

Infectious diseases: an ecological perspective

Mary E Wilson

Microbes have played a decisive role in human history. Between 1348 and 1352 in many European countries plague was estimated to have killed a third to a half of the population.^{1,2} It was not swords and guns but imported microbes, carried by explorers over oceans, that defeated native populations in the Americas,³ and in Australia and southern Africa the arrival of Europeans killed off local populations by introducing infectious diseases. Local flora and fauna were also irreversibly altered. Many of these fertile, temperate, and now less populated lands were subsequently settled by Europeans.³

By the middle of the 20th century, infectious diseases were no longer the major causes of mortality in developed countries. The eradication of smallpox reinforced the perception that infectious diseases could be eliminated. Improved sanitation, clean water, and better living conditions, along with vaccines and antimicrobial agents, brought many infectious diseases under control in industrialised countries, but infections continued to kill millions each year in the developing world. Infectious diseases remain the most common single cause of death in the world today. Of the 51 million deaths worldwide in 1993, an estimated 16.4 million resulted from infectious and parasitic diseases.⁴ In sub-Saharan Africa, communicable diseases account for more than 70% of the burden of ill health (as measured by disability adjusted life years), in contrast to about 10% in industrialised countries.⁵

Increasingly humans have changed the earth in ways that make it easier for microbes to move and to reach vulnerable populations. Widespread use of antimicrobial agents and chemicals produces selective pressure for the survival and persistence of more resistant populations of microbes, and also of more resilient insect vectors.⁶ Patterns of infectious diseases are changing globally and on a massive scale.^{7,8} Although poor and disadvantaged people are hardest hit, emerging infectious diseases have been reported in all regions of the world. A massive outbreak of cryptosporidiosis in Milwaukee, USA, in 1993 affected more than 400 000 people.⁹ Hantavirus pulmonary syndrome was recognised for the first time in 1993 after an outbreak of fatal pulmonary disease in the south-western United States.¹⁰ recognised as a distinct clinical syndrome in 1981, has reached every country of the world, and the cumulative worldwide total of infected people could reach 30-40 million by the year 2000.

Diseases such as Lassa fever, AIDS, and Ebola disease have focused attention on viral infections, but pathogens involved in these changed infectious diseases also include bacteria, fungi, protozoa, and helminths. Drug resistance is increasingly reported not only in bacteria but also in viruses, fungi, protozoa, and helminths. Arthropods, such as mosquitoes, lice, and ticks, are becoming more resistant to pesticides. Outbreaks of infectious diseases have caused die offs in species as diverse as beans, rice, seals, dolphins, lions, chickens, and horses. In 1845 the potato blight fungus, *Phytophthora infestans*, already known in North America, was first detected on the other side of the Atlantic. It spread from the Isle of Wight and destroyed potato crops across Europe. But the impact was greatest in Ireland, where an estimated 1 million people died from starvation.¹¹ In 1970 a fungus attacked hybrid corn and spread throughout the United States, destroying 15% of the corn crop.¹² Apart from their direct impact on human health, such events hold important lessons about the ecology of disease.

More than mere microbes

More than a century ago Koch presented his famous postulates for ascertaining the cause of infection. Subsequent decades saw the discovery of many infectious microbes, including viruses. One by one, diseases and microbes were matched—and it became clear that determining the cause of disease was not simple. Today we understand that the concept of the microbe as the cause of an infection is inadequate and incomplete because it ignores the influence of the host, the milieu, and the social and physical environment. Yet medical science still tends to focus on the microbe as the foe, and our response has often been to seek and destroy the invader.

A more enlightened understanding would embrace an ecological perspective. Humans have reached such numbers and have developed such technologies that human activities have a global impact and have changed the earth for all other biological life.¹³ Humans are part of a vast evolutionary process and all life is interdependent. Students of human health must look at the health and resilience of the ecosystem and approach analysis at a systems level.

