SECTION 2

**FRAMEWORKS FOR
UNDERSTANDING POPULATION
DYNAMICS AND INFECTIOUS
DISEASES IN ASIA**

2

Ecological and Social Influences on Emergence and Resurgence of Infectious Diseases

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Introduction

During the third quarter of the 20th century, the age-old scourge of infectious disease, the biblical ‘Fourth Horseman of the Apocalypse’; was widely assumed to be receding in the developed world. The antibiotic era had begun with great success in the 1940s; vaccine know how was accelerating, pesticides were available for controlling mosquito populations, and surveillance and control measures (border controls, quarantine, other social controls, public education) were becoming internationally coordinated. Not surprisingly, by the early 1970s, various eminent scientists and government authorities proclaimed the imminent end of the infectious disease era.

In retrospect, this proclamation was premature. By late 20th century, it had become evident that the world faced a generalised upturn in emerging and resurgent infectious diseases (Weiss and McMichael, 2004). Over 30 new infectious diseases were identified in the last quarter of last century, including HIV/AIDS, ‘mad cow disease’ as a source of human variant Creutzfeldt Jakob Disease (CJD), hepatitis C, Nipah virus and many viral haemorrhagic fevers. Since 2000, this narrative has continued worldwide, and particularly in the Asia-Pacific region, with severe acute respiratory

syndrome (SARS) and the avian flu virus. Meanwhile, many of the long-established infectious diseases such as tuberculosis, malaria and dengue fever have increased.

On the whole, this return and revival of new and old infectious diseases is a reflection of the distinctive conditions in a modern globalising world, i.e. persistent poverty (especially in urban slums), rapid increases in population size and density, urbanisation, mobility (air-travel, refugees, rural-urban migration, etc.), long-distance trade, conflict and warfare. There are also contributions from human-induced global environmental changes, i.e. the disturbance and destabilisation of ecosystems and biophysical processes such as the climate system. Political ignorance, denial and obduracy (as with HIV/AIDS) often compound the problem. Meanwhile, diarrhoeal disease and acute respiratory infections, especially in conditions of poverty and squalor, continue to kill millions of infants and children every year.

Cholera — the seventh pandemic

Cholera well illustrates how large-scale changes in social, economic and environmental conditions can affect the pattern of infectious disease occurrence. This disease is currently seeing its largest-ever and longest-ever pandemic — the seventh. Meanwhile, a new eighth cholera pandemic (entailing a new strain of the cholera bacterium) is currently emerging in South Asia.

Epidemics of a cholera-like disease have been described in the Ganges delta in India over the past four centuries (Lee and Dodgson, 2000). Cholera (its genotype apparently reinforced with a newly acquired toxin-producing gene) first extended its range beyond South Asia in 1817. This initial extension followed the Great Kumbh annual religious festival in the Upper Ganges, in which Hindu pilgrims from all over India came to bathe in the sacred waters. Their subsequent dispersal and contacts with British troops mobilising in the northwest frontier region sparked a cholera pandemic 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-travelling steamboats enabled cholera to cross the Atlantic. The disease reached North America in 1832, and spread rapidly around the United States coastline and inland via major rivers.

This current seventh pandemic has extended further than ever before, affecting Asia, Europe, Africa, North America and Latin America. It began in 1961 and is by far the longest lasting cholera pandemic to date (Lee and Dodgson, 2003; WHO, 2003a). The pandemic entails the El Tor strain, which, in mid-twentieth century, replaced the more lethal classical biotype of the nineteenth-century pandemics. The extraordinary scale of this pandemic seems particularly to reflect the great increase in human movement between continents, the greater rapidity and distance of modern shipping-based trade, the growth of urban slums with unsafe drinking water, and the increased nutrient enrichment of coastal and estuarine waters by phosphates and nitrates in agricultural and domestic run-off water (and which enhance proliferation of vibrio-harbouring phytoplankton and zooplankton) (McMichael, 2001).

Infectious disease in populations: an ecological perspective

Our understanding of the changing patterns of infectious diseases in populations can be much enriched by both an ecological and an historical perspective. The worldwide dispersal of the human species over the past 50,000–100,000 years, accompanied by cultural evolution and inter-population contacts, has profoundly transformed the relationship between *Homo sapiens* and the microbiological world. During this grand odyssey, there have been several major transitions at the key historical junctures, each entailing the emergence of various new or unfamiliar infectious diseases (McNeill, 1976).

