Emerging infectious diseases: the Fifth stage of the epidemiologic transition?

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Epidemiologic transition theory

The demographic record of anatomically modern human beings suggests that, for the vast majority of our 130 000-year existence, birth rates and death rates have remained at very high levels – somewhere between 30 to 50/1 000 (Omran, 1971). Although birth rates have probably been quite stable for most of human history, death rates have been volatile – a volatility caused by the ever-present deadly force of locally-concentrated epidemic infectious and parasitic diseases (IPDs) in our early ancestors, but punctuated by the episodic influence of pandemic plagues and infections that wiped out relatively large segments of the population (McNeil, 1977). The historical record also suggests that persistently high levels of "extrinsic" mortality (dominated by IPD deaths, but also including accidents, homicide, suicide, and predation) are the primary reason that survival to sexual maturity has been denied to the majority of human beings ever born. It has only been within the last few hundred years that social and economic changes have permitted people in the developed world to avoid the causes of death that have killed the vast majority of our ancestors. Sadly, the same cannot be said for developing nations. In these countries, where the majority of the human population resides, IPDs are still a major influence on the day-to-day lives of most people.

The transition from high to low vital rates has been referred to as the demographic transition – a phenomenon that has been documented and discussed extensively in the scientific literature (Davis, 1963; McNamara, 1982; Teitelbaum, 1975). The mortality component of this transition has been further elaborated within what is called epidemiologic transition theory (Omran, 1971). According to Omran, the transition from high to low death rates has been characterized by a secular transformation of vital rates along a three-stage process – population changes that have led to rapid increases in life expectancy at birth, a shift in the age distribution of death from the young to the old, and an accompanying shift in the underlying causes of death.

The First stage of the epidemiologic transition – Omran's *Age of Pestilence and Famine* – refers to a mortality state that prevailed for most of human history. During this stage, extremely high death rates were vacillating between peaks and troughs in response to Malthusian positive checks such as epidemics, famines, and war. In the middle of the 19th century, in many now developed nations, the Second stage – Omran's *Age of Receding Pandemics* – began. Epidemic peaks in mortality became less frequent, and in some cases disappeared as endemic infections were reduced. As a consequence, life expectancy at birth climbed rapidly from about 35 to 50 years. The Second stage also produced two of the most significant demographic changes in human history; explosive population growth and population ageing. During the Third stage of the epidemiologic transition, Omran's *Age of Degenerative and Man-made Diseases*, death rates stabilized at relatively low levels (about 10/1 000). In addition, the major causes of death shifted from infectious and parasitic diseases to chronic disorders associated with ageing, such as cardiovascular diseases, and cancers. This stage was thought to occur at varying rates across nations because the mortality transition was being driven by socially determined factors in developed nations, and by medical technology throughout the developing world. It was also suggested that the early health and longevity benefits of this transition would be first experienced primarily by infants, children, and women of childbearing ages, subgroups of a population most susceptible to infectious and parasitic diseases.

Early in the epidemiologic transition, life expectancy at birth rose rapidly because declines in death rates were concentrated among the young. Later, in the 20th century, the rise in life expectancy at birth was attributed mostly to declines in death rates that occurred in those surviving to middle and older ages. A shift in the underlying causes of death, and in the ages at which these deaths occurred explains why the rapid rise in life expectancy at birth observed during this century has decelerated (Olshansky, Carnes & Cassel, 1990). Saving the lives of children adds many years to life, whereas the survivors at older ages are confronted by high overall mortality risks even though death rates for major causes of death (such as cardiovascular diseases) are declining.

In his original formulation, Omran (1971) never argued explicitly that infectious and parasitic diseases would be eliminated, nor did he discuss future trends in age-related diseases. The key concept of

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epidemiologic transition theory was the suggestion that the causes of death that had dominated human history would be replaced by the chronic degenerative diseases that are associated with survival extended into older ages. In other words, age at death shifted primarily from the young to the old, as the principal causes of death shifted from infectious and parasitic diseases to chronic degenerative diseases.

Extending epidemiologic transition theory

In the latter half of the 20th century, a totally unexpected phenomenon occurred. Death rates from some chronic degenerative diseases began to decline rapidly. For example, between 1968 and 1995 (particularly between 1968 and 1982), death rates from heart disease in the United States (responsible for 1 of every 4 deaths in 1968) declined by over 25 percent – a dramatic change over a remarkably brief period of time. Furthermore, these declining death rates were concentrated in people at middle and older ages, a phenomenon neither anticipated, nor discussed in epidemiologic transition theory. This new trend in mortality occurred not just in the United States, but throughout the nations of the developed world, and in more advantaged subgroups within the developed nations. In fact, this new pattern of mortality was so dramatically different from the Third stage that some researchers proposed that Omran's epidemiologic transition theory should be extended to account for this phenomenon (Olshansky & Ault, 1986; Rogers & Hackenberg, 1989).

One extension, proposed by Olshansky and Ault (1986), called this "new" pattern of mortality "the fourth stage of the epidemiologic transition," labeling it *The Age of Delayed Degenerative Diseases*. This Fourth stage was still characterized by the lingering presence of the major degenerative causes of death described in Omran's Third stage, but with an average age at death that was significantly delayed. The delays in age at death from degenerative causes were attributed to the influence of medical technology, a force used by Omran to explain the mortality transition observed in developing nations. The term now used to describe these improvements in survival is "manufactured time", which is a phenomenon that can be quantified by examining survival trends for people diagnosed with chronic fatal diseases (Olshansky, Carnes & Grahn, 1998). The Fourth stage was also characterized by gains in life expectancy at birth that had become more influenced by declining death rates at older than at younger ages. The influence of infectious and parasitic diseases was inappropriately dismissed in this proposed Fourth stage of the epidemiologic transition, because it was believed that these causes of death had come almost entirely under the control of modern medicine.

