Science Progress (2008), 91(1), 1–38 doi: 10.3184/003685008X284628

The epidemiological transition: the current status of infectious diseases in the developed world *versus* the developing world

JOHN W. SANDERS, GREG S. FUHRER, MARK D. JOHNSON and MARK S. RIDDLE

ABSTRACT

Wealthy, industrialized countries of the developed world successfully underwent the "epidemiologic transition" from infectious diseases to degenerative diseases, but developing countries have not yet achieved that transition. This article reviews the current status of Omran's Theory of Epidemiologic Transition, comparing the burden of infectious diseases in the developed world versus *the developing world. The advent of modern sanitation and hygiene practices, effective vaccines, and antibiotics have significantly diminished the burden in the developed world, but infectious diseases remain the most common cause of death worldwide. The persistence of this disease burden has been due to a failure to employee effective strategies and to unforeseen developments, such as the emergence of HIV and the re-emergence of malaria and tuberculosis driven by newly developed drug resistance. The challenge in accurately assessing infectious disease burden and developing effective interventions is reviewed along with the most common diseases and current intervention strategies.*

Keywords: *epidemiology, epidemiologic transition, infectious disease, developing world, developed world, HIV, malaria, tuberculosis, diarrhea, tropical disease*

Disclaimer: The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the Department of Defense, the Department of the Navy, or the Naval Services at large.

CDR John W. Sanders is an Internal Medicine and Infectious Disease Specialist in the United States Navy. His research interests have focused on tropical diseases, especially enteric infections. He has served as the Head of the Enteric Disease Research Program at Naval Medical Research Unit, #3 in Cairo, Egypt, the Head of the Infectious Disease Division at National Naval Medical Center in Bethesda, MD (USA), and is currently the Officer-in-Charge of the Naval Medical Research Center Detachment in Lima, Peru.
He is the corresponding author:
E-mail: sandersj_home@yahoo.com

LT Greg S. Fuhrer is an Internal Medicine Resident at the National Naval Medical Center, Bethesda MD, USA, and is interested in the field of Infectious Diseases.

LT Mark D. Johnson is an Infectious Disease Fellow at the National Naval Medical Center, Bethesda, MD, USA, and has participated in research projects in Peru and Turkey.

LCDR Mark S. Riddle is a Preventive Medicine Physician / Epidemiologist who is currently the Deputy Head of the Enteric Diseases Department at the Naval Medical Research Center, Silver Spring, MD, USA. He was previously the Head of Analysis and Clinical Trials for Enteric Diseases at the Naval Medical Research Unit, #3 in Cairo Egypt. His research interest is focused on enteric infections, but he has broad experience conducting clinical research and performing outbreak investigations in Egypt, Turkey, and Africa.

Introduction

For most of recorded history, infectious diseases have been among the leading causes of suffering and death throughout the world. However, from the middle of the 19th century through the middle of the 20th century, deaths from infectious diseases declined rapidly throughout the developed world[1–4]. In the late 1960s and early 1970s, many leaders in public health were confident that they were witnessing the end of infectious diseases as a major health threat, so much so that US Surgeon General William H. Stewart is frequently quoted as saying it was time to ‘‘close the book on infectious diseases’’ and focus on more chronic ailments such as cancer and heart disease (it appears that Dr. Stewart may not have really made this statement, but it certainly reflects the sentiment of the day) [5,6]. Unfortunately, this victory over infectious diseases was largely only true in the developed world. Current estimates and future projections show that infectious diseases remain the number one cause of death in developing countries, currently accounting for >25% of deaths worldwide, and over 40% of deaths in developing countries, significantly more than in developed countries[7–9] (See Figure 1). However, the success over infectious diseases was not maintained

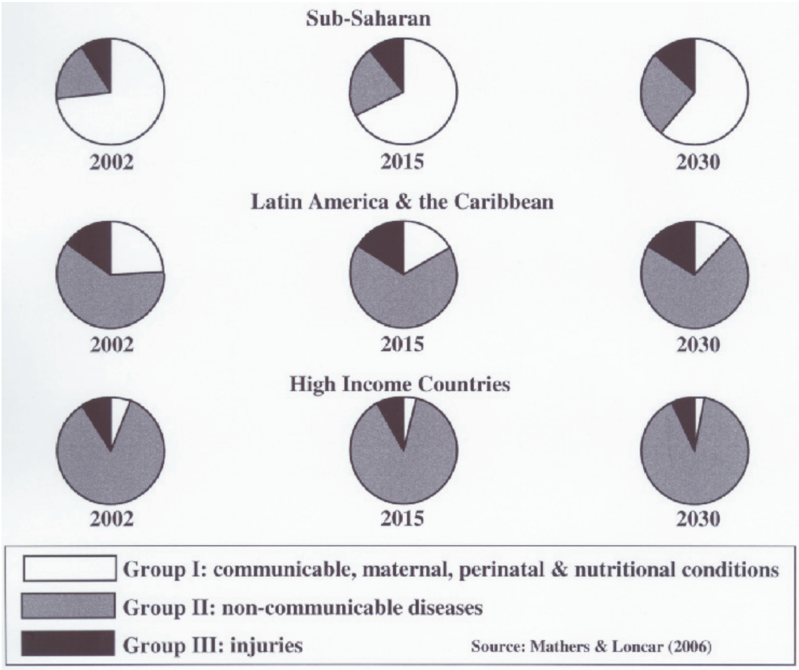

Fig. 1. *Current and projected causes of death in low income versus high income countries.*

even in the developed world. Due to emerging and re-emerging diseases, death rates from infections in the United States increased 58% between 1980 and 1992[10].

In 1971, Abdel Omran proposed the theory of an ‘‘epidemiologic transition’’ to account for the tremendous progress in health seen in industrialized countries over the 19th and 20th centuries[11]. He suggested that all societies progress through three stages of disease: ‘‘the age of pestilence and famine’’, characterized by high, fluctuating mortality rates with life expectancies under 30 years; ‘‘the age of receding pandemics’’, characterized by rising life expectancies to over 50 years, but a persistent heavy burden from infectious diseases; and the ‘‘age of degenerative and man-made diseases’’ during which life expectancy increases further, the burden of infectious diseases declines considerably, and degenerative diseases, such as cancer and cardiovascular disease, become more prevalent. It seemed clear that industrialized countries had moved from the second to the third stage, and it was assumed that developing countries would soon share in a similar decline in infectious disease burden. While progress has certainly been made in many areas of the world, especially when measured simply by mortality

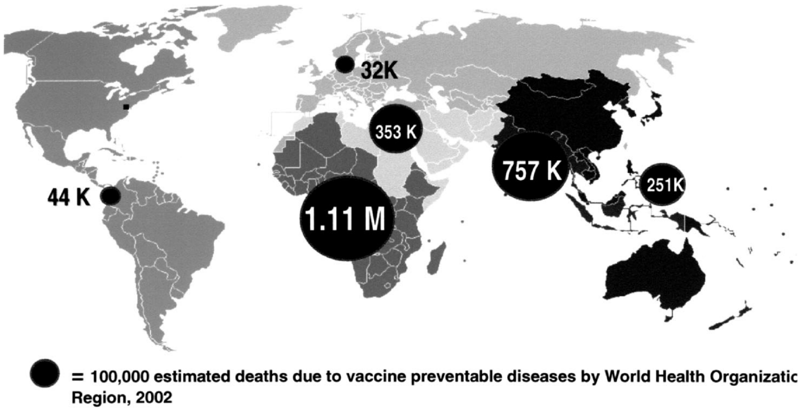

Fig. 2. *Worldwide distribution of deaths caused by vaccine preventable diseases.*

rates, the transition is far from complete in many developing countries. Furthermore, mortality is not the only important measure of the burden of infectious diseases. Other important measures of disease burden, such as cognitive and developmental delays or economic impact can reveal an even greater persistent difference in the epidemiologic transition stages between the developed and developing worlds.

The hope that the 20th century would see the end of a significant burden of infectious diseases and a convergence of health between developed and developing countries was impeded, and in many cases reversed, by several factors. There has simply been a failure to fully employ many of the same strategies in the developing world that were so successful in controlling infectious diseases in the developed world. For instance, immunization programs have been among the most successful and cost-effective public health programs, accounting for the prevention of 2 million child deaths in 2003 alone[12]. However, there were still an estimated 2.5 million childhood deaths from vaccine preventable diseases, most of which occurred in developing countries (see Figure 2)[12]. There has also been an emergence of new diseases. During the 1970s, no one expected that HIV, which was initially recognized in 1981, would emerge and cause a pandemic that to date has affected 65 million people and has resulted in 25 million deaths (a vast majority of which are in developing countries)[13] (see Table 1). There has also been a re-emergence and spread of other diseases endemic to developing countries, such as tuberculosis (TB) and malaria, often driven and complicated by newly emerged drug resistance[14].