The coevolution of humans and infectious agents of course has 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 our *Homo sapiens* ancestors spread out of Africa into new environments and climates where they encountered unfamiliar microbes. Since the advent of agriculture and animal husbandry, three other great transitions have occurred in the human-microbe relationship (Weiss and McMichael, 2004). 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, over the course of a thousand years or so, the ancient civilisations of greater Eurasia (Egypt, India, Rome, China) made contact, swapped their dominant microbes and painfully equilibrated. Third, from the 15th century onwards, expansionist sea-faring Europe, pre-eminent technologically, inadvertently exported its lethal, empire-winning, germs to the Americas and later to the South Pacific, Australia and Africa.

We seem now to be living through the fourth great historical transition, one that extends globally for the first time. Today’s apparent increased lability in the occurrence, spread and biological behaviour of infectious diseases reflects the impact of widespread demographic, commercial, environmental, behavioural, technological and other rapid changes in human ecology. Modern clinical medicine, via blood transfusion and hypodermic syringes, has created new opportunities for microbes that have contributed to the rises in hepatitis C, HIV/AIDS and several other viral infections.

Perhaps a new equilibration will occur as the post-genome era of molecular biotechnologies yields new ways to constrain the natural biological impulses of microbes. However, the future will certainly not entail a world free of infectious disease. We must recognise and accommodate the existence of the myriad of microbial species that are part of the interdependent system of Life on Earth. A tiny proportion of those microbes now, as will others in future, causes infectious diseases in humans. Human ecology is now characterised by rapid changes around the world and it is important to sharpen our understanding of the social, economic, technological and environmental influences on infectious disease occurrence.

Social, Economic and Associated Influences

Infectious diseases remain the world’s leading cause of death, accounting for one in three of all deaths. Each year, 17 million people, mostly young children, die from infectious diseases, with acute respiratory infections killing almost 4 million people, diarrhoeal diseases killing 3 million, HIV/AIDS killing 2.5 million, tuberculosis killing 2 million, and malaria killing 1.5 million people annually (WHO, 2003b). The discrepancy in

mortality profiles between the rich and the very poor countries is huge; infections cause 1 to 2% of all deaths in the former, but >50% in the latter. Indeed, among the world's poorest sub-populations, infectious disease causes almost two-thirds of deaths.

Diseases such as tuberculosis, leprosy, cholera, typhoid and diphtheria are known to be pre-eminently diseases of poverty. As happened historically with tuberculosis, HIV infection now seems 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 labour, educational deprivation and sexual commerce (Farmer, 1999). The health ramifications of economic disadvantage that occur under free trade agreements are well illustrated by hepatitis A and cyclosporiasis (a protozoal infection) that occurred in the United States in the 1990s. Outbreaks of these diseases were caused by faecally contaminated strawberries and raspberries imported from Central America. The North American Free Trade Agreement had degraded environmental and labour standards (such as providing toilet facilities for workers) in response to the demands of open competition and profitability. With modern air-transport, diners in New York were able to consume these berries two days after they were picked and were quickly exposed to these faecally transmitted infections.

Socially disordered populations living in circumstances of privation, unhygienic conditions and close contact are susceptible to infectious diseases. History abounds with examples. The severity of the bubonic plague (Black Death) in mid 14th century Europe appears to have partly reflected, the nutritional consequences and attendant impoverishment caused by several preceding decades of unusually cold and wet weather with crop failures (McMichael, 2001). This adverse experience, occurring in conjunction with the incipient destabilisation of the hierarchical feudal system, would have heightened the vulnerability of the European populations to epidemic disease.

The urban environment has recently become the dominant human habitat; approximately half of the world's population now lives in cities or large towns, compared with an estimated 5% about two centuries ago. Cities have been referred to as highways for 'microbial traffic' (Morse, 1992). Urbanism typically entails a breakdown in traditional family and social structures,

and brings greater personal mobility along with extended and labile social networks. These features, accompanied by access to modern contraception, have facilitated a diversity of sexual contacts, and hence the spread of STDs. The growth in sex tourism in today's internationally mobile world, which capitalises in exploitative fashion on the desperation of poverty, amplifies the risk of STD transmission in many of today's developing countries.