Another Fourth stage extension, *The Hybristic Stage*, was developed by Rogers and Hackenberg (1989) to address factors of potential demographic importance not considered in the original three-stage model. These factors included 1) an interplay between infectious and chronic diseases within individuals that could give rise to an increase in infectious and parasitic diseases associated with the rising prevalence of chronic conditions, a phenomenon influenced by rapid population ageing, 2) the important influence of extrinsic social pathologies such as accidents, homicide, and suicide (particularly at younger ages), 3) the critical role of individual behaviours in the timing of expression of ageing related mortality, which are factors that can have both positive (e.g., improved lifestyles) and negative (e.g., cigarette smoking) effects on longevity, and 4) the negative effects on longevity associated with a combination of social and behavioural factors, including economics, public policy, and human behaviour (e.g., the relatively recent emergence and spread of HIV/AIDS, and the inability to eliminate some infectious and parasitic diseases in spite of the availability of immunizations).

The *Age of Delayed Degenerative Diseases* model did not account for the four mortality modifiers identified in the *Hybristic Stage* model. The emergence of causes of death judged to be strongly influenced by individual behaviour and lifestyle including such major causes as cardiovascular disease and cancer was predicted by the Hybristic model as the so-called "hybristic diseases." The *Hybristic Stage* model did not consider, however, the potential influence of genetic factors on the age of expression of chronic degenerative diseases. Neither of the proposed extensions of Omran's model addressed the possible re-emergence of infectious and parasitic diseases. Although Omran recognized the interaction between environment and resistance to infectious disease, epidemiologic transition theory focused primarily on how the manipulation of environmental factors could facilitate *reductions* in death rates from IPDs (Omran, 1971:520). The dominance of the Omran paradigm made it difficult for scientists to foresee the important influence that the re-emergence of these ancient killers could have on human mortality (Olshansky, *et al.*, 1997; Wilson, Levins, & Spielman, 1994).

Global re-emergence of infectious and parasitic diseases

Any discussion about the re-emergence of infectious and parasitic diseases should begin with a recognition that nearly all of the communicable diseases causing morbidity and mortality in the world today could be avoided with technologies that already exist – clean water, sewage disposal and treatment, more sanitary living conditions, antibiotics, immunizations, and changes in behaviour. In other words, controlling the health and mortality consequences associated with most known IPDs is more a financial, or political challenge than a technological obstacle. It should be noted, however, that just a few decades ago this

attitude led the medical community to declare that humanity was on the verge of one of the most important social revolutions in history – the complete elimination of IPDs (Burnet & White, 1962). Ironically, this optimistic announcement coincided with the emergence of serious obstacles that blocked the pathway to the elimination of these ancient killers.

As alluded to earlier, the persistence of health threats posed by IPDs is due, in part, to an inability to use existing technology to control or eliminate these diseases. Of more serious concern, however, are the unanticipated threats to public health that have been caused by "new" diseases that have surfaced during the last quarter of the 20th century. The new diseases recognized since 1973 are listed in Table 1.

Several diseases listed in Table 1 are notable: the emergence of Ebola and Hanta virus in 1977, the E-coli bacterium 0157:H7 in 1982, the HIV identified in 1983, the Hepatitis C virus in 1989 and the Sin nombre virus in 1993. These diseases have already had a profound effect on human health in every part of the globe, as evidenced by their global mapping (see Figure 1).

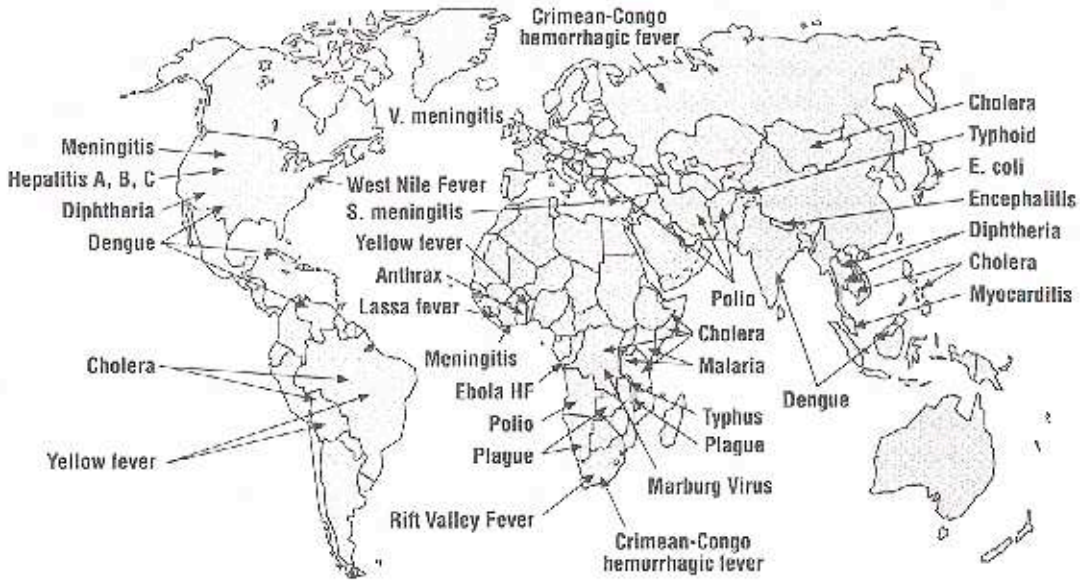
In a literal sense, it is probably incorrect to refer to these diseases as new. For example, it is likely that the HIV has existed for hundreds, or even thousands of years, crossing over from animal populations occasionally to kill small isolated subgroups of human beings. Encroachments into yet-to-be, unidentified HIV environments, caused by expanding human populations, and by a population density that is large enough to sustain the virus have given the HIV the opportunity to use human beings as a permanent host. It is estimated that the HIV has infected more than 47 000 000 people throughout the world. HIV/AIDS has quickly become the fourth leading cause of death globally (WHO, 1996), and its relative importance to total mortality is still growing. To illustrate the magnitude of the problem, more than 2 200 000 people died from HIV/AIDS-related illnesses in 1998, a number equivalent to the total number of deaths

