing its developmental pathway, and by initiating autoimmune disorders. Modern living entails a more hygienic childhood, with the elimination or deferral of childhood infections that have long influenced the development of the young immune system. Most dramatically, this led to the rise of polio in developed countries in the 1950s because children were no longer exposed to the polio virus in early childhood when the infection is normally harmless. More subtly, this increase in hygiene, along with fewer siblings, has reduced the intensity of childhood exposure to a range of infectious agents, including the many commensal bacteria that, historically, colonized the infant gut. This significant shift in human ecology affects the early-life programming of the immune system, inclining it towards a more 'atopic' (allergic) pattern of response. This may help explain the recent widespread rise of childhood asthma and hay fever. Likewise, the progressive elimination of bowel parasites such as round-worms, whip-worms and pin-worms (parasites which coevolved with hominids over several million years) may have contributed to the rise in inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, in Western populations over the past half century.

Infectious agents can also influence the occurrence of autoimmune disorders, in which the immune system erroneously attacks normal body tissues. A basic evolutionary device of parasitic microorganisms is to acquire an outer protein surface that resembles that of the host's tissue. This 'molecular mimicry' provides camouflage against attack by the host immune system, since proteins recognized by the host immune system as 'self' are not normally attacked. Occasionally the immune system gets it wrong, and attacks both the microorganism and the part of 'self' that it resembles. It is likely that insulin-dependent diabetes (which usually

begins in childhood), multiple sclerosis and rheumatoid arthritis all involve this type of viral infection-triggered autoimmune mechanism.

7. Conclusion

As ever, the world is replete with microbes jostling for supplies of nutrients, energy and molecular building blocks. From the microbe's viewpoint, the appropriate microbe (often in mutant form), fortuitously in the right place at the right time, can extend, re-start or even found a dynasty. It has happened many times before and it will continue to do so.

As the scale of human impact on the biosphere escalates, and as the structures and fluidity of human societies change along with the levels of susceptibility of local human populations, so, perennially, these environmental and social-economic changes create opportunities for infectious agents, both new and resurgent. Today, this process is occurring at an accelerated rate, and, increasingly, on a global scale, as we undergo a fourth, and larger-than-ever, transition in the overall relationship between the human species and the microbial world.

If we are to achieve a more enlightened, ecologically attuned, coexistence with the microbial world, and a capacity to anticipate and minimize infectious disease risks, then the main challenges for researchers are to develop a broadly-based inter-disciplinary collaboration and a capacity to deal with complexities, uncertainties and spatial-temporal scales that extend beyond conventional research practice.

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