Three general forces can affect the burden of infectious diseases in humans: change in abundance, virulence, or transmissibility of microbes; an increase in probability of exposure of humans to microorganisms; and an increase in the vulnerability of humans to infection and to the consequences of infection. A wide range of biological, physicochemical, behavioural, and social factors influence one or more of these forces. Many are interrelated, and multiple synergies exist.

Migration

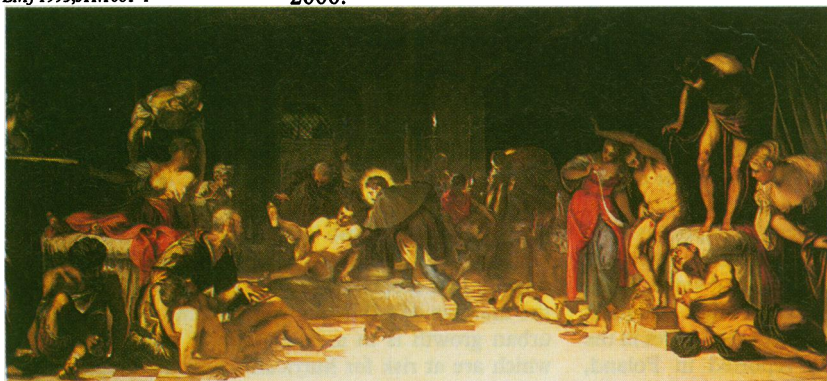
Migration of people has always played a large part in introducing infections into new populations.¹⁴ John Snow wrote in 1849: "Epidemics of cholera follow major routes of commerce. The disease always appears first at seaports when extending into islands or continents."¹⁵ The magnitude and speed of migration

Departments of Population and International Health and Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115-6023, USA

Mary E Wilson, assistant professor

email: mewilson@warren.med.harvard.edu

BMJ 1995;311:1681-4



The services of St Roche, patron of those struck by plague, were much in demand in the Middle Ages

today is unparalleled in history. In 1994 there were an estimated 22 million refugees and 25 million displaced people worldwide.¹⁶ In the early 1990s, according to the World Tourism Organisation in Madrid, more than 500 million people annually crossed international borders on commercial aeroplane flights. An estimated 70 million people, primarily from developing countries, work either legally or illegally in other countries.¹⁷ Much migration is unplanned and unwanted and leads to settlement in areas or under conditions that place people at increased risk of infectious diseases.

Because of political conflict or instability, economic pressures, and environmental changes, masses of people are being displaced.¹⁶ Many refugees seek asylum in developing countries. Refugee camps, resettlement areas, and temporary shelters are often characterised by crowded living conditions, poor sanitation, limited access to clean water, little medical care, poor nutrition, and lack of separation from insects and animals in the environment. These features increase the probability of exposure to infections in such vulnerable populations. Many examples document the ravages of infectious diseases such as cholera, measles, malaria, and shigella dysentery in these settings. After the movement of 500 000-800 000 Rwandan refugees into Zaire in 1994, almost 50 000 refugees died during the first month as epidemics of cholera and *Shigella dysenteriae* type 1 swept through the refugee camps.¹⁷

The massive movement occurring in the world today includes animals, plants, seeds, insects, and all manner of biological life in addition to humans. Through their conveyances by air, water, and land, humans have given wings to plants, animals, and microbes, extending and speeding up their spread.¹⁸ Air travel accelerated the spread of HIV around the globe. Introductions of new species of plants and animals can change the ecology in an area, sometimes extinguishing local species because of predation, disease, competition, and changes in the habitat.¹⁹ Introducing insect vectors can affect human health if the vector is capable of transmitting pathogens to humans.