Table 1
Disease-Causing Microbes and Infectious Diseases Recognized Since 1973

Year	Microbe/disease	Type	Health problem
1973	Rotavirus	virus	Major cause of infantile diarrhoea worldwide
1975	Parvovirus B19	virus	Severe anemia
1976	Cryptosporidium parvum	parasite	Acute and chronic diarrhoea
1977	Ebola	virus	Ebola hemorrhagic fever/uncontrolled bleeding and kidney failure
1977	*Legionella pneumophila*	bacterium	Legionnaires' disease
1977	Hantavirus	virus	Hemorrhagic fever
1977	*Campylobacter jejuni*	bacterium	Short-term diarrhoea
1980	Human T-lymphotropic virus 1 (HTLV-1)	virus	T-cell lymphoma-leukemial cancer of the blood
1981	Toxic strains of *Staphylococcus Aureus*	bacterium	Toxic shock syndrome
1982	*Escherichia coli* 0157:H7	bacterium	Hemorrhagic colitis; hemolytic uremic syndrome
1982	HTLV-II	virus	Hairy cell leukemia
1982	*Borrelia burgdorferi*	bacterium	Lyme disease
1983	Human immunodeficiency virus (HIV)	virus	Acquired immune deficiency syndrome (AIDS)
1983	*Helicobacter pylori*	bacterium	Peptic ulcer disease
1985	Enterocytozoon bieneusi	parasite	Persistent diarrhoea
1986	Cyclospora cayetanensis	parasite	Persistent diarrhoea
1988	Human herpesvirus-6 (HHV-6)	virus	Roseola subitum / skin rash
1988	Hepatitis E	virus	Liver infection, epidemic hepatitis
1989	*Ehrlichia chaffeensis*	bacterium	Human ehrlichiosis / influenza-like infection
1989	Hepatitis C	virus	Chronic liver infection
1991	Guanarito virus	virus	Venezuelan hemorrhagic fever
1991	Enccohalitozoon hellem	parasite	Conjunctivitis
1991	New species of Babesia	parasite	Atypical babesiosis / infection with fever, chills and fatigue
1992	*Bartonella henselae*	bacterium	Cat-scratch disease / bacillary angiomatosis
1993	Sin nombre virus	virus	Adult respiratory distress syndrome
1993	Encephalitozoon cuniculi	parasite	Infection with fever, chills and fatigue
1994	Sabia virus	virus	Brazilian hemorrhagic fever
1995	Human herpesvirus 8 HHV 8	virus	Associated with Kaposi's sarcoma in HIV/AIDS patients

Source: WHO, The World Health Report 1996: 112.

Fig. 1
Selected outbreaks of infectious and parasitic diseases (IPDs) reported between July 1996 and December 1999



Source: WHO Outbreaks report (online), available at http://www.who.int/emc/outbreak news/index.html (December 1999)

from all causes combined in the United States in the same year (WHO, 1999 fact sheet).

The Ebola story is similar. Outbreaks of the Ebola virus have been restricted to small geographically isolated subpopulations in Africa. As in the case of the HIV, the Ebola virus has probably existed within animal populations for a long time. Unlike the HIV, however, the rapid progression of debilitating symptoms and lethality in human beings continues to keep the Ebola virus contained within a small geographic area. The consequences could be devastating if this deadly virus were somehow transported to a densely populated urban area.

The *Helicobacter pylori* bacterium has also been labeled as new when it was discovered in 1983 that this bacterium was the primary cause of peptic ulcer disease. Previously, the general consensus was that this disease was caused by stress. As with the HIV and Ebola virus, the only thing new about *H. pylori* was the discovery of a causal relationship between this bacterium and a specific disease.

The Hepatitis C Virus (HCV) is an example of a genuinely new disease that spread rapidly across the globe since it was identified in 1989 (Lavanchy, 1999). Approximately 3% of the world's population (about 170 000 000 persons) are now infected with HCV. It is estimated that 20% of the carriers of HCV develop cirrhosis of the liver, and that between 1% to 5% of those with cirrhosis will develop liver cancer within 10 years (WHO, 1999 fact sheet). If the virus indeed plays a causal role in this disease etiology, a wave of liver cancer could sweep across the globe in the coming decades, comprising a global threat to health that is linked to a virus that first appeared a mere two decades ago.