The emergence of HIV and other infectious diseases, such as Ebola and Marburg hemorrhagic fevers, bovine spongiform

Table 1 Worldwide distribution of HIV, 2006

	People living with HIV	New infections	AIDS deaths	Adult prevalence, (%)
Primarily developed				
North America and Western and Central Europe	2 million	65,000	30,000	0.5%
Primarily developing				
Sub-Saharan Africa	24.5 million	2.7 million	2 million	6.1%
Asia	8.3 million	930,000	600,000	0.4%
Latin America	1.6 million	140,000	59,000	0.5%
Eastern Europe and Central Asia	1.5 million	220,000	53,000	0.8%
Middle-East and North Africa	440,000	64,000	37,000	0.2%
Caribbean	330,000	37,000	27,000	1.6%
Oceania	78,000	7,200	3,400	0.3%
Total	38.6 million	4.1 million	2.8 million	1%

Adapted from UNAIDS, 2006 Report on Global AIDS Epidemic.

encephalopathy (''mad cow disease''), severe acute respiratory syndrome (SARS), West Nile virus, and avian influenza, has resulted in an increased awareness of infectious diseases in the developed world[14,15]. Furthermore, a growing recognition among developed countries that they are vulnerable to diseases that might emerge from developing countries, as well as genuine humanitarian concern for the condition of those in need, has led to a greater interest in diseases endemic to the developing world[14–16]. Tremendous progress has been made against several diseases, including the development of anti-retroviral therapy which has dramatically cut the number of deaths from AIDS[17,18], and the development of new vaccines against devastating infections, but these developments have not always been translated to the developing world[13,19]. Rotavirus is the most common cause of severe childhood diarrhea in the world, accounting for 37 to 231 infant deaths per year in the United States and European Union[20,21] but between 400,000 and 500,000 deaths worldwide[22,23]. Vaccines for rotavirus have been recently approved and are quickly being incorporated into pediatric vaccine schedules in developed countries but not yet in most developing countries[22,23]. Human papillomavirus (HPV) vaccine has also become available and is rapidly being widely utilized in developed countries, but in the developing world, where HPV-related morbidity and mortality from cervical cancer primarily occurs, there are great challenges to making it available[24–26].

Fortunately, numerous philanthropic governmental and non-governmental organizations are making great efforts to provide financial and technical support to increase the availability of such life-saving measures to developing countries. Examples include the Expanded Program on Immunization (EPI), which was developed in the 1970s by the World Health Organization (WHO) in collaboration with the United Nations Children's Fund (UNICEF) and others to provide basic vaccine coverage to children throughout the world[12], the Global Alliance for Vaccines and Immunization (GAVI), a public-private global health partnership created in 1999, which provides financial assistance for vaccines to children in the poorest countries of the world[27], the Global Fund to Fight AIDS, TB, and Malaria, which provides financing for projects designed to fight those diseases[28], and the President's Emergency Plan For AIDS Relief (PEPFAR), a 5-year US$15 billion initiative to rapidly augment AIDS treatment and prevention programs[29]. Each of these programs has had both successes and failures and are justly critiqued[29–31], but the focus of governments on these health issues and the tremendous infusion of resources from private organizations, such as the Bill and Melinda Gates Foundation, has resulted in renewed optimism[12,27,31].

In this article, we will explore the current status of the ''epidemiologic transition,'' discussing the methods credited for achieving this transition, some of the barriers that have slowed the transition in the developing world, and some of the difficulties in even measuring the burden of disease and the progress of the transition. We will also review several of the most common diseases, including strategies for prevention and efforts to establish surveillance systems to monitor for emerging diseases or to target appropriate interventions.

Historical perspective

In the United States in 1900, infectious diseases accounted for 44% of all deaths, led by pneumonia, tuberculosis, and enteric infections (diarrhea and typhoid fever)[32,33]. The burden of illness fell especially

Table 2 Percentage of deaths caused by infectious diseases in 12 major cities in the USA in 1900 and 1936

Disease	1900	1936
Tuberculosis	39.3	17.9
Pneumonia	9.6	9.3
Diarrhea and enteritis	7.0	N/A
Typhoid Fever	2.4	0.1
Meningitis	2.4	0.3
Diphtheria and Croup	2.3	0.1
Malaria	1.2	0.1
Smallpox	0.7	0.0
Influenza	0.7	1.3
Measles	0.7	0.0
Scarlet Fever	0.5	0.1
Whooping Cough	0.6	0.2

Adapted from Cutler, *Demography*, 2005; **42**, 1–22.

hard on the young, with 30.4% of all deaths occurring in children less than five years old[32]. Remarkable progress was made over the early 20th century to alleviate this burden, so that by 1936, only 18% of deaths were due to infectious diseases (see Table 2)[33], and by 1997, when only 1.4% of deaths were in children less than five, the leading infectious causes of death, pneumonia, influenza, and HIV, only accounted for 4.5% of deaths overall[32]. This progress was largely due to interventions started in the 19th century with the development of the ''germ theory'', an understanding that microorganisms are the cause of many diseases[34]. Following the development of the germ theory, there were significant advances in three main areas which led to dramatic declines in death rates due to infectious diseases: sanitation and hygiene, immunizations, and antibiotics[32,34].

Sanitation and hygiene

In the 19th century, there was a steady migration from rural areas to urban areas as the Industrial Revolution created more economic opportunities in cities across Europe and the United States[33,35,36]. The increased populations quickly overwhelmed the basic infrastructure of those cities, causing overcrowding and increased exposure to contaminated food and water, leading to increased mortality, an effect termed the ''urban penalty''[33,36]. (This same ''urban penalty'' is currently being described in developing countries experiencing similar urban migrations)[37–39]. In the late 1800s in the United States, infant mortality was 140% higher and life expectancy was 10 years shorter in urban areas than in rural areas[33]. The situation was similar in Poland[36]. Although the germ theory was just being developed, people recognized that inadequate sanitation and hygiene were associated with disease, often attributing the cause of illness to ''miasmas,'' poisonous vapors that were offensive to smell and were thus thought to emanate from contaminated water and filthy areas[33]. This recognition led to many efforts, some focused on the individual, some municipal, and some international, to improve sanitation and hygiene[32,33,40].

In 1850, the *Report of the Sanitary Commission of Massachusetts 1850*, also called the Shattuck Report after the chairman of the commission, Lemuel Shattuck, was published with comprehensive recommendations to improve and protect health[41,42]. The Shattuck Report made broad recommendations for both municipalities and individuals for the promotion of health, reflecting the prevailing attitude that the personal aspects of hygiene involved proper considerations of personal cleanliness, food, water, clothing, work, exercise, and other personal habits[41–43]. Concurrently, numerous organizations were emerging dedicated to improving personal hygiene, some as part of educational curricula[43], some as part of Christian cleanliness movements,[44] and often simply to improve health[33]. Many of these campaigns focused on food preparation (hand washing, boiling milk, *etc*.), breast-feeding, and personal hygiene, and there is evidence that these actions by individuals and households had some success in decreasing disease[33].

At the same time, large scale interventions were being implemented by municipal governments, including the institution of animal and insect control programs, which were very successful in reducing malaria and eliminating the dog-to-dog transmission of rabies; milk pasteurization and meat inspection, dramatically cutting rates of food-borne illnesses, including tapeworms and trichinosis; and sanitation services, refuse management, and clean water technologies[33]. Each of these interventions was beneficial, and it is difficult to separate out the effect of each intervention, but it appears that the advent of clean water technology, filtration and chlorination, was the most important public health intervention of the 20th century[33]. Cutler and Miller recently published an elegant analysis of mortality data in 13 major U.S. cities from 1900 to 1936, during which time deaths from infectious diseases fell from 44% to 18%, showing that the provision of clean water accounted for nearly half of the overall reduction in mortality, two-thirds of the reduction in child mortality, and three-quarters of the reduction in infant mortality, as well as the near eradication of typhoid fever[33]. Very interestingly, the reduction in enteric diseases (diarrhea and typhoid fever) could not have accounted for the total reduction of mortality alone, as it appears that other common diseases (pneumonia, tuberculosis, meningitis, and diphtheria/croup) also decreased in response to the provision of clean water. Furthermore, they showed that the effects of clean water grew over time, suggesting that there was a complementary effect between the municipal public health interventions and the ongoing private hygiene education efforts[33]. However, unlike the private hygiene efforts, which had the greatest effect on those with the most education, a reasonable indicator of wealth, the provision of clean water had the greatest impact on the poor[33]. Although building and maintaining municipal water systems was enormously expensive, costing about $300 million (USD) for every 10 years of service, the social rate of return was huge, with an estimated $23 saved for every $1 spent[33].

There were also significant sanitation efforts on an international scale. In response to successive epidemics of cholera throughout Asia and Europe during the early to mid-19th century, representatives from 11 European nations attended the first International Sanitary Conference in Paris in 1851 to establish quarantine policies intended to stop the transnational spread of disease[40]. Although their results were limited by both national, political, and economic concerns, as well as scientific disagreements over widely varied theories as to the cause and mode of spread of disease, the meeting established a precedent for international scientists and politicians to work together to control the spread of disease. This led to ten international sanitary conferences from 1851–1900 with ever broadening goals of disease control, inspiring the formation of many national health agencies, and establishing standardized methods of sanitation, quarantine, and disease surveillance[40]. As the germ theory of infectious disease became more widely accepted, and as new discoveries of the cause of various diseases were described, these methods became increasingly codified, often being incorporated into the national laws of participating countries as part of the development of national public health agencies, such as the U.S. Public Health Service (USPHS)[32,40].