Many areas of the world are now receptive to the occurrence of viral infections, such as dengue fever, because of the introduction of *Aedes albopictus*^{20 21} and the expansion of the range of *Aedes aegypti*.²² The ballast water of ships travelling between Japan and Coos Bay, Oregon, was found to harbour 356 different species of marine organisms.²³

Islands are especially vulnerable to invasions. An estimated 1900 species of endemic plants and more than 5000 species of insects preceded human colonists in Hawaii. Over centuries, arrivals of humans brought to the Hawaiian islands rats, mongooses, mosquitoes, cockroaches, English sparrows, many other animals, and more than 4500 species of alien plants.²⁴

When a virulent clone of a pathogen emerges, as has happened with *Neisseria meningitidis*, many pathways from one geographical area to another are available.²⁵ In 1987 group A meningococcal disease spread throughout Haj pilgrims in Mecca; they carried the virulent clone home to the United States, the United Kingdom, Pakistan, other parts of Saudi Arabia and the Gulf states, and elsewhere.²⁶ The time frame of past centuries has been telescoped by the magnitude and speed of modern travel. Borders are porous and microbes readily cross them. When an outbreak of diphtheria occurs in the new independent states of the former Soviet Union, populations in other countries also feel the impact: cases linked to the exposures in the Russian Federation have been reported in Poland, Finland, Germany, and the United States.²⁷ On the basis of serological studies, it is estimated that up to

60% of adults in America and Europe are susceptible to diphtheria.²⁷

Climatic effects

Changes in climate and the environment have many direct and indirect effects on human health.²⁸⁻³⁰ Temperature and humidity influence the abundance and distribution of vectors and intermediate hosts.³¹⁻³³ Global warming can reshape vegetation zones³⁴ and can be expected to change the distribution and abundance of vector borne infections, such as malaria. Warmer temperatures may allow insects and pests to survive winters that normally would have limited their populations.³⁵ An increase in malaria in Rwanda coincided with record high temperatures and rainfall.³⁶ In 70 communities in Mexico, median temperature during the rainy season was the strongest predictor of dengue fever: higher temperatures increased vector efficiency.³⁷

Global warming may be contributing to a global epidemic of coastal algal blooms, though runoffs rich in nitrates, phosphorus, chemical pollutants, and organic material and overharvesting of fish that graze on plankton may contribute as well.³⁸ Consequences to human health are direct and indirect. Toxic dinoflagellates can sicken humans who eat shellfish. Toxic algal blooms have also been associated with massive dying off of marine life.

Extreme climatic events, such as droughts and floods, are expected to increase with predicted global climate changes.¹³ Many disease outbreaks have occurred after extreme climatic conditions. These include vector borne infections such as malaria and Venezuelan encephalitis, animal borne infections such as hantaviruses, and water borne infections such as cholera and hepatitis E.

Settlement patterns

Climatic and environmental changes also lead humans to migrate, to develop new lands, and to live in settings that favour the spread of infectious diseases. Simultaneously we are seeing increased urbanisation and exploration and clearing of new lands. Both carry risks for infectious diseases. The huge periurban settlements that have grown, especially in tropical regions, have risks for infectious diseases similar to those precipitated by resettlement. Dengue fever is one example of an infection that spreads readily in the tropical urban environment. Residents come from different geographical regions and may revisit families in rural areas regularly, providing a conduit for the carriage of microbes. Clearing and settlement of new lands disturbs an existing ecosystem and may uncover microbes in soil or animals, sometimes carried by arthropod vectors, that were previously unrecognised as human pathogens. Venezuelan haemorrhagic fever, caused by the rodent borne Guanarito virus, was first recognised in 1989 after a severe outbreak. Increasing migration into the endemic area and development of new land may have provided more favourable conditions for the rodents and placed more people in contact with them.³⁹

Population growth means people are living in higher densities, heightening the risk for rapid spread of infections. As of 1990 an estimated 1.3 billion people in the developing world lacked access to clean water and nearly 2 billion lacked an adequate system for disposing of faeces.⁵ More people are being pushed to the margins of habitable land. Much of the increased urban growth is in areas within 75 miles of the sea, which are at risk for hurricanes and floodings, and in areas at increased risk for earthquakes. Increased density of populations and inadequate resources also



DAVIES/PANOS

Much migration is unplanned and leads people to live where they are at increased risk of infectious diseases



BETTY PRESS/ANOS

For refugees, such as these Rwandans, limited access to water, and crowded living conditions increase the probability of exposure to infections

make for social and political instability.⁴⁰ These multiple vulnerabilities often converge in a population or geographical region.