Another genuinely new disease is a genetic variant of the bacterium that causes cholera – *Vibrio cholerae* 0139. This virus first appeared in the Bay of Bengal in 1992, and then spread quickly to 10 other South Asian countries (WHO, 1998). Although the spread of this generic variant has waned in recent years, the prevalence of *V. cholerae* O1 biotype El Tor, which first appeared in Indonesia in 1961, more than doubled in a single year between 1997 and 1998 (WHO, 1999a). This dramatic rise in cholera to almost 300 000 cases, and over 10 000 deaths in 1998 alone occurred mostly in West Africa, and was believed to result from climate changes related to El Niño (WHO, 1999a).

In recent years, dramatic increases in incidence have been reported for a number of infectious diseases that have probably been around for thousands of years. For example, dengue is a mosquito-borne disease that is common in tropical and sub-tropical regions of the world. The relatively mild dengue fever was first identified in the 18th century and its deadly complication, dengue hemorrhagic fever (DHF), was first described at the end of the 19th century (Halstead, 1992). Although the prevalence of both diseases rose rapidly after the 1954 epidemic in the Philippines spread to other Asian nations, the most dramatic increases followed the 1981 epidemic in Cuba (Pinheiro & Corber, 1997). Today, dengue is endemic in virtually every continent except Europe. The deadly DHF form of dengue had been reported in only 9 countries prior to 1970, but has now reached epidemic levels throughout Asia, and most of the Americas. The rapid spread of the mosquito vector across the globe has put an estimated 2 500 000 people at risk for dengue. Be-

tween 1981 and 1995, the number of dengue/DHF cases have more than tripled in many Asian countries and the number of cases more than doubled in the Americas during the 3-year period between 1995 and 1998 (Pinheiro & Corber, 1997). In the first 10 months of 1998, the total number of dengue/DHF cases in Brazil (475 000) was greater than the total number of cases reported just a few years earlier for all of South America.

Over the last two decades of the 20th century, the number of yellow fever epidemics has risen, and more countries than ever are reporting cases of the disease. Deforestation, urbanization and global climate changes have expanded the habitat for the mosquito that carries the virus responsible for yellow fever (*Aëdes aegypti*). Just as in the case of dengue, the mosquitos have responded by increasing in number, and becoming more widely distributed geographically. The proliferation and ease of international travel are also thought to contribute to the ongoing spread of this disease (WHO, 1999, fact sheet). There are an estimated 200 000 cases of yellow fever every year, and this number is rising.

Influenza is a disease that has been known for thousands of years, and still contributes to global trends in mortality. Probably the first influenza pandemic recorded was in 1580. There have been 31 subsequent pandemics described in the literature that could be attributed to influenza. The ones most familiar to people today include the Spanish Flu pandemic (designated A(H1N1)) of 1918–1920 that killed more than 20 000 000 people, and the 1957 Asian Flu and 1968 Hong Kong Flu pandemics (both designated A(H2N2)) that together killed more than 1 500 000 people. Given the regularity with which pandemics punctuate the flu epidemics that occur across the globe every year, scientists thought that another pandemic had begun when it was discovered in 1997 that a child in Hong Kong was infected with a virus (designated A(H5N1)) previously known to infect only birds. Although there were only 18 confirmed cases and 6 deaths associated with what is now known as the Avian Flu virus, public health officials were worried because of the apparent direct transmission of the disease from bird to human host (Centers for Disease Control, 1998). After the virus had jumped to human beings, another pandemic was possible. The most troublesome aspect of the annual flu epidemics, and of the less common, but more dangerous flu pandemics is that the most vulnerable hosts are children and the elderly. Global population ageing has dramatically increased the number of elderly residing in nursing homes and extended care facilities, resulting in high concentrations of people who are particularly vulnerable to the flu viruses that will appear in the coming years.

Prior to the 20th century, the bacterial disease *Diphtheria* was one of the leading causes of childhood mortality. Improved living standards, and the development of immunizations caused the prevalence and death rate from this disease to decline. Periodic outbreaks still occurred among unvaccinated people living in developing and developed countries, especially during World War II, and among people of lower socioeconomic status (Vitek & Wharton, 1998). In the late 1970s, a new strain of the disease-causing bacterium made it possible for diphtheria to make a comeback in the former Soviet Union. When the Russian Federation was formed, the frequency and content of the childhood and adult vaccinations for diphtheria were altered. As a consequence, a diphtheria epidemic began in 1990, and by 1995 there were more than 50 000 cases of the disease reported across the states making up the Federation (Vitek & Wharton, 1998). Although a diphtheria vaccine was quickly made more widely available, the incident raised serious concerns about the efficacy of this, and of other infectious disease programmes. As the majority of cases were adults, officials were concerned that adults who were immunized as children had not acquired immunity to the disease, and that without an adult revaccination programme, the older population would be vulnerable to the disease (Galazka & Robertson, 1995).

Of all the infectious diseases that have plagued humanity throughout history, malaria would be one of the most devastating of them in terms of either morbidity or mortality. The global malaria eradication programme begun in the middle of the 20th century was successful at first, when dramatic reductions occurred as treatments for the disease were developed, and insecticides were used to attack the mosquito vector. Since the early 1970s, however, the prevalence of malaria has risen at an alarming rate due to a reduction in vector control programmes and the lack of an effective replacement for DDT. There are now an estimated 300 to 500 000 000 new cases of malaria each year that cause between 1 500 000 and 2 700 000 deaths (World Health Organization, 1996). Now that malaria is endemic in 91 countries, and almost 50% of the world's population is at risk (90% of the population of Africa), this disease is a serious and growing threat, especially for children and pregnant women (Gubler, 1998; Nchinda, 1998).