Vaccinations

Other than the provision of clean water, immunizations had the greatest impact on reducing the burden of infectious diseases in the 20th century[45]. Immunization programs have also been among the most cost effective public health interventions[32,46]. In the United States, state and local health departments instituted vaccination programs, aimed primarily at poor children after the licensure of the combined diphtheria and tetanus toxoids and pertussis vaccines in 1949[32]. In 1955, the introduction of the Salk poliovirus vaccine led to federal funding of childhood vaccination programs, ushering in an era of universal childhood vaccination in the U.S.[32]. The addition of more vaccines has led to the near elimination of diseases that had once been common causes of significant childhood morbidity and mortality, such as poliomyelitis, diphtheria, tetanus, measles, mumps, rubella, pertussis, and *Haemophilus influenzae* type b meningitis[12,32]. Similar dramatic reductions in childhood morbidity and mortality were seen in the U.K.[45]. The greatest success in the use of vaccines came in 1977, after a decade long campaign involving 33 countries, when smallpox was eradicated from the world[32].

Antibiotics

The first US civilian patient whose life was saved by penicillin was in March 1942[32]. That event was the start of the rapid discovery and the development of antimicrobials that would dramatically reduce deaths from previously untreatable infections, such as pneumonia and meningitis. Streptomycin, the first antibiotic effective against tuberculosis, was discovered in 1943. Mortality from tuberculosis quickly fell from 39.9 deaths per 100,000 persons in 1945 to 9.1 deaths per 100,000 persons in 1955[32]. Over the last 60 years, many new classes of antibiotics designed to more effectively treat bacterial infections, as well as drugs targeting other infections, such as malaria, fungal infections, and viral infections (including HIV) have been developed. These drugs have been remarkably effective at reducing mortality from many of these diseases[32].

Epidemiological transition revisited

It is unarguable that the 'Western World' successfully transitioned from undeveloped to developed, with attendant declines in infectious disease mortality. Many other countries around the world appear to be on their way to achieving this transition as well. However, not all countries have been able to achieve such progress, and there is ongoing debate and concern regarding this model given the delayed transition, or even regression, of population health among countries in many other parts of the world[47–50].

Omran's theory was based strongly on observations of the time (as well as historical data leading up to the late 1960s), and naturally supported the developed theory to explain the increase in life expectancy and subsequent emergence of mortality due to 'degenerative and man-made' diseases. However, over the past 30 years his theory has been put to the test by subsequent observation and unforeseen developments (*e.g.*, economic crisis in Africa, HIV, collapse of former Soviet Union, cardio-vascular revolution), and while the concepts of epidemiologic transitions still hold true, there are a number of notable exceptions to Omran's original thesis.

Figure 3 displays the estimated life expectancy at birth (both sexes combined) for select geo-economic regions between the years of 1965 and 2000. While much has been learned from studying life expectancy trends from a country level and stratified by age, gender and race[51–58], some larger themes which prompt further contemplation on the theory of epidemiologic transition can be drawn from the illustration of trend patterns across these geo-economic regions[47,59,60]. There has been slower progress in life expectancy gains between 1965 and 1980 seen among countries in sub-Saharan Africa compared to their north African counterparts[59]. While in 1965 countries of sub-Saharan Africa were not quite up to par with the Middle East and North Africa (MENA), there is further divergence in life-expectancy between these two regions after that time. This period of history included re-establishment of rule after colonial independence and Cold War maneuverings, during which time war and other forms of political violence were common to many of these African nations. Concurrently, there was a lack of investment in infrastructure, public health and other societal modernizations necessary to move beyond Omran's second phase. Other contributing factors include the economic crisis which hit sub-Saharan Africa in the 1980s[61], and the associated reappearance of infectious diseases other than HIV, as well as many other probable factors[59]. Unlike other regions which have progressed out of the second phase, most countries of sub-Saharan Africa are notable for resistant declines in infant and child mortality (main drivers of life expectancy) and there are very few countries in this region where the infant and child death has dropped below 100 per 1,000[59,62]. Interestingly, it is has been described that infant mortality rate, probably both as a result of and as a contributing factor, is highly correlated with state failure[63].

Another important element in the slow progression of some countries is the discrepancy of the transition between racial-ethnic and/or economic groups, beginning among individuals with higher socioeconomic status and eventually spreading to those with lower socioeconomic status[64]. This finding deals mainly with the reality of socioeconomic inequalities occurring at every step, from exposure and resistance to diseases, to care seeking behavior, and access to appropriate care. It has been estimated that if the under-5 mortality rate

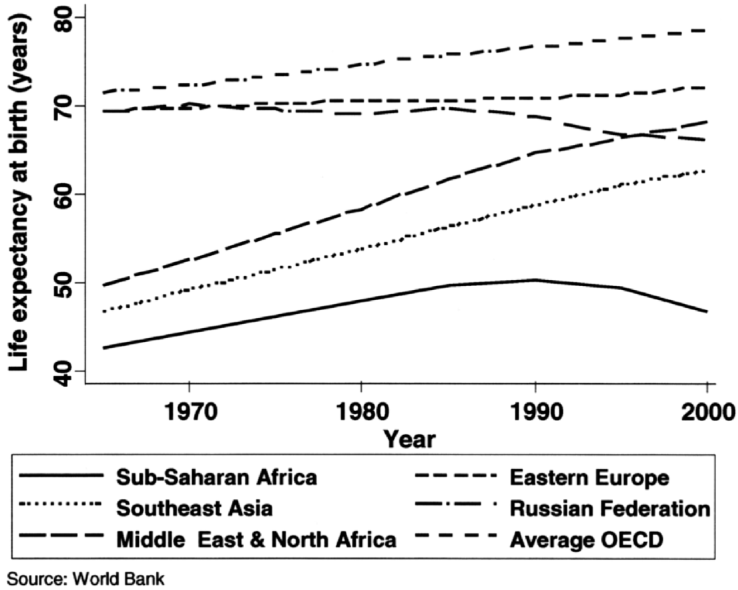

Fig. 3. *Trends in life expectancy at birth for select geo-economic regions between 1965 and 2000.*

in the poorest 80% of the population of the developing world could be reduced to that of the richest 20%, overall mortality would be reduced by 40%[64].

A second general observation that can be made from review of these data is the stagnation in Eastern Europe and the former Soviet Union[65]. By 1965, average life expectancy at birth of member countries in the Organisation for Economic Co-operation and Development (OECD), Eastern European, and former Soviet Union countries could be classified as having reached the 'third phase' of Omran's transition theory. However, as seen in Figure 3, from this point forward these three groups take divergent trajectories. The continued improvements of OECD member countries is thought most likely to attributed to a ''fourth phase'', the cardiovascular revolution, which Olshanksky and Ault have suggested to add to Omran's model, which postulates gains based on improvements in the prevention and treatment of cardiovascular disease[48]. However, Eastern European countries and the former Soviet Union, while having centralized modern health systems responsible for the entire care of the populace, faced challenges in transitioning to the fourth stage, which required individual's being actively involved in their own health (*e.g.*, behavior change). Furthermore, the economies of these countries were involved in an arms and space race with western countries, which impacted their ability to create an efficient health system to deal with chronic diseases[57,66].

Up until the mid-1980s Eastern Europe and the former Soviet Union, were on a parallel track, however, what is striking is the subsequent decline in life-expectancy of the former Soviet Union beyond this time. It is apparent that countries of the former Soviet Union experienced social and economic upheaval during this time which resulted in dismantling of public services, including the health system, at a time when people were suffering food shortages and psychological stress[67–69]. Russia and Ukraine are experiencing a re-emergence of infectious diseases (*e.g.*, tuberculosis and diphtheria) and a continued burden of circulatory diseases and violence, of which young people are the main victims[65].

Lastly, Figure 3 clearly demonstrates a grave trajectory for sub-Saharan Africa. The force of HIV/AIDS through heterosexual and mother-to-child transmission and widespread economic crises have had a destabilizing effect threatening an already weak public health system, further contributing to the pressures of infectious diseases and other health threats on these countries[47]. Poverty and inequality exacerbates disease transmission, which in turn results in increased poverty and inequality – a crippling negative feedback loop. But if this were not enough, sub-Saharan Africa, in addition to many other developing countries, is also experiencing an increasing burden of 'man-made' diseases resulting in the notion of ''double burden of communicable and non-communicable disease'', which further strains the capacity and resources of these countries[70].