Rapid urbanisation, boosted by the urge to enter the cash economy in a globalising marketplace, boosts the risk of old infectious diseases such as childhood pneumonia, diarrhoea, 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 typically increases the risks of infection via the processes of family breakdown and social instability, leading to intravenous drug abuse, and sexual transmission of infections (Cohen, 2003).

Food sources and production

The spectacular outbreak of 'mad cow disease' (bovine spongiform encephalopathy, BSE) in the UK in the mid 1980s underscores the infectious disease risks inherent in changes in food sources and food production methods. In that particular case, the source of the problem lay with the intensification of meat production, entailing the cost-cutting use of recycled bovine offal (including parts of the nervous system). This unnatural practice of feeding animal protein to herbivores inadvertently exposed the artificially 'carnivorous' cattle to a surprising quasi-infectious agent, the prion protein.

Across cultures, there is a widespread predilection for eating meat from various exotic species of animals. This exacerbates the risk of exposure to unfamiliar infectious agents. Indeed, such exposure probably triggered the 2003 epidemic of Severe Acute Respiratory Syndrome, SARS, in the Guangzhou region of Southern China (Peiris and Guan, 2004). The natural reservoir species for the SARS coronavirus remains uncertain. However, infection of Civet cats with SARS-related viruses has been reported, although it is not yet known if this is the original source species. Surveys have shown that the live markets and restaurants in Guangzhou sold various species of small carnivores (e.g. civet cat, racoon dog and ferret badger) that were captured in China, Laos, Vietnam and Thailand, transported to

markets (often across national borders), and that were thereby brought into close proximity (Bell *et al.*, 2004). Thus, infectious agents have much opportunity to move between edible species. Indeed, the recent regionalisation and high-volume intensification of what was previously a local practice, in order to meet the burgeoning urban demand in Southern China, has greatly amplified the health risks of what were previously localised cultural practices in rural settings.

In Africa, consumption of bush-meat (much of it from hunted primates, which are now under increasing threat of extinction) entails a serious risk of acquiring new infectious diseases from zoonotic sources. As an ominous example, molecular genetic studies have shown that the HIV virus has crossed from chimpanzees into humans at least three times (Hahn *et al.*, 2000).

On the international economic front, globalisation of the food market has amplified the movement of pathogens from one region to another. For example, the commercial movement of fruits and vegetables facilitates the redistribution of anti-microbial resistance genes between strains and types of organisms. In the 1990s, alfalfa sprouts grown from a contaminated seed sent to a Dutch shipper caused outbreaks of infections with *Salmonella* species in both the USA and Finland (Mahon *et al.*, 1997).

Travel and trade

Microbes do not respect political and administrative borders. The mobility of humans, animals and birds is a constant stimulus to changes in the pattern of infectious disease occurrence. Vector mosquito species can travel with trade and transport (as apparently did the bubonic plague-infected black rat, travelling westwards across the Silk Road, towards the Black Sea and Europe, in the 14th century). 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. In the case of SARS, infected travellers are often not easy to identify; a prominent carrier was a doctor attending a conference who displayed no signs of illness at all (McLean *et al.*, 2005).

Dengue fever, numerically the most important vector-borne viral disease of humans, provides a good example of 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 behaviourally adaptable to a cold climate), and the increase in imported cases resulting from increased air travel (Kuno, 1995). 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 human kind on its travels and migrations around the world (Monath *et al.*, 1994). 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 tyres from Asia into Africa and the Americas (Reiter and Sprenger, 1987).

Neisseria meningitidis, a global pathogen, causes seasonal epidemics of meningitis in the 'meningitis belt' of Sahelian Africa. Studies with molecular markers have shown that in recent decades, Muslim pilgrims brought an epidemic strain of *N. meningitidis* from Southern Asia to Mecca, where they passed it on to pilgrims from sub-Saharan Africa, who after returning home, initiated strain-specific epidemic outbreaks in several locations (Moore *et al.*, 1989).