The re-emergence and spread of malaria have become commonplace. A typical course of events occurred in the western highlands of Kenya. In the early 20th century, an expanding network of roads and railways led to the inadvertent transport of the malaria-carrying mosquitos from the low-lying area of Lake Victoria to the previously uninfected highland areas (Malakooti, Biomndo & Shanks, 1998). The development of tea estates and agriculture in the highlands also contributed to the rise in malaria. Deforestation increased the breeding grounds for mosquitos, and laborers already infected with malaria migrated to work on the estates. Yet mosquito reduction programmes and disease treatments (pyrimethamine and chloroquine) were so successful

that this part of Kenya had been declared free from malaria throughout the 1960s (Roberts, 1964).

The resurgence of malaria in Africa has been attributed to many factors: a protozoan parasite that has become resistant to treatment, mosquito vectors that have grown resistant to insecticides, the abandonment of DDT for environmental reasons, climate and land use changes that have been favourable to the mosquitos, inadequate financial resources to combat malaria and other diseases (such as HIV/AIDS), conflicts forcing migration into malarial areas, civil unrest and for economic factors (Malakooti, Biomndo & Shanks, 1998; Nchinda, 1998). The malaria problem is not restricted to Africa. During the 1990s, there has been a dramatic increase in the prevalence of malaria in South America (Roberts *et al.*, 1997), and epidemics have arisen in parts of Asia and India (Gubler, 1998).

Recurring themes in many of the recent IPD histories have been the growing problem of resistance to antibiotics by the organisms that cause disease, and the resistance to insecticides by the vectors that spread disease (Levy, 1998). Short generation times, and rapid population growth permit microbes to adapt rapidly to antimicrobial agents (Murray, 1991). For example, when first reported in Europe in 1988, the vancomycin-resistant *enterococcus* (VRE) bacterium appeared to be restricted to hospital settings (Urley *et al.*, 1988). Recent evidence suggests that VRE has escaped hospitals, and has been introduced into other health-care settings (McDonald *et al.*, 1998). In the United States, it is estimated that 15% of nosocomial (hospital-acquired) enterococcal infections are resistant to treatment by vancomycin (Centers for Disease Control, 1993). Alarmingly, recent data suggest that the antimicrobial agents used to enhance the growth rate of feed animals may have given rise to a VRE that can be transmitted from animals to human beings (Wegener *et al.*, 1999).

Evidence for a rising tide of multi-drug resistant bacteria is growing. The list includes, but is not restricted to, *E. coli, Staphylococcus aureus, Shigella flexneri, Shigella dysenteriae, Vibrio cholerae, Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae, Neisseria meningitidis, Helicobacter pylori, Campylobacter jejuni, Salmonella Typhimurium, Salmonella Hadar, Bacteroides fragilis, Neisseria gonorrhoeae, Mycobacterium tuberculosis* (Aubry-Damon & Courvalin, 1999; Okeke, Lamikanra & Edelman, 1999). Some of these bacteria are resistant to all presently known antibiotics.

The importance of the emergence of resistant disease vectors should not be underestimated. In recent decades, the emergence, or re-emergence of many diseases can be attributed to the growing resistance of arthropod vectors to insecticides. As examples, consider the mosquitos that transmit malaria, dengue/DHF, yellow fever, encephalitis and filariasis, the ticks that carry Lyme disease and ehrlochiosis, the fleas and lice that carry *Bartonella* and rickettsiosis, and the sand flies that transmit leishmaniasis (Brogdon & McAllister, 1998). The combination of resistant bacteria and resistant disease vectors represents an important and alarming development in the constantly evolving relationship that exists between pathogens and human health.

Factors other than the biology of IPDs and their vectors have also contributed to the re-emergence and spread of IPDs throughout the world. Some of these factors are new phenomena in the history of human-microbial interactions (Olshansky *et al.*, 1997; WHO, 1999b). Population ageing, growth and movement are aspects of human demography that can have a profound impact on the maintenance and spread of IPDs. Tremendous advances in transportation technology not only move goods and people around the globe in a matter of hours, but they also transport microbes and their vectors. Social, political and economic factors that cause the movement of people can increase the contact between microbes and people – whether by voluntary movements of people from rural to urban areas, or by the involuntary movement of political refugees into IPD-rich environments. The disruption of air, land, and water by earthquakes, droughts, floods, hurricanes, El Niño, volcanoes, and other acts of nature can have a significant impact on the movement and geographic dispersion of microbes, their vectors and their subsequent interactions with human beings. Environmental changes caused by human beings (e.g., dam and road building, deforestation, flood control projects, irrigation) also contribute to the spread of IPDs. The overuse of antibiotics and insecticides is a major concern – a nearly unregulated activity that could have disastrous consequences for human beings in the ongoing arms race with microbes. Finally, an inadequate or deteriorating infrastructure of public health can cause delays or failures in the response to health threats posed by communicable diseases, a phenomenon that has already contributed to the re-emergence of IPDs in both developed and developing countries.