New vulnerabilities

Technological gains are often offset by new vulnerabilities. Interventions can often have unintended and unexpected consequences. Wide use of antimicrobials has led to high rates of resistance among many bacteria.⁶ Mass processing and distribution of food has resulted in occasional massive outbreaks of infections, such as salmonellosis and *Escherichia coli* O157:H7, that could not have occurred without the wide distribution networks. Large municipal water systems made it possible to infect more than 400 000 people with *Cryptosporidium parvum* within a few days.⁹ Modern medical techniques applied with inadequate training and resources have had disastrous consequences, as shown by dramatic outbreaks of nosocomial Lassa fever in Nigeria⁴¹ and Ebola disease in Zaire.⁴² Transmission of virus to patients and medical staff resulted from exposure to contaminated needles and from lack of adequate barriers during surgery.

Changes in climate lead to creation of new habitats that are energy expensive and provide new avenues for spread of infection. Air and water cooling systems have been associated with outbreaks of legionnaires' disease. The natural habitat for *Legionella pneumophila*, the cause of the disease, is streams, lakes, and other bodies of water, where it is present in small numbers. Human inventions such as water cooling towers and water distribution systems provide favourable conditions for the survival and proliferation of the bacteria and the means for dissemination. *L pneumophila* survives in concentrations of chlorine typically used to treat water.

Influenza in Louisiana, USA, appeared in August and early September 1993, a time unusual for influenza transmission in the temperate zone,⁴³ but August had had record breaking high temperatures and low rainfall. The outbreaks, two in nursing homes and one on a barge, had common features: shared living areas and shared recirculated (air conditioned) air. Factors historically associated with influenza outbreaks are crowding and low humidity. The new habitat of large air conditioned areas may predispose to influenza transmission outside the expected period.

Many patients with cystic fibrosis can now survive for decades through attentive medical care. Recent outbreaks of *Pseudomonas (Burkholderia) cepacia* in cystic fibrosis centres in Toronto, Canada, and in Edinburgh were associated with high mortality.⁴⁴

Molecular markers allowed documentation of a lineage adapted for efficient transmission in people with cystic fibrosis. This highly transmissible clone, which was responsible for epidemics in these British and North American centres, adheres better to human epithelial cells than do other isolates of this bacterium. The appearance of this distinctive clone in different continents was thought to be related to attendance at international summer camps. Human interventions at multiple points set the stage for microbial selection and assisted its amplification and spread.

Fatal mixtures

The world today is in a state of turbulence and rapid change. The emergence of infections in many geographical areas is but one manifestation of instability and stress in the system. Today there are unprecedented opportunities for mixing of people, animals, and microbes from all geographical areas in an environment that has been altered by industry, technology, agriculture, chemicals, and climate change and by the demands of population growth. Diverse genetic pools are mixing in rates and combinations and in a time frame too short to allow adaptation through genetic change. Many interventions have been carried out with too narrow an understanding of their impacts.

The invisible weapons of today's conflicts are microorganisms. In most of the wars throughout history, infectious diseases killed more troops than did the weapons of war. Since the second world war more civilians than combatants have died from war. In recent conflicts the victims have often been those whose lives have been upset by the upheaval—refugees, displaced populations, children without access to immunisation and oral rehydration fluids, the hungry and vulnerable masses who succumb to infections that are neither exotic nor new.¹⁶ Earlier in this century mortality from tuberculosis in many European countries showed a striking increase in response to war.⁴⁵

There is an urgent need to integrate knowledge about infectious diseases with knowledge of climate and environmental change, migration and population growth, demography, and the consequences of conflict. All are inextricably linked and play a part in the changed patterns we are seeing in infectious diseases.