In total, these observations raise questions about the one way progression through the stages of Omran's theory. It appears that countries can exist in two stages at once and possibly even revert back to early stages from which they had previously transitioned. With the emergence or reemergence of infectious diseases, we have learned that the threat of infection cannot be eradicated, but must be viewed in terms of effective control. Furthermore, if efforts of disease control are challenged by politics, war, or inequality, all that is gained can suddenly be lost (*e.g.*, HIV/AIDS in sub-Saharan Africa and reversion in former Soviet Union). It is also clear that transition to the third and fourth stages requires favorable political, social and economic conditions to allow effective strategies for which all societies are not equally prepared to adopt (*e.g.*, stagnation in Eastern Europe).

The spectrum of disease impact

''If knowledge is power, the field of public health has remained incredibly weak'', states William H. Foege in his foreword to Murray and Lopez's, *The Global Burden of Disease*[71]. The availability of quality health statistics at the country, regional, and global levels are needed not only for prioritization of health problems, but to recruit and sustain worldwide political and financial support, to build government commitment to solving health problems, and to ensure performance and accountability of investments in these problems[72]. While health statistics are adequate within most developed countries, it has been estimated that nearly three-fourths of 152 low-income and middle-income countries have no reliable data even on cause of death[73], leading to health policy decision making which can be described as ''stumbling around in the dark''[74].

Basic health statistics important for epidemiological and public health purposes generally fall into the categories of mortality and causes of death, morbidity and health status, risk factors, service provision, and health resources[72]. Additionally, advances have occurred in how disease burden is understood and measured. Figure 4 depicts the landscape in which disease burden is measured, including traditional and more novel measures, as well as the levels (*e.g.*, individual, societal, global) in which this disease burden may have its impact, and the challenges to accurately measuring and interpreting these statistics.

While data on mortality and causes of death are a mainstay to provide important data, these data do not capture those diseases which may not be fatal but contribute a significant burden on individuals and societies. In 1996, Murray and Lopez, introduced a novel measure of disease burden, the disability-adjusted life year (DALY)[71]. The DALY is a burden of disease measure that extends the measurable burden of potential years of life lost due to premature death (PYLL) with the addition of equivalent years of 'healthy' life lost by virtue of being in states of poor health or disability. Thus, the DALY combines in one measure the time lived with disability and the time lost due to premature mortality. In other terms, a single DALY can be seen as one lost year of 'healthy' life. This measure of disease burden represents the gap between current health status and an ideal situation where an individual lives into old age free of disease and disability. While there is ongoing debate regarding the ethical implications in the use of this measure, including the previous mentioned issue of lack of quality data on which these estimates are based, the inability to deal adequately with co-morbidities, the devaluation of the lives of disabled people, and a lack of transparency in the process of ascribing disability weights for many

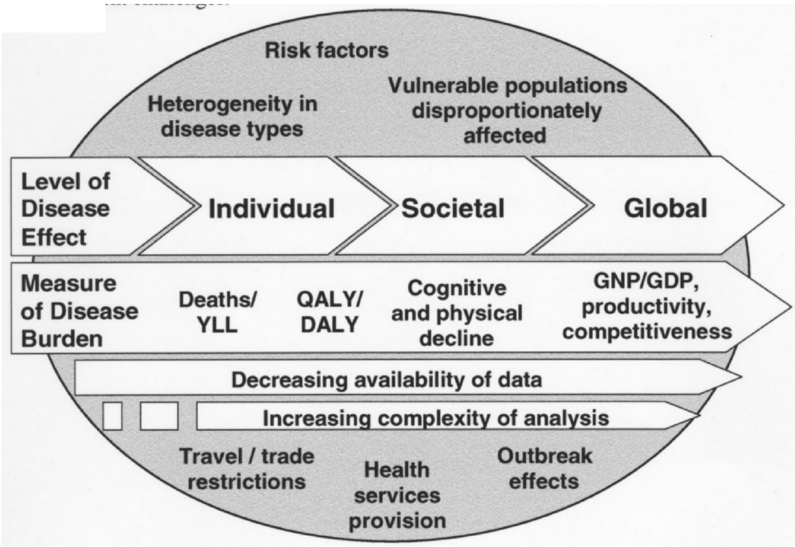

Fig. 4. *Schematic burden of disease measurement: level of effect and measurement challenges.*

conditions, the use of the DALY as a health gap measure has been critical for the advancement of progress in global public health[75–77].

However, the impact of infectious diseases in both the developing and developed world can be considered (but more difficultly measured) beyond these traditional and novel health estimates. There are broader economic impacts that need to be considered in the ascertainment of the burden of disease beyond the individual level[78]. Rather than the measures of life expectancy or DALYs, these impacts are measured in decreased worker productivity and gross national product. For example, a body of knowledge is accumulating which links stunted growth, school absenteeism, decreased cognitive function and physical development to a number of nutritional, environmental exposures and infectious diseases in the developing world[79–84]. It has usually been considered that wealth is the main determinant (and predictor) of health[85] through purchase of better nutrition, medical care, public health infrastructure and education, but recently this relationship has also been described to work in the reverse–that is the notion that ''health drives wealth''[86]. Bloom and Canning described four mechanistic categories which drive this equation:

(1) *Productivity* – healthier populations will have higher labor productivity because of both cognitive, physical and emotional improvements,

(2) *Education* – people in healthier populations have higher life-expectancy which would result in stronger incentives to improve their own personal development through education because they need to plan for a longer survival, and healthier children have higher attendance, higher cognitive function and increased productivity,
(3) *Investment in physical capital* occurs in healthier populations because life expectancy creates a need for people to save for their retirement which requires increased investment and results in more opportunities for foreign investment, and
(4) the '*Demographic Dividend*' has been described as a transient but significant boost to the economy associated with the declines in infant mortality and fertility associated with transitioning countries[86].

These influences are not just theoretical, as Bloom *et al*., have further demonstrated that for every one-year increase in life expectancy labor productivity increases by 4 percent[87].

The impact of disease is even greater when considering the global impact of outbreaks on travel, tourism, business and trade. The most striking example came from the SARS epidemic of 2003, during which there were 8,096 reported infections resulting in 774 deaths in 26 countries[88]. The global economic costs associated with this outbreak far outweighed the health impact and have been estimated to be in the range of $30–100 billion US dollars[89], which equates to approximately $4–12 million per case. These costs were distributed principally among travel and tourism sectors, though a wide range of sectors were impacted[90,91]. This notion of disproportionate economic impact relative to human health impact has raised concern that future pandemics (*e.g*. influenza) may have considerable effects on the global economy and, therefore, paralleling the surveillance efforts to identify and control transmission of epidemic disease, significant research and policy development needs to be done to effectively handle risk perception, communication and management[89].

Beyond tourism and travel industry, infectious diseases have been shown to have considerable economic impact on livestock and agriculture trade industries. Recent outbreaks from produce imported to the United States including Guatemalan raspberries contaminated with *Cyclospora*, Mexican strawberries contaminated with hepatitis A, and cantaloupe from Mexico contaminated with *Salmonella* have been associated with decreased demand for these products resulting in devastating effects on the economies of the producers of the particular product and on different agricultural products from the same country[92]. It should be remembered, that these large economic losses not only affect the affluent owners of these businesses, but also the entire supply and production chains down to the lower wage earners. Foot and mouth disease is another example of the potential devastating impact of infectious diseases in the livestock industry[93–100], and concerns about the spread of avian influenza have resulted in negative economic effects on afflicted countries estimated between 0.1–0.2% of GDP, disproportionately afflicting the poor who rely more on poultry income[101–103]. The global economic impact of a true pandemic of influenza is projected to be enormous and is likely to trigger a global recession[104,105].

The challenge of development

Beyond compelling reasons of social justice, industrialized country governments and private corporations should do what it takes to drastically reduce the current burden of disease in the developing world base solely on enlightened self-interest[106,107]. Therefore, the question then remains not 'why' and 'where', but 'how' and 'what' should be the interventions to best affect the needed change. During the United Nations Millennium Summit in September of 2000, a Millennium Declaration that was adopted by 189 nations and signed by 147 heads of state and governments targeted eight primary goals to address current developmental challenges[108]. These goals include eradicating extreme poverty and hunger, achieving universal primary education, promoting gender equality and empowering women, reducing child mortality, improving maternal health, combating HIV/AIDS, malaria and other diseases, ensuring environmental sustainability, and developing a global partnership for development. These goals have 18 quantifiable targets measured by 48 indicators, and a majority of these goals are directly or indirectly related to mitigating the impact of infectious diseases in the developing world, underscoring their relationship to poverty, and serving as primary targets of funding through bilateral donors, international financial institutions, multinational pharmaceutical industries, and philanthropic organizations. In a recent review of donor funding related to disease burden, Shiffman examined donor funding for 20 historically high-burden communicable diseases between 1996 and 2003 and factors related to variation in levels of funding among diseases[109]. Interestingly, the study showed that funding does not correspond closely with burden (see Figure 5). Many factors are likely to explain this variation including targeting of particular diseases for global elimination (*e.g.*, polio and onchocerciasis), efforts on diseases that are spreading rapidly (*e.g.*, HIV), a focus on diseases for which cost-effective interventions are available, and interest group mobilization within richer countries to address certain diseases. Acute