The West Nile virus, newly emergent in North America as a human infection, further illustrates the impact of long-distance trade and travel. The disease originated in Africa, and it occurs sporadically in the Middle East and in parts of Europe. It was unknown in North America until it arrived in New York in 1999, perhaps via an infected mosquito on an aeroplane. Birds were affected first and later humans. The apparently favourable environmental conditions for the virus to survive and spread within New York City were these:

- (i) Early season rain and summer drought provided ideal conditions for *Culex* mosquitoes.
- (ii) July 1999 was the hottest July on record for New York City.
- (iii) Suburban/urban ecosystems support high numbers of select avian host and mosquito vector species adapted to those conditions, enabling close interaction of mosquitoes, birds and humans.
- (iv) High populations of susceptible bird species existed, especially crows.

West Nile virus subsequently spread widely across the United States, and by early 2004, it had established itself as an endemic virus, harboured by animals including birds and horses, and transmitted via mosquitoes. In July 2003, Mexico declared a state of emergency when West Nile virus arrived in that country. There is concern that the disease could spread more rapidly in Central and South America than in North America, because the warmer Latin American countries nurture large bird populations and year-round mosquito populations (Mackenzie *et al.*, 2004).

On another front, the escalating international trade in exotic pets also yields unexpected infectious disease outbreaks. For example, the monkey pox virus was recently introduced into the USA in imported African rodents, with subsequent transmission to pet prairie dogs and from them to the other pets and the pet owners (Di Giulio and Eckburg, 2004).

Land use and environmental change

Humans have always changed their environments. With population growth and the intensification of economic activities, such changes are rapidly increasing in magnitude, reflected in tropical deforestation, irrigation, dam building, urban sprawl, road building, intensified crop and animal production systems, and pollution of coastal zones. The increasing scale of this encroachment on, and the disturbance of the natural environment accelerates the emergence of new infectious diseases.

The Nipah virus provides a good recent example. Human contact with this bat-borne virus followed the establishment of pig farms close to the tropical forest in Northern Malaysia, where the Nipah virus first crossed over from fruit bats to pigs and thence to pig farmers in 1999 (Chua *et al.*, 1999). Thousands of pigs and several hundred infected farmers and their family members died from the infection. The destruction of natural forest in many other locations has also encouraged fruit bats to relocate nearer human habitation. Indeed in 1997, the Hendra virus, deriving from Australian fruit bats, fatally infected a veterinarian examining a sick horse in Queensland, Australia (Halpin, 1999).

Rodents are a prominent source of new and re-emerging infections, as occurred in the 1990s with Hanta viruses in the USA. Rodent-borne hantavirus is widespread in agricultural systems in South America and

East Asia, in arid grasslands in North America and elsewhere. In mid 1993, an unexpected outbreak of acute, sometimes fatal, respiratory disease occurred in humans in Southwest USA (Parmenter *et al.*, 1993). This ‘hantavirus pulmonary syndrome’ was caused by a previously unrecognised virus that is maintained in the natural environment, primarily within the native deer-mouse, and which is transmitted via rodent excreta. The 1991–1992 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’ (Parmenter *et al.*, 1993; Engelthaler *et al.*, 1999).

Various other environmental changes also influence the occurrence of human infection. In the USA, nature conservation and increased contact with woodland in the Eastern states has led to the emergence of Lyme disease (borreliosis). The ixodic ticks that transmit the spirochaete *Borrelia burgdorferi* normally feed on deer and white-footed mice, with the latter being the more competent viral host species. However, forest fragmentation has led to changes in biodiversity. This includes the loss of various predator species such as wolves, foxes, raptors and others, and a resultant shift of ticks from the less competent to the more competent host species (white-footed mice). These changes, along with middle-class suburban sprawl into woodlands, have interacted in the emergence of this disease (Glass *et al.*, 1995; Schmidt *et al.*, 2001).

Global Environmental Changes and Anticipating the Future

Many of the large-scale environmental changes that humankind is now imposing on the biosphere have profound implications for the future pattern of infectious disease occurrence and transmission. Much of the recent formal research in this emerging topic area has been done in relation to global climate change. However, it is important to recognise that many of these environmental changes will affect infectious diseases, and that they will often do so in concert, including via interactive effects. Further more, the disease impact of changing environmental conditions will usually be modulated by the level of susceptibility of the human population, a function of population density, immune status, the nutritional status, the extent of mobility, the

level of social organisation/disorganisation, flexibility of political systems and of governance, and various other such social-environmental factors.