We have more scientific data about the present and past than ever before. We have biopsies of the earth, the ice cores, that reveal secrets of past climatic patterns. Frozen bodies, preserved insects, mice, and mummies examined by the polymerase chain reaction and other techniques help to create a fuller knowledge of life in past centuries. Will this translate into understanding and changed behaviour in a way that preserves the health of humans and the biosphere? Many events suggest that there is a mismatch between what we know and what we have been able to do. The barriers to identifying and intervening in infectious diseases are more often social and political than scientific.

Much recent attention has focused on exotic and previously unrecognised lethal pathogens. While it is important to study these pathogens and to identify the events that lead to their appearance and spread, it is essential not to ignore pathogens that are familiar and thus often less feared. Influenza, which killed 20 million people in the year after the end of the first world war, is still a killer and has the capacity to change rapidly and spread widely throughout the world.⁴⁶ Two attributes of the influenza virus—its potential for rapid genetic change and its ease of transmission—make it a continued threat that is often overlooked and underestimated.

Examples of changed patterns in infectious diseases

Diseases by previously unrecognised or uncharacterised agents:

- Hantavirus pulmonary syndrome (*Sin Nombre virus*)
- Lyme disease (*Borrelia burgdorferi*)
- Cat scratch disease (*Bartonella henselae*)
- Cryptosporidiosis (*Cryptosporidium parvum*)
- Ehrlichiosis (*Ehrlichia chaffeensis*)

Geographical expansion of known infectious disease:

- Dengue fever (dengue viruses)
- Yellow fever (yellow fever virus)
- Malaria (*Plasmodium falciparum*)
- Cholera (*Vibrio cholerae*)

Increased incidence of previously controlled disease:

- Tuberculosis (*Mycobacterium tuberculosis*)
- Diphtheria (*Corynebacterium diphtheriae*)

Increased resistance to drugs:

- Pneumococcal infections (*Streptococcus pneumoniae*)
- Staphylococcal infections (*Staphylococcus aureus*)
- Shigellosis (*Shigella dysenteriae*)
- Malaria (*Plasmodium falciparum* and *P vivax*)

Altered expressions of diseases:

- Meningococcal infections (*Neisseria meningitidis* clone)
- Bacillary angiomatosis (*Bartonella henselae*)
- Leishmaniasis in HIV infected people
- Mycobacterium avium* complex in HIV infected people

New agents (no evidence yet for previous existence):

- Escherichia coli* O157:H7
- Vibrio cholerae* O139
- Equine morbillivirus

Progress without breakthroughs?

It is difficult to imagine any breakthroughs in social, political, or scientific arenas that will halt population displacement or the rise in poverty and disease. What can be done? Others have written persuasively about the need for enhanced surveillance and global networks. These must be integrated across disciplines and geographical regions. Several elements seem essential; we should

- Recognise the links between population growth, climatic and environmental change, global migration, and human health and security
- Develop databases that combine information about climate, demography, population movements, and diseases in humans, animals, and plants
- Identify markers for regions or populations at high risk of epidemic disease so that we can intervene to reduce the impact of disease
- Continue efforts slow population growth
- Take steps to reduce mass migration and displacement of populations
- Reduce consumption
- Pay more attention to land use and production and disposal of toxins and chemicals
- Take a broader view and longer time frame when analysing the potential impact of interventions
- View human life as part of a constantly evolving biosphere.

Throughout history infectious diseases have waxed and waned. In today's world, socioeconomic, political, environmental, and climatic changes have converged to allow many infectious diseases to flourish. But a rise in infectious diseases is only one of the manifestations of global instability. Any meaningful response must integrate knowledge from multiple disciplines and approach the problem at the systems level. To be successful, we must apprehend infectious diseases in their evolutionary and ecological context.