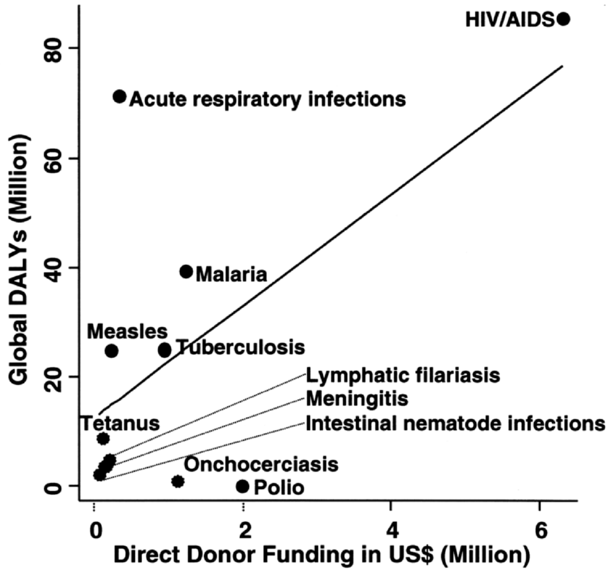

Fig. 5. *Global DALYS for select infectious diseases and donor funding (adapted from Shiffman[109]).*

respiratory infections do not tend to gain the attention from donors as they are considered readily treatable by industrialized states, and therefore do not gain the attention as a significant public health threat from political elites (with the exception of SARS and avian flu)[109].

Beyond these considerations of disease burden, there are questions regarding at what cost-effectiveness thresholds should current interventions be considered, what role does debt relief play, the country ownership and donor commitment partnership, and the lack of useful data for which to evaluate program effectiveness[110,111]. Decisions on what type of intervention projects and programs to support are often difficult. Some programs focus on specific population behavior change for a particular disease, some on developing or distributing a new technology, such as a vaccine, some on large projects with distributive effects across a range of health problems, such as increased transportation infrastructure, building more schools[112], or investment in agriculture[113]. Clearly, there is a vast funding gap to address all the current challenges, but successful, sustainable and cost-effective choices are most needed so that none of this funding goes to waste. And herein lies another challenge in development. It is clear that financial aid works in a good policy environment, which includes improvements in economic institutions, policies and country ownership of health programs, which is vital for sustainment. Often the value of development projects is to strengthen institutions and policies through reform in even the most distorted environments, but it requires patience and a focus on ideas, not money[114]. The challenge is that those countries most in need of aid are also those in which good governance and sound institutions are most often lacking[115,116], an association which is quite evident when one looks at the relationship between under-5 mortality and perceived corruption (Figure 6.).

Current infectious disease challenges and intervention plans

Given the enormous difficulties outlined above in measuring the true burden of infectious diseases in the developing world, in determining the appropriate medical as well as political strategies for intervening against these diseases, and to accurately measure the impact of those interventions, it would be challenging to provide a thorough and accurate list of diseases and interventions. Furthermore (and fortunately), advances in technology, such as the development of new vaccines, might supersede current strategies. However, with these limitations in mind, this section will provide a brief summary of several of the most significant infectious diseases challenging the developing world. Table 3 outlines some of the dramatic differences in the burden of these diseases between the developed and the developing world.

Human immunodeficiency virus (HIV)

HIV/AIDS is the fourth leading cause of death worldwide and the leading cause of death in sub-Saharan Africa[117]. Sub-Saharan Africa accounts for almost 70% of HIV infections and 83% of AIDS-related deaths, reflecting a high infection burden, poor access to care, and economic instability[118]. India reported a total of between 3.4 and 9.4 million persons infected with HIV, more than any other nation except maybe South Africa[119]. The contribution of factors that facilitate transmission – high prevalence of other sexually transmitted diseases (STD), low rate of male circumcision, the unequal status of women, migration, poverty, and patterns of social mixing – differs by country.

Transmission of HIV predominantly occurs through three mechanisms: sexual transmission, exposure to infected blood or blood products, or perinatal transmission (including breast-feeding). Although it appears that likelihood of transmission is heavily affected by social, cultural, and environmental factors and likely also by molecular, viral, or immunological host factors, risk of transmission varies for type of exposure: $\leq 3\%$ for receptive anal intercourse, $\leq 0.1\%$ for receptive

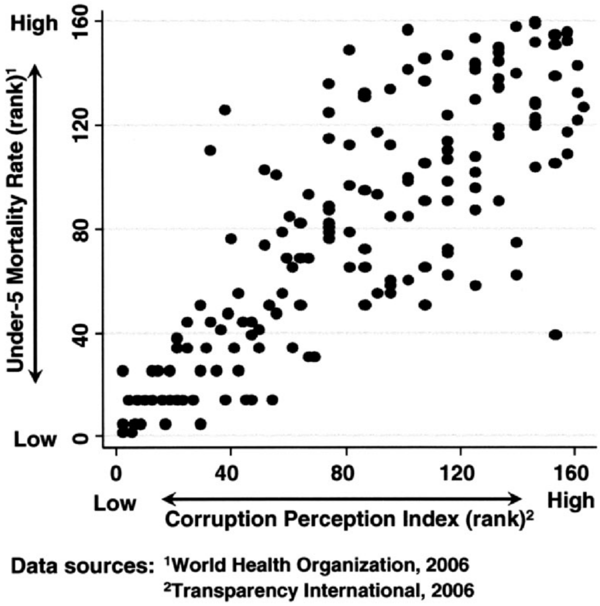

Fig. 6. *Comparison of under-5 mortality rate and Corruption Perception Index for 163 countries.*

vaginal intercourse, $\leq 0.1\%$ for insertive vaginal or anal intercourse, 0.3% for needle stick injury, 0.6% for use of contaminated intravenous drug-related equipment, and 0.1% for mucous membrane contact[120]. Although male-to-male sex remains the predominant mode of transmission in most industrialized countries, heterosexual contact remains the principal mode of transmission in sub-Saharan Africa[121]. Mother-to-child perinatal transmission account for 15–25% of all new infections worldwide[122].

Highly active antiretroviral therapy reduces transmission (especially from mother to child), opportunistic infections and mortality, but it is not affordable for most persons in resource-poor countries. WHO global guidelines call for scaling-up antiretroviral therapy access with a low cost fixed-dose formulation as initial treatment[123]. Secondary prophylaxis and appropriate diagnosis and management of life-threatening opportunistic infections and HIV-associated cancers remain an important aspect of the care of HIV-infected persons.

Several examples demonstrate that it is possible to reduce the spread of HIV with existing technology and interventions, albeit limited by cultural norms. Thailand's HIV prevalence, fueled primarily by high rates of commercial sex work and low levels of condom use, rose rapidly in the 1980s, prompting an aggressive program of governmentmandated condom use which has dramatically reduced the rate of new infections[120,124,125]. In Uganda, HIV prevalence has fallen to 5% in 2001 from a peak of 21%, in large part due to a government program reinforced by strong political support that focuses on reducing the number of sexual partners, confidential HIV testing, engaging the religious leadership, and emphasizing STD control and prevention[120,124,125]. The strategies of Uganda and Thailand reflect distinct acceptable cultural practices and emphasize the need for development of regionally or nationally individualized prevention approaches. These approaches are likely to include the combination of efforts toward education, access to condoms, and access to antiretroviral therapy.

Tuberculosis

Tuberculosis (TB) remains the second most common infectious cause of mortality worldwide, second only to human immunodeficiency virus (HIV)[126]. TB is spread *via* airborne droplets, and one-third of the world's population is believed to be infected. There are more than 8 million new cases of active TB per year, but only 18,000 of those occur in the U.S. Approximately 1.7 million people died of TB in 2003, including 229,000 patients co-infected with HIV[127]. In India alone, tuberculosis kills nearly 500,000 people annually[128]. In 2000, an estimated 273,000 new cases of multidrug-resistant tuberculosis, or 3.2% of all cases of tuberculosis, occurred worldwide[129].