There have also been notable changes in the transmission routes of infectious diseases. Historically, IPDs were transmitted through contaminated food and water, through the air, or by disease vectors such as mosquitos and ticks. Now, many of the most deadly infectious diseases are transmitted through drug abuse, blood transfusions, and through sexual contact. Such diseases now include HIV and hepatitis B and C. Thus compared to the pre-existing infectious diseases, some new diseases possess fundamentally different characteristics – diseases with different modes of transmission that require the development of new preventive efforts. For example, while it is relatively easy to control the spread of cholera by purifying water, it is difficult to control *salmonella* infection by completely supervising food handling, and it is perhaps even more

difficult to control HIV/AIDS through encouraging safe sexual practices.

Many infectious diseases throughout the world, but particularly in less developed countries (LDCs), arise from the direct or indirect effects of poverty (Gwatkin & Heuveline, 1997). Gwatkin *et al.* (1999) examined the world's poorest 20% of the population based on per capita incomes adjusted for purchasing power. Overall, most of the world's 20% came from states in India, sub-Saharan Africa, Bangladesh, and Southeast Asia, with relatively fewer coming from provinces in China, the Middle East, Latin America and the Caribbean. Furthermore, 59% of the communicable diseases occurred among the poorest 20% of the world's population. Even within developing and developed countries, there are dramatic interclass variations in the risk of infectious diseases – with the poor much more likely to die from IPDs (Gwatkin & Hueveline, 1997). Ironically, most of the deaths now occurring from IPDs throughout the world, regardless of social class, can be prevented with existing medical technology and interventions (Murray & Lopez, 1996).

The last two years of the 20th century have been particularly notable for the re-emergence of IPDs. The global epidemics associated with HIV and hepatitis C continue to flourish. In addition, there have been major outbreaks of a number of other debilitating and deadly diseases. In Africa, there have been outbreaks of cholera, yellow fever, meningitis, Ebola, typhus, and Crimean-Congo hemorrhagic fever. In Asia, there have been outbreaks of cholera, diphtheria, dengue, typhoid, and resistant forms of meningitis. In North and South America, there have been notable examples of dengue, diphtheria, cholera, and yellow fever. In 1999, a strain of West Nile-like encephalitis appeared in the state of New York, a disease that had never before been seen on the North American continent.

Does the re-emergence of infectious and parasitic diseases represent a new Fifth stage in the epidemiologic transition? Or, alternatively, does the decline in death rates observed for IPDs over the past 200 years represent only a temporary lull in the force of extrinsic mortality. If so, does the re-emergence of IPDs in recent decades signal a return to the First stage of the epidemiologic transition, the stage that encompassed most of human history? In the remainder of this paper, a case will be made for both arguments.

The Fifth stage of the epidemiologic transition?

The re-emergence of IPDs during the last quarter of the 20th century is associated with demographic features that distinguish it from the Fourth or Hybristic stage of the epidemiologic transition. A unique set of demographic and health circumstances in low mortality populations has contributed to a significant rise in IPDs, and to a pronounced shift toward older ages in the age groups of a population that are most affected by their re-emergence. The uniqueness of the demographic features has led some researchers to hypothesize that some population subgroups have entered a new Fifth stage of the epidemiologic transition – *The Re-emergence of Infectious and Parasitic Diseases* stage.

As population ageing sweeps across the globe, the absolute number and proportion of the total population of elderly is rising rapidly – approaching 20–25% in some developed nations. This represents a new and dramatic shift in the age structure of the human population. For most of human history, less than 1% of the population was aged 65 and over. In addition to ageing-related diseases, the compromised immune system of the elderly makes them particularly vulnerable to infectious diseases, especially pneumonia and influenza. The demographic momentum of population ageing ensures that the number of people who are immunologically compromised will grow – a trend that will accelerate rapidly over the coming decades as the baby boom cohorts of the mid-20th century reach older ages.

Population ageing has a societal consequence that also contributes to the rise and spread of IPDs. As the size of the older population increases, so does the number of people living within health care facilities for the elderly. Although serving a critical need, these facilities promote the rapid spread of infectious disease because they usually contain dense populations of people whose immune systems are either fragile, or compromised – compromised by age, as well as by medical treatments for degenerative diseases. Acquired or nosocomial infections are often quite virulent under these conditions, but until recently they have been contained within the buildings in which they arose. Evidence is accumulating, however, that virulent strains of the nosocomial infections are escaping to the general population due to rapid increases in the number of nursing homes and assisted living facilities (Centers for Diseases Control, 1999). Although not linked to population ageing, a comparable situation exists in prisons where HIV/AIDS and tuberculosis have spread rapidly. In both cases, infectious diseases have spread rapidly through crowded populations and, by escaping geographical containment, have augmented the infectious disease burden of the general population.

The human immunodeficiency virus (HIV) and the disease it causes (AIDS) have created a dramatic and unprecedented impact on the rise and spread of IPDs. Two decades ago, HIV was an obscure virus of little concern to public health officials. Today, it is globally distributed, and has infected an estimated 47 000 000 people. HIV is particularly insidious because it operates, in part, by attacking the immune system. As a consequence, HIV not only contributes directly to the IPD burden, but by compromising immune systems it also contributes to the burden indirectly by increasing the chances of op-

portunistic infections by other IPDs. For example, the recent increase and spread of antibiotic-resistant forms of tuberculosis has been directly attributed to rising rates of infection from HIV (WHO, 1999b).