- 1 McNeill WH. *Plagues and peoples*. New York: Anchor Press/Doubleday, 1976.
- 2 Wilson ME. The power of plague. *Epidemiology* 1995;6:458-60.
- 3 Crosby AW. *The Columbian exchange. Biological and cultural consequences of 1492*. Westport, CT: Greenwood, 1972.
- 4 World Health Organisation. *The world health report 1995, Bridging the gap*. Geneva: WHO, 1995.
- 5 World Bank. *World Development Report 1993*. New York: Oxford University Press, 1993.
- 6 Neu HC. The crisis in antibiotic resistance. *Science* 1992;257:1064-73.
- 7 Lederberg J, Shope RE, Oaks SC Jr, eds. *Emerging infections: microbial threats to health in the United States*. Washington, DC: National Academy Press (Institute of Medicine), 1992.
- 8 Wilson ME, Levins R, Spielman A, eds. *Disease in evolution: global changes and emergence of infectious diseases*. New York: New York Academy of Sciences, 1994.
- 9 MacKenzie WR, Hoxie NJ, Proctor ME, Gradus MS, Blair KA, Peterson DE, et al. Massive waterborne outbreak of Cryptosporidium infection associated with a filtered public water supply, Milwaukee, Wisconsin, March and April, 1993. *N Engl J Med* 1994;331:161-7.
- 10 Nichol ST, Spiropoulou CR, Morzunov S, Rollin PE, Ksiazek TG, Feldmann H, et al. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. *Science* 1993;262:914-8.
- 11 Raeburn P. *The last harvest. The genetic gamble that threatens to destroy American agriculture*. New York: Simon and Schuster, 1995.
- 12 Board on Agriculture, National Research Council. *Managing global genetic resources: agricultural crop issues and policies*. Washington, DC: National Academy Press, 1993.
- 13 Intergovernmental Panel on Global Climate Change. *Policy makers summary of the potential impacts of global climate change: working group II second assessment report*. New York: IPCC (in press).
- 14 Wilson ME. Travel and the emergence of infectious diseases. *Emerging Infect Dis* 1995;1:39-46.
- 15 Winkelstein W Jr. A new perspective on John Snow's communicable disease theory. *Am J Epidemiol* 1995;142:S3-9. (Citing Snow J. *On the mode of communication of cholera*. London: John Churchill, 1849.)
- 16 Toole MJ. The rapid assessment of health problems in refugee and displaced populations. *Medicine Global Survival* 1994;1:200-7.
- 17 Goma Epidemiology Group. Public health impact of Rwandan refugee crisis: what happened in Goma, Zaire, in July, 1994? *Lancet* 1995;345:339-44.
- 18 McCarthy SA, Khambaty FM. International dissemination of epidemic Vibrio cholerae by cargo ship ballast and other nonpotable waters. *Applied Environ Microbiol* 1994;60:2597-601.
- 19 Elton CS. *The ecology of invasions by plants and animals*. Trowbridge and London: English Language Book Society, 1972.
- 20 Centres for Disease Control. *Aedes albopictus* introduction into Continental Africa, 1991. *MMWR* 1991;40:838-8.
- 21 Grist NR. New mosquito in Africa. *Lancet* 1993;339:1363.
- 22 Gubler DJ, Clark GG. Dengue/dengue hemorrhagic fever. *Emerging Infect Dis* 1995;1:55-7.
- 23 Carlton JT, Geller JB. Ecological roulette: The global transport of non-indigenous marine organisms. *Science* 1993;261:78-82.
- 24 Weiner J. *The beak of the finch: a story of evolution in our time*. New York: Knopf, 1994.