Although infection with TB is extremely common, primary TB infection is controlled in about 90% of people, resulting in latent infection but no symptoms or further spread of disease. In approximately 5% of individuals, acute infection results in primary disease, and in approximately 5% of people with latent infection, reactivation to active disease will occur years to decades later[130]. Interventions against tuberculosis focus on preventing infection, halting progression from infection to active disease, and treating active disease. The Bacille Calmette Guerin (BCG) vaccine remains the only TB vaccine available. Although there is consistent evidence of efficacy of BCG against serious forms of disease in children (73% for meningitis and 77% for miliary TB), the evidence for protection against pulmonary disease in adults in inconsistent[131]. Pioneering studies begun in 1993 in India provide useful insight into potential for benefit from more aggressive and structured tuberculosis-control programs. By improving access to care, improving laboratory-based diagnosis, emphasizing direct observation of treatment, and the use of standardized anti-tuberculous regimens and reporting methods, an estimated 200,000 deaths have been prevented since that time. Indirect economic savings from decreasing

Table 3 *Mortality and DALY's for selected diseases in representative developed and developing countries*

	United States	Bangladesh	Somalia	Worldwide
Diarrheal illness	Death rate: 0.5 DALY rate: 29	Death rate: 47.4 DALY rate: 1,598	Death rate: 164.2 DALY rate: 5,375	DALY: 62,000,000 Deaths: 1,800,000
Malaria	Death rate: 0.0 DALY rate: 0.0	Death rate: 1.2 DALY rate: 85	Death rate: 49.8 DALY rate: 1,859	DALY: 46,500,000 Deaths: 1,272,400
Tropical cluster[a]	Death rate: 0.0 DALY rate: 0.0	Death rate: 0.1 DALY rate: 270	Death rate: 4.2 DALY rate: 304	DALY: 12,200,000 Deaths: 129,160
Intestinal nematodes	Death rate: 0.0 DALY rate: 0.0	Death rate: 0.1 DALY rate: 55	Death rate: 0.2 DALY rate: 299	DALY: 2,950,000 Deaths: 11,770
Respiratory tract disease[b]	Death rate: 20.7 DALY rate: 128	Death rate: 105.2 DALY rate: 2,933	Death rate: 373.4 DALY rate: 13,419	DALY: 128,858,000 Deaths: 4,868,000
Tuberculosis	Death rate: 0.3 DALY rate: 3	Death rate: 51.6 DALY rate: 1226	Death rate: 116.6 DALY rate: 3058	DALY: 34,735,900 Deaths: 1,566,000
HIV	Death rate: 4.5 DALY rate: 131	Death rate: 100 DALY rate: 4* (Incomplete DALY data)	Death rate: 54.8 DALY rate: 1565	DALY: 84,457,800 Deaths: 2,777,175

Table 3 (continued)

	United States	Bangladesh	Somalia	Worldwide
Sexually transmitted diseases[c]	Death rate: 0.1 DALY rate: 20	Death rate: 1.9 DALY rate: 239	Death rate: 1.4 DALY rate: 344	DALY: 11,347,000 Deaths: 179,700
Vaccine preventable diseases[d]	Death rate: 0.5 DALY rate: 23	Death rate: 31.3 DALY rate: 1120	Death rate: 217.6 DALY rate: 7725	DALY: 44,974,600 Deaths:1,259,702

Based on 2002 WHO estimates; *Death and DALY rates per 100,000; Worldwide rates in absolute numbers;
[a]Includes trypanosomiasis, chagas, filiariasis, onchocerciasis, leishmaniasis, dracunculus, schistosomaiasis.
[b]Includes pneumonia, influenza, epiglottitis, rsv, measles, pertussis, and diphtheria.
[c]Excluding HIV/AIDS.
[d]Includes pertussis, polio, diptheria, measles, dengue, and Japanese equine encephalitis.

morbidity and mortality outweighed the cost of program implementation by eight-fold[128].

Malaria

When considering overall morbidity and mortality, malaria is the most significant parasitic disease in the world. Indeed, the latest WHO estimates from 2002 indicate that malaria accounted for 1.27 million deaths worldwide during that year alone, and over 46 million DALY's[8]. While humans in 107 countries and territories are at risk of disease, Africa suffers the vast majority of this global burden. Malaria is transmitted to humans by the bite of the *Anopheles* mosquito. Clinical manifestations include fever, shock, severe hemolysis, liver dysfunction, and central nervous system dysfunction[132].

The USA suffers essentially none of the global burden of malaria. This was not always the case however, as malaria was formerly a significant cause of morbidity and mortality in the southeastern USA. Vector control measures with pesticides and self-protection measures including screens, air conditioning, and insect repellent have all contributed to the elimination of malaria from the United States and Europe. Notably, the anopheles mosquito still exists in these regions, but the above measures were successful enough in interrupting the malaria life cycle such that the disease has been eliminated from these regions. Today, similar measures, with the addition of highly effective insecticide-treated nets and the use of intermittent preventative antimalarial therapy, are variably being used to combat malaria in affected regions. The fight against malaria is complicated however by the rising prevalence of drug and pesiticide resistance[132].

Respiratory infections

Respiratory tract infections, especially lower respiratory tract diseases including pneumonia (excluding Tuberculosis) and influenza, are among the leading causes of infectious disease deaths worldwide. In the developing world, respiratory infections are often exacerbated by protein malnutrition and vitamin deficiency, which may be secondary to some other infections, such as with intestinal helminths. While the death rate from respiratory infections in the USA is nearly one-twentieth that in Somalia, these conditions still account for 60,100 of the 64,000 deaths caused by infectious diseases in the United States in 2002 (WHO)[8].

The majority of respiratory tract infections are transmitted through mucosal contact by infected respiratory secretions and/or airborne droplets. Therefore, while hygiene efforts, such as frequent hand-washing, may achieve a degree of prevention, vaccination against specific pathogens is the most effective strategy for reducing respiratory illnesses. Unfortunately, due to insufficient public health and vaccine delivery programs, financial hardship, and public views regarding vaccines, vaccination for respiratory illnesses is inadequate in many developing countries[8]. Furthermore, the American Lung Association indicates that in 2001, of those for whom vaccination is recommended, only 70% of whites and 48% of African Americans in the United States received the pneumococcal vaccine and only 65% of those older than 65 were given the influenza vaccine. Therefore, reducing the burden of infectious respiratory disease in both the developing and developed world is dependent on improving vaccination programs.

Diarrheal disease

Based on data collected between 1992 and 2000, diarrheal illnesses caused severe dehydration, electrolyte disturbances, and malnutrition resulting in 2.5 million deaths worldwide, accounting for about 20% of all deaths in children under 5 years old[8,133]. Given the fact that the vast majority of diarrheal illnesses are transmitted *via* the fecal oral route, their morbidity and mortality is concentrated in developing countries which have inadequate public sanitation systems. Using the countries listed in Table 1 as examples, the disparity in the distribution of the burden of diarrheal illness is readily apparent. Etiologic organisms include bacteria (*Vibrio cholerae*, *E. coli*, *Shigella*, *Campylobacter* and *Salmonella*), parasites (*Giardia*, *Cryptosporidia* and *Entamoeba histolytica*), and viruses (rotavirus)[134]. Unlike the bacterial and parasitic causes of diarrhea, rotavirus causes significant illness in pediatric populations in both the developing and developed countries alike, but the mobidity and mortality from disease is much higher in the developing world[22,135]. Recent developments in rotavirus vaccines present great opportunities for reducing diarrheal burden due to rotavirus[136], but the main strategy for reducing diarrheal disease burden is the provision of clean water and food.

Vaccine preventable diseases

An estimated 30 million children each year still lack proper vaccination[137]. Every year as many as 3 million children die from vaccine-preventable diseases, including 600,000 from measles, 200,000 from tetanus, 300,000 from pertussis, and 390,000 from *Haemophilus influenzae b* meningitis. An additional 600,000 people die from the consequences of hepatitis B infection acquired during childhood every year. The burden of vaccine-preventable diseases vary by country, partly because of differences in vaccine distribution and access to care, but also because of geography, climate, crowding, nutritional status, travel, and possibly genetic differences in populations that affect disease severity[138].

The polio eradication campaign, launched by the World Health Assembly (WHA) in 1988, and led subsequently by the World Health Organization (WHO), has been successful in decreasing global effects of disease. Live oral polio vaccine (OPV) is used in most parts of the world to halt or prevent transmission of the virus[139]. Since 1988, the effects of polio, previously considered a lethal or lifelong crippling disease, has decreased by more than 99% to 1265 worldwide cases in 2004. The percentage of children worldwide living in polio-free countries has increased from 10% in 1988 to approximately 70% currently. The success of the program has had the indirect benefit of creating changes in public health infrastructure, which should improve means to deliver other vaccines.

Sexually transmitted diseases

Sexually transmitted diseases (STDs) are the most common infections worldwide, with more than 76% occurring in the developing world[140]. Sexually transmitted diseases (STDs) are responsible for an enormous burden of morbidity and mortality in developing countries through effects on reproductive and child heath and their role in facilitating HIV infection[141,142]. Complications of STDs affect mostly, although not exclusively women and children; because of delayed or inadequate diagnosis and treatment, complication rates are high in developing countries.

Helminth infections

Helminths, or parasitic worms, include *Ascaris*, *Trichura* (''whip-worm''), hookworms, tapeworms and *Strongyloides*. Intestinal helminth infections result in a great deal of morbidity without causing nearly as much mortality as the diarrheal illnesses. Malnutrition, vitamin deficiency, and low-grade bleeding resulting in iron deficiency are the most common causes of morbidity, often resulting in developmental delay and growth arrest in children[143]. Similar to the diarrheal illnesses, transmission of these infections is related to filthy conditions. Therefore the burden of disease is greatest in those regions with substandard public sanitation and reduction efforts are focused on the appropriate disposal of human and animal waste.