Global climate change

The now-certain prospect of human-induced global climate change raises long-term questions about how infectious diseases will respond in the coming century and beyond. Many infectious agents, their vector organisms and their reservoir non-human species, are sensitive to climatic conditions and to resultant environmental changes.

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 spreads primarily by the *Aedes aegypti* mosquito. (Dengue causes an estimated 100 million cases annually in tropical and sub-tropical countries.) Similarly, inter-annual variations in climatic conditions in Australia, especially those due to the El Niño cycle, influence the pattern of outbreaks of Ross River virus disease (Tong *et al.*, 2002; Woodruff *et al.*, 2002).

Climate change, via both a shift in background climate conditions and changes in regional climatic variability, will affect the potential (spatial and seasonal) 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 perfectly relevant to estimate how the world's intrinsic infectious disease transmission properties would alter in response to climate change. Indeed, such research is in the classic tradition of experimental science, which seeks to hold all other factors constant, while estimating the effect induced by 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 defences. Hence, we must strive to develop methods of modelling that 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 (Martens, 1999; Hales *et al.*, 2002). However, this genre of future scenario-based modelling has not yet been able to address all aspects of the topic. 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? There are still 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.

In the meantime, there is suggestive evidence that the climate change observed over the past 30 years has influenced cholera outbreaks in Bangladesh (Rodo *et al.*, 2002), the extension of tick-borne encephalitis in Sweden (Lindgren and Gustafson, 2001), and more debatable, the range and seasonality of malaria in some parts of Eastern Africa (Patz *et al.*, 2002).

Anticipating future infectious disease risks

A tantalising question is whether we can estimate the future probabilities of infectious disease emergence and resurgence. This is obviously extremely difficult given that we could not have foreseen the emergence of HIV/AIDS, Mad Cow Disease or SARS. High-precision deterministic models are not achievable since the world is inherently stochastic, and hence microbial mutation occurs in random fashion (as it is intrinsic to Darwinian biological evolution), and the evolution of human culture and behaviour is unpredictable. Nevertheless, there are techniques for modelling the approximate likely range and form of future infectious disease epidemics (Brockman *et al.*, 2005).

However, we do know that the following situations create auspicious conditions for (new) microbes to become human infections:

- (i) Increasingly intense modification/exploitation of natural environments, often entailing new human-microbe contacts.
- (ii) The disturbance of natural ecosystems and their various internal biotic controls. This results in the disruption of the natural constraints on infectious pathogens and on their host species and vector organisms.
- (iii) Poverty, crowding, social disorder and political instability.

Consider influenza where the molecular-biological and clinical aspects are well understood. However, the underlying ecological dimensions (e.g. the poultry-pig-human interactions) remain less definitive (Weiss and McMichael, 2004). A typical scenario is where wild fowl infected with avian flu come in contact with intensely-farmed poultry, with pigs acting as a mediating (and perhaps genetically recombining) host; this is followed by the co-infection of a farm-worker who already carries the preceding strain of human flu, leading to a highly infectious genetically-recombinant form which spreads to the other people, some of whom board an airplane bound for a major population centre.

We can better approach the anticipation of future risks if we have both ecological and historical insights. Much can be learnt from past experience about the sorts of composite situations that increase the probability of either new microbes entering human populations or known infectious agents extending their range, their seasonality or their virulence (particularly the salutary experience, over recent decades, of having induced widespread antimicrobial resistance among many infectious pathogens).

Conclusion

As ever, the world is replete with microbes striving for supplies of nutrients, energy and molecular building blocks. The right microbe fortuitously in the right place can extend, re-start or found a dynasty. It has happened many times before and it will continue to do so.

We can better engage with the topic if we apply both ecological and historical perspectives to it. Since we live non-negotiably in a microbially-dominated world, we must think more in ecological terms about our relations with microbes. The lesson of recent times is that we cannot conquer the microbial world. However, we could (and must) get better at coexisting.

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 these large-scale changes create various opportunities for infectious agents, both new and resurgent. Today, this process appears to be occurring at an accelerated rate, and on a global

scale. We are undergoing a fourth and larger-than-ever transition in the overall relationship between the human species and the microbial world.

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