- 25 Schwartz B, Moore PS, Broome CV. Global epidemiology of meningococcal disease. *Clin Microbiol Rev* 1989;2:S118-24.
- 26 Moore PS, Reeves MW, Schwartz B, Gellin BG, Broome CV. Intercontinental spread of an epidemic group A *Neisseria meningitidis* strain. *Lancet* 1989;ii:260-3.
- 27 Centers for Disease Control. Diphtheria acquired by US citizens in the Russian Federation and Ukraine—1994. *MMWR* 1995;44:237, 243-4.
- 28 Leaf A. Potential health effects of global climate and environmental change. *N Engl J Med* 1989;321:1577-83.
- 29 Chivian E, McCalley M, Hu H, Haines A. *Critical condition: human health and the environment*. Cambridge, MA: MIT Press, 1993.
- 30 McMichael AJ. *Planetary overload: global environmental change and the health of the human species*. Cambridge: Cambridge University Press, 1993.
- 31 Watts DM, Burke DS, Harrison BA, Whitmore RE, Hisslak A. Effect of temperature on the vector efficiency of *Aedes aegypti* for dengue 2 virus. *Am J Trop Med Hyg* 1989;36:143-52.
- 32 Shope R. Global climate change and infectious diseases. *Environmental Health Perspectives* 1991;96:171-4.
- 33 Reeves WC, Hardy JL, Reisen WK, Milby MM. Potential effect of global warming on mosquito-borne arboviruses. *J Med Entomology* 1995;31:323-32.
- 34 Root TL, Schneider SH. Ecology and climate: research strategies and implications. *Science* 1995;269:334-41.
- 35 Tickell SC. Global warming: trends and effects. *Parasitology* 1993;106:S5-9.
- 36 Loevisohn ME. Climatic warming and increased malaria incidence in Rwanda. *Lancet* 1994;343:714-8.
- 37 Koopman JS, Prevost DR, Marin MAV, Dantes HG, Aquino MLZ, Longini IM Jr, et al. Determinants and predictors of dengue infection in Mexico. *Am J Epidemiol* 1991;133:1168-78.
- 38 Smayda TJ. Novel and nuisance phytoplankton blooms in the sea: evidence for a global epidemic. In: Graneli E, Sundstrom L, Deler L, Anderson DM, eds. *New York: Elsevier Science*, 1990.
- 39 Tesh RB. The emerging epidemiology of Venezuelan hemorrhagic fever and Oropouche fever in tropical South America. In Wilson ME, Levins R, Spielman A, eds. *Disease in evolution: global changes and emergence of infectious diseases*. New York: New York Academy of Sciences, 1994.
- 40 Homer-Dixon TF. On the threshold. Environmental changes as causes of acute conflict. *International Security* 1991;16(2):76-116.
- 41 Fisher-Hoch SP, Tomori O, Nasidi A, Perez-Orozco GI, Fakile Y, Hutwagner L, et al. Review of cases of nosocomial Lassa fever in Nigeria: the price of poor medical practice. *BMJ* 1995;311:857-9.
- 42 Centres for Disease Control. Update: outbreak of Ebola viral hemorrhagic fever—Zaire, 1995. *MMWR* 1995;44:468-9; 475.
- 43 Kohn MA, Farley TA, Sundin D, Tapia R, McFarland LM, Arden NH, et al. Three summertime outbreaks of influenza type A. *J Infect Dis* 1995;172:246-9.
- 44 Sun L, Jiang R-Z, Steinbach S, Holmes A, Campanelli C, Forstner J, et al. The emergence of a highly transmissible lineage of cbl+ *Pseudomonas* (Burkholderia) cepacia causing CF centre epidemics in North America and Britain. *Nature Med* 1995;1:661-6.
- 45 Dubos R, Dubos J. *The white plague: tuberculosis, man, and society*. New Brunswick, NY: Rutgers University Press, 1987 (1952).
- 46 Crosby AW. *America's forgotten pandemic: the influenza of 1918*. Cambridge: Cambridge University Press, 1989.