Tropical diseases

''Tropical Cluster'' diseases, which include Chagas Disease, filariasis (''elephantiasis''), onchocerciasis (''river blindness''), dracunculiasis, and schistosomiasis, are similar to the intestinal helminth infections in that collectively they represent a massive amount of morbidity worldwide[144]. However, they are also similar to the intestinal helminth infections in that they are less significant causes of death when compared to the diarrheal illnesses and respiratory infections. Regardless, 2002 WHO estimates for the burden of the Tropical Cluster is that nearly 130,000 deaths and over 12 million DALY were attributable to this collection of diseases[8]. As ''Tropical'' implies, the majority of the world's burden is suffered by populations residing in the tropics. Each of these infections is either vector borne or dependent on a non-human intermediate host. Therefore, efforts to control these infections are primarily focused on vector control[144].

Tropical infections lacking adequate control measures

The WHO characterizes several insect-borne diseases with epidemic potential, including dengue, leishmaniasis, and African trypanosomiasis (sleeping sickness), as lacking effective control measures. Currently, dengue lacks specific treatment options, whereas therapy for leishmaniasis and African trypanosomiasis relies largely on, respectively, antiquated antimony and arsenic based drugs.

Dengue virus is spread by mosquitoes and causes an acute febrile illness characterized by headaches, severe musculoskeletal pain, and rash[145]. About 2–5 billion people live in areas where dengue is endemic with an estimated 100 million cases of dengue fever annually. The more severe manifestation of disease, dengue hemorrhagic fever/dengue hemorrhagic shock (DHF), presents hypotension and hemorrhage[146]. Approximately 500,000 cases of DHF occur annually worldwide. Case fatality rates vary from 3–5% in some Asian countries to 0.17% in the Americas[147]. Mosquito control is currently the most effective measure for disease control, but efforts to develop vaccines are underway[145,148].

Leishmaniasis, a disease caused by a protozoan parasite spread by the bite of a sand fly, is endemic in areas of the tropics, subtropics, and southern Europe, and was responsible for killing 51,000 people in 2001. Several clinical syndromes, including visceral, mucocutaneous, and cutaneous leishmaniasis, are caused by different species of *Leishmania*. Most of the estimated 500,000 annual cases of visceral leishmaniasis occur in poorer rural and suburban areas of Bangladesh, Brazil, India, Nepal, and Sudan[149]. Control efforts are focused on vector control and by eliminating animal reservoirs of disease, such as stray dogs[150].

The final decade of the 20th century witnessed an alarming resurgence of human African trypanosomiasis, or sleeping sickness, caused by the tsetse fly borne protozoan parasite, *Trypanosomiasis brucei*. Without treatment of meningoencephalitis, relentless progression of CNS deterioration results in coma and death. In 1998, 300,000 new cases of disease, limited to sub-Saharan Africa, were reported to the WHO[151]. Approximately 50,000 deaths per year are attributed to African trypanosomiasis, trailing only malaria in mortality due to parasitic diseases in sub-Saharan Africa. Control efforts are focused mainly on vector (tsetse fly) control[152].

Future challenges

In contrast to the optimism of 50 years ago, there are currently no public health leaders suggesting that it is time to ''close the book'' on infectious diseases. Instead, there has been a forced recognition of emerging and re-emerging infections, a realization that disease can quickly spread internationally, and a growing understanding of the significant burden of disease in the developing world, including the hidden economic costs of infection. Furthermore, it is clear that similar to HIV, emerging or rapidly spreading diseases will likely have a disproportionate effect on the developing world. For instance, projections are that an influenza pandemic similar to the 1918 pandemic would result in 62 million deaths, 96% of which would occur in the developing world[153]. Based on these realizations, future planning has to be directed at preventing potential pandemic spread of emerging diseases and on directed interventions against current burdensome diseases. The most appropriate strategy for achieving these goals is the development of novel surveillance networks designed for either detecting new patterns of disease, such as the emergence or spread of a new diseases[154–156], or for clarifying appropriate intervention targets, such as the use of rotavirus vaccine in areas with significant disease burden[157]. Further cooperation among governments and non-governmental organizations for the development of these surveillance networks and for novel intervention strategies is key for easing the burden of infectious diseases on both the developed and the developing world.

References

1. Armstrong, G.L., Conn, L.A. and Pinner, R.W. (1999) Trends in infectious disease mortality in the United States during the 20th century. *JAMA*, **281**, 61–66.
2. Taylor, R., Lewis, M. and Powles, J. (1998) The Australian mortality decline: all-cause mortality 1788–1990. *Aust. N.Z. J. Public Hlth*., **22**, 27–36.
3. Wolleswinkel-van den Bosch, J.H., Looman, C.W., Van Poppel, F.W. and Mackenbach, J.P. (1997) Cause-specific mortality trends in The Netherlands, 1875–1992: a formal analysis of the epidemiologic transition. *Int. J. Epidemiol*., **26**, 772–781.
4. De Flora, S., Quaglia, A., Bennicelli, C. and Vercelli, M. (2005) The epidemiological revolution of the 20th century. *Faseb. J*., **19**, 892–897.
5. Historian, T.O. o.t. P.H.S. accessed on May 28, 2007 at (http://lhncbc.nlm.nih.-gov/apdb/phsHistory/faqs.html).
6. Sassetti, C.M. and Rubin, E.J. (2007) The open book of infectious diseases. *Nat. Med*., **13**, 279–280.
7. Morens, D.M., Folkers, G.K. and Fauci, A.S. (2004) The challenge of emerging and re-emerging infectious diseases. *Nature*, **430**, 242–249.
8. WHO. (2002) Reducing Risks, Promoting Healthy Life. World Health Report.
9. Mathers, C.D. and Loncar, D. (2006) Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*., **3**, e442.
10. Pinner, R.W., Teutsch, S.M., Simonsen, L., Klug, L.A., Graber, J.M., Clarke, M.J. and Berkelman, R.L. (1996). Trends in infectious diseases mortality in the United States. *JAMA*, **275**, 189–193.
11. Omran, A.R. (1971) The epidemiologic transition. A theory of the epidemiology of population change. *Milbank Mem. Fund Q*., **49**, 509–538.
12. Vaccine preventable deaths and the Global Immunization Vision and Strategy, 2006–2015. (2006) *MMWR Morb. Mortal. Wkly. Rep*., **55**, 511–515.
13. UNAIDS. UNAIDS, Accessed on May 20, 2007 at (http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp).
14. Fauci, A.S. (2005) Emerging and reemerging infectious diseases: the perpetual challenge. *Acad. Med*., **80**, 1079–1085.
15. Lashley, F.R. (2006) Emerging infectious diseases at the beginning of the 21st century. *Online J. Issues Nurs*., **11**, 2.
16. Fauci, A.S. (2006) Emerging and re-emerging infectious diseases: influenza as a prototype of the host-pathogen balancing act. *Cell*., **124**, 665–670.
17. Walensky, R.P., Paltiel, A.D., Losina, E., Mercincavage, L.M., Schackman, B.R., Sax, P.E., Weinstein, M.C. and Freedberg, K.A. (2006) The survival benefits of AIDS treatment in the United States. *J. Infect. Dis*., **194**, 11–19. Epub. 2006 Jun 1.
18. Smit, C., Geskus, R., Uitenbroek, D., Mulder, D., Van Den Hoek, A., Coutinho, R.A. and Prins, M. (2004) Declining AIDS mortality in Amsterdam: contributions of declining HIV incidence and effective therapy. *Epidemiology*, **15**, 536–542.
19. Dorling, D., Shaw, M. and Davey Smith, G. (2006) Global inequality of life expectancy due to AIDS. *BMJ*, **332**, 662–664.
20. Fischer, T.K., Viboud, C., Parashar, U., Malek, M., Steiner, C., Glass, R. and Simonsen, L. (2007) Hospitalizations and deaths from diarrhea and rotavirus