HIV and survival to old age are not the only pathways to a weakened immune system. One of the defining attributes of the Fourth stage of the epidemiologic transition is the postponement of deaths from chronic degenerative diseases. Medical interventions are an important contributor to the postponement of these diseases. For example, chemotherapy and radiation therapy are responsible for reductions in case fatality rates, and the extension of survival for many patients with cancer. An unavoidable side effect of these therapeutic interventions that delay death and extend survival is that the immune system of the patient is weakened. As a consequence, these interventions also expand the pool of individuals at risk for IPDs, and this subgroup of the population will continue to expand as population ageing continues. Ironically, the consequence of medical interventions that are successful can be assimilated to the reaction of a water balloon to a finger prod; poke the balloon in one spot (successful intervention), and a bulge (unintended consequence) will appear elsewhere.

Another factor used in the argument for a Fifth stage of the epidemiologic transition has been the "new" diseases that have emerged as a result of human action. Technically, these diseases are not new. What is new is the recent appearance of drug-resistant strains (genetic variants) of the bacteria and other organisms that cause familiar diseases – diseases such as malaria, meningitis, pneumonia, and tuberculosis among others. The demographic and longevity effects of these re-emerging IPDs also differ from those in any previous stage of the epidemiologic transition. Sexually transmitted diseases such as chlamydia, gonnorhea and syphilis are on the rise, and are known to reduce fecundity and fertility rates in those infected. Some genuinely new infectious diseases, such as hepatitis C, can actually raise the risk of what are otherwise known (perhaps inappropriately) as chronic degenerative diseases, such as cancer and cardiovascular diseases. Furthermore, if some degenerative diseases of late life are caused by IPD exposure early in life, then a rise in IPDs could either push back, or reverse the delay of degenerative diseases that would characterize a population in the Fourth stage of the epidemiologic transition.

Large increases in the absolute size of the immunocompromised population resulting from global population ageing, a rise in the number of people living in nursing homes, and in prisons, medical treatments for cancer, and a growing number of people infected with HIV have together created an entirely new set of conditions that contribute to the rise in IPDs, and a shift in their age distribution to older ages. Other forces influencing today's unique characteristics of IPDs are permanent changes in the human age structure, forces that will have lasting and profound effects on future trends in IPDs. All of these forces combined represent a strong argument according to which the recent emergence of IPDs is a distinctively novel development in the history of human mortality. There are enough new attributes of this period of rising IPDs for it to be considered a Fifth stage in the epidemiologic transition. As is the case with Omran's original three-stage model, it is anticipated that the Fifth stage of the epidemiologic transition will occur at varying speeds, and for somewhat different reasons depending on the country.

The First stage of the epidemiologic transition revisited?

Although the arguments for a Fifth stage are compelling, an equally plausible argument for a totally different interpretation about mortality transitions can also be made. The re-emergence of infectious and parasitic diseases can be viewed as neither new nor novel, but rather a continuation of a mortality pattern that was initially used to define the First stage of the epidemiologic transition. Several arguments support this view.

During the last 200 years, literally billions of people have benefitted from the progress that has been made in gaining some control over IPDs – including antibiotics, immunizations, medical diagnosis and treatment, sanitation, and environmental manipulations. Despite this impressive progress, IPDs are still the single greatest source of human mortality today. Proponents of epidemiologic transition theory distinguish modern patterns of mortality from those of the past. They provide descriptive labels for their classification of demographic attributes, and the effects that these attributes have on the health and life expectancy of a population. These classifications can be useful when making mortality comparisons between population subgroups, or across short periods of time within a population. These transition models can also be misleading, however, because their classification of short-term trends in mortality can lose, or obscure the significance of the larger time frame within which these trends are occurring.

The vast majority of human history falls within what is termed the First stage of epidemiologic transition theory, a volatile stage of mortality characterized by peaks and troughs. To those living within a trough that persists for several generations, or a century, it would appear as though a "new" mortality pattern had emerged, one characterized by death rates that are lower than those experienced by preceding generations. As death rates have fluctuated throughout human history, relatively long periods of declining or increasing mortality are not unusual in either the short, or the long term. If history repeats itself, as it has countless times, the last 200

years of declining mortality should not be viewed as a "turning point" in human mortality that is worthy of its own special designation. This trend may be nothing more than a temporary period of favorable mortality that will be followed by an equally temporary period of unfavorable mortality. From this perspective, the re-emergence of IPDs is simply a predictable and typical phase of the First stage, rather than a "new" stage in the epidemiologic transition of human health.

A biological perspective provides another reason that the current re-emergence of IPDs should be considered nothing more than an ongoing interaction between human beings and microbes. It is natural, but inaccurate, for human beings to think of this interaction in only one direction. How do microbes cause sickness, and what can be done to lessen their impact on human health? Microbes existed for billions of years before anatomically modern human beings appeared some 130 000 years ago. The biological reality is that life on earth could thrive without human beings, but could not survive without microbes.

In terms of their numbers, biomass, diversity, and geographic distribution, microbes are the most successful organisms on earth. They have survived and thrived because their short generation times and high reproductive rates enable them to adapt quickly to environmental challenges. To these simple but elegant life forms, human beings are just another component of their biotic environment. Biologists and the medical community were aware of the potential consequences for public health when antibiotics were developed and introduced, but the benefits of the present outweighed the theoretical costs in the future. Similarly, scientists were aware of the potential dangers when they developed pesticides to protect agricultural plants, and to kill the insect vectors that carry disease. The rapid adaptive responses made by microbes and their vectors are recurrent confirmation of evolution by natural selection's being the organizing principle upon which life is based. Antibiotic-resistant bacteria and viruses that resist treatment (including HIV) are predictable by-products of the severe selection pressures that have been placed upon these organisms by human beings. They have adapted successfully to every biological weapon thrown at them in the past, and their prodigious capacity for reproduction will defeat any new weapons used against them in the future. Although microbes may lose eventually nearly every battle, the fear in the biomedical community is that human beings will lose the war, if we continue using the current rules of engagement.

In the 20th century, human beings have achieved notable (sometimes short-term) victories over such diseases as smallpox, poliomyelitis, tuberculosis, measles, mumps, and diphtheria. In terms of how human beings perceive elapsed time, 50 years is long. As such, it would be easy to think that the microbial killers are no longer a serious threat, and that the milieu of interactions between human beings and disease-causing microbes has been permanently and favourably altered. Neither history, nor biology supports this position. Elapsed time of 50 years or even 500 years is minuscule when considered on an evolutionary time scale. The importance of infectious diseases as a source of mortality has fluctuated widely throughout human history. Organisms flourish or become extinct with, or without the influence of human beings. The human response to microbial threats depends on science, finance, and the organization and implementation of public health programmes, which are actions requiring uninterrupted long-term reflection. Microbes do not think, and more importantly, they do not need to depend on thought for their survival. They simply respond to the environmental challenges that confront them. Academic scholars can identify stages of epidemiologic transition, but for infectious microorganisms, the ebb and flow of their ecological and evolutionary success simply unfold. Trends toward emergence, re-emergence, or disappearance of IPDs are real short-term trends, but have little significance for the ongoing interactions between human beings and the microbes that cause human disease.

Conclusions

McKeown raised the interesting question whether medicine was a dream come true, saving individuals from otherwise fatal diseases; a mirage, substituting one disease for another; or a nemesis, actually doing harm (McKeown, 1979). Investigating trends in causes of death reveals some of the elusiveness of the answer. Certainly on an international scale there have been some great achievements in combating infectious diseases, most notably the eradication of smallpox, and the near elimination of polio. Examining trends in causes of death from the perspective of epidemiologic transition theory is like following a mirage, however, due to the growing amorphous distinction between chronic and infectious diseases.

Despite these concerns, epidemiologic transition theory (Omran, 1971) has proved to be a useful tool for categorizing levels of mortality, and for comparing the relative risks of death across population subgroups over time. Extensions of this model to a Fourth (Olshansky & Ault, 1986), or Hybristic (Rogers & Hackenberg, 1989) stage may have been conceptually justified, but neither of these extensions, nor the original model itself captures the unique set of mortality conditions that are associated with the rising threats from infectious diseases that have surfaced during the last quarter of the 20th century.

A significant number of "new" IPDs have emerged in recent years. These IPDs have already had a profound impact on human mortality, and there is scientific justification to suspect that infectious diseases will continue to have a significant impact on human

health in the future. In fact, an argument can be made that an unique set of demographic and health conditions has now made the human population more vulnerable to IPDs than at any previous time in history. These conditions include an age structure that will lead to a growing population of elderly who are vulnerable to IPDs, the global spread of a "new" virus (HIV) that weakens the immune system needed to ward off IPD attacks, an international network of transportation that can deliver IPDs to just about any place in the world within a day, dramatic encroachments into new habitats that expose human populations to "new" zoonotic diseases, and an alarming rise in the number of antibiotic-resistant strains of bacteria, and of insect vectors that are resistant to pesticides and insecticides, all near-perfect conditions for a global epidemic, or pandemic of IPDs.

Although human beings are now facing mortality risks that are uniquely different from any earlier time period of the modern era, it is unlikely that this time frame warrants being labelled a new stage of the epidemiologic transition. The typical lifespan of human beings defines the time scale that is most easily perceived by human beings, a time frame that rarely exceeds 100 years. As such, a human perspective can easily overlook the biological time frame that is required to fully understand and interpret the never-ending interactions that occur between human beings and the organisms that cause human disease, because it is an evolutionary time scale that encompasses the origin of anatomically modern human beings.

Should the "unique" mortality patterns and risks that are observed today be labelled a new Fifth stage of the epidemiologic transition, another expansion of the Fourth stage, or the re-emergence of the First stage? This question is probably only of concern to academic scholars. Labels are far less important than the elevated risks from IPDs that human populations are now experiencing, and the reasons why these risks are climbing. Warning signals have surfaced repeatedly in recent years, reminders that the ongoing battle with IPDs is far from over. From the first sign of *Staphylococcus aureus* resistance to vancomycin in Japan in 1977 (Hiramatsu *et al.*, 1997), and person-to-person transmission of hantavirus pulmonary syndrome in Argentina (Enria *et al.*, 1996), to the Avian flu virus (H5N1) transmitted directly from bird to human being for the first time in Hong Kong in 1997, and the presence of West Nile-like encephalitis in New York State in 1999, there have been plenty of warning signs. To respond, the continued global monitoring of these alarming events should be intensified, and the continued use and misuse of antibiotics, and of other pharmaceuticals in the escalating battle with microbes should be re-evaluated within the context of recent trends in morbidity and mortality for the diseases that they are intended to influence.

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