among children < 5 years of age in the United States, 1993–2003. *J. Infect. Dis.*, **195**, 1117–1125. Epub. 2007 Mar 6.
21. Soriano-Gabarro, M., Mrukowicz, J., Vesikari, T. and Verstraeten, T. (2006) Burden of rotavirus disease in European Union countries. *Pediatr. Infect. Dis. J.*, **25**, S7–S11.
22. Stebbins, S. (2007) Rotavirus: Disease and vaccine update, 2007. *J. Fam. Pract.*, **56**, S6–S11.
23. Glass, R.I., Bresee, J.S., Turcios, R., Fischer, T.K., Parashar, U.D. and Steele, A.D. (2005) Rotavirus vaccines: targeting the developing world. *J. Infect. Dis.*, **192 Suppl. 1**, S160–166.
24. Agosti, J.M. and Goldie, S.J. (2007) Introducing HPV vaccine in developing countries–key challenges and issues. *N. Engl. J. Med.*, **356**, 1908–1910.
25. Kane, M.A., Sherris, J., Coursaget, P., Aguado, T. and Cutts, F. (2006) Chapter 15: HPV vaccine use in the developing world. *Vaccine*, **24 Suppl. 3**, S132–139.
26. Twombly, R. (2006) U.S. girls to receive HPV vaccine but picture unclear on potential worldwide use, acceptance. *J. Natl. Cancer Inst.*, **98**, 1030–1032.
27. Wittet, S. (2000) Introducing GAVI and the Global Fund for Children's Vaccines. *Vaccine*, **19**, 385–386.
28. Walgate, R. (2002) Global Fund for AIDS, TB and malaria opens shop. *Bull. World Health Organ.*, **80**, 259.
29. PEPFAR and the fight against HIV/AIDS. (2007) *Lancet*, **369**, 1141.
30. Drager, S., Gedik, G. and Dal Poz, M.R. (2006) Health workforce issues and the Global Fund to fight AIDS, Tuberculosis and Malaria: an analytical review. *Hum. Resour. Health*, **4**, 23.
31. Nossal, G.J. (2003) Gates, GAVI, the glorious global funds and more: all you ever wanted to know. *Immunol. Cell. Biol.*, **81**, 20–22.
32. Control of infectious diseases. (1999) *MMWR Morb. Mortal. Wkly. Rep.*, **48**, 621–9.
33. Cutler, D. and Miller, G. (2005) The role of public health improvements in health advances: the twentieth-century United States. *Demography*, **42**, 1–22.
34. Burns, H. (2007) Germ theory: invisible killers revealed. *BMJ*, **334 Suppl. 1**, s11.
35. Plane, D.A., Henrie, C.J. and Perry, M.J. (2005) Migration up and down the urban hierarchy and across the life course. *Proc. Natl. Acad. Sci. U.S.A.*, **102**, 15313–15318. Epub. 2005 Oct. 17.
36. Budnik, A. and Liczbinska, G. (2006) Urban and rural differences in mortality and causes of death in historical Poland. *Am. J. Phys. Anthropol.*, **129**, 294–304.
37. Freudenberg, N., Galea, S. and Vlahov, D. (2005) Beyond urban penalty and urban sprawl: back to living conditions as the focus of urban health. *J. Community Health*, **30**, 1–11.
38. Vlahov, D., Galea, S., Gibble, E. and Freudenberg, N. (2005) Perspectives on urban conditions and population health. *Cad. Saude Publica.*, **21**, 949–957. Epub. 2005 May 2.
39. Vlahov, D., Gibble, E., Freudenberg, N. and Galea, S. (2004) Cities and health: history, approaches, and key questions. *Acad. Med.*, **79**, 1133–1138.
40. Stern, A.M. and Markel, H. (2004) International efforts to control infectious diseases, 1851 to the present. *JAMA*, **292**, 1474–1479.

41. Shattuck, L. (1850) Louisiana State University, Baton Rouge The Medical and Public Health Law Site; [cited 2007 May 25]. Available from: http://biotech.law.lsu.edu/cphl/history/books/sr/.
42. Wilcox, L.S. (2005) Health education from 1775 to 2005. *Prev. Chronic. Dis*., **2 Spec no**, A01. Epub. 2005 Nov. 1.
43. Christmas, W.A. and Dorman, J.M. (1996) The Storey of college health hygiene. Thomas A. Storey, MD (1875–1943) and the promotion of hygiene. *J. Am. Coll. Health*, **45**, 27–34.
44. Strasser, S. (1996) Next to Godliness. [Review of: Hoy, S. Chasing dirt: the American pursuit of cleanliness. Oxford University Press, 1995; Williams, M. T. Washing “the great unwashed”: public baths in urban America, 1840–1920. Ohio State University Press, 1991]. *Rev. Am. Hist*., **24**, 461–5.
45. Pollard, A.J. (2007) Childhood immunisation: what is the future? *Arch. Dis. Child*., **92**, 426–433.
46. Tengs, T.O., Adams, M.E., Pliskin, J.S., Safran, D.G., Siegel, J.E., Weinstein, M.C. and Graham, J.D. (1995) Five-hundred life-saving interventions and their cost-effectiveness. *Risk Anal*., **15**, 369–390.
47. Vallin, J. and Mesle, F. (2004) Convergences and divergences in mortality. A new approach to health transition. *Demographic Research*, accessed April 7th, 2007 at http://www.demographic-research.org **2**, 12–44.
48. Olshansky, S.J. and Ault, A.B. (1986) The fourth stage of the epidemiologic transition: the age of delayed degenerative diseases. *Milbank Q*, **64**, 355–391.
49. Frenk, J., Bobadilla, J.L., Stern, C., Frejka, T. and Lozano, R. (1991) Elements for a theory of the health transition. *Health Transit. Rev*., **1**, 21–38.
50. Caselli, G. (1995) The key phases of the European health transition. *Pol. Popul. Rev*., 73–102.
51. Gurven, M., Kaplan, H. and Supa, A.Z. (2007) Mortality experience of Tsimane Amerindians of Bolivia: Regional variation and temporal trends. *Am. J. Hum. Biol*., **19**, 376–398.
52. Hill, K., Vapattanawong, P., Prasartkul, P., Porapakkham, Y., Lim, S.S. and Lopez, A.D. (2006) Epidemiologic transition interrupted: a reassessment of mortality trends in Thailand, 1980–2000. *Int. J. Epidemiol*., **36**, 374–384. Epub. 2006 Dec. 20.
53. Castillo-Salgado, C., Mujica, O. and Loyola, E. (1999) A subregional assessment of demographic and health trends in the Americas: 1980–1998. *Stat. Bull. Metrop. Insur. Co*., **80**, 2–12.
54. Serow, W.J., Cowart, M.E. and Camezon, J. (1998) Epidemiologic transition theory and aging: Hispanic populations of North America and the Caribbean. *J. Health Hum. Serv. Adm*., **20**, 333–347.
55. Hill, K., Barker, B. and Vos, T. (2007) Excess Indigenous mortality: are Indigenous Australians more severely disadvantaged than other Indigenous populations? *Int. J. Epidemiol*., ?????
56. Hetzel, D.M. (2001) Death, disease and diversity in Australia, 1951 to 2000. *Med. J. Aust*., **174**, 21–24.
57. Rychtarikova, J., Vallin, J. and Mesle, F. (1989) Comparative study of mortality trends in France and the Czech Republic since 1950. *Popul*., **44**, 291–321.
58. Shkolnikov, V.M., Andreev, E.M., Anson, J. and Mesle, F. (2004) The peculiar pattern of mortality of Jews in Moscow, 1993–95. *Popul. Stud. (Camb)*., **58**, 311–329.

59. Caselli, G., Meslé, F. and Vallin, J. (2003) Epidemiologic transition theory exceptions. *Max Planck Institute for Demographic Research*, accessed May 2, 2007 from http://www.demogr.mpg.de/Papers/workshops/020619_paper40.pdf.
60. Vallin, J. (2007) Commentary: 'Epidemiologic transition' interrupted or sweep to the second stage of 'health transition'? *Int. J. Epidemiol.*, **36**, 384–386. Epub. 2007 Apr. 30.
61. Coussy, J. and Vallin, J. (1996) Crisis and demographic transition in Africa. *Chron. CEPED.*, 1–5.
62. Timaeus, I.M. (1998) Impact of the HIV epidemic on mortality in sub-Saharan Africa: evidence from national surveys and censuses. *AIDS*, **12 Suppl 1**, S15–27.
63. King, G. and Zeng, L. (2001) Improving Forecasts of State Failure. *World Politics*, **53**, 623–658.
64. Victora, C.G., Wagstaff, A., Schellenberg, J.A., Gwatkin, D., Claeson, M. and Habicht, J.P. (2003) Applying an equity lens to child health and mortality: more of the same is not enough. *Lancet*, **362**, 233–241.
65. Meslé, F. (2004) Mortality in Central and Eastern Europe: long-term trends and recent upturns. *Demographic Research*, accessed April 7th, 2007 at http://www.demographic-research.org **2**, 46–70.
66. Okolski, M. (1992) Anomalies in demographic transition in Poland. *Geogr. Pol.*, **59**, 41–53.
67. Tkatchenko, E., McKee, M. and Tsouros, A.D. (2000) Public health in Russia: the view from the inside. *Health Policy Plan*, **15**, 164–169.
68. Tulchinsky, T.H. and Varavikova, E.A. (1996) Addressing the epidemiologic transition in the former Soviet Union: strategies for health system and public health reform in Russia. *Am. J. Public Health*, **86**, 313–320.
69. Shkolnikov, V., Meslé, F. and Vallin, J. (1996) Health crisis in Russia. I. Recent trends in life expectancy and causes of death from 1970 to 1993. *Popul.*, **8**, 123–154.
70. Boutayeb, A. (2006) The double burden of communicable and non-communicable diseases in developing countries. *Trans. R. Soc. Trop. Med. Hyg.*, **100**, 191–199.
71. Murray, C.J.L. and Lopez, A.D. (1996) *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Published by the Harvard School of Public Health on behalf of the World Health Organization and the World Bank; Distributed by Harvard University Press, Cambridge, MA (USA).
72. Boerma, J.T. and Stansfield, S.K. (2007) Health statistics now: are we making the right investments? *Lancet*, **369**, 779–786.
73. Mathers, C.D., Fat, D.M., Inoue, M., Rao, C. and Lopez, A.D. (2005) Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bull. World Health Organ.*, **83**, 171–177.
74. (2005) Stumbling around in the dark. *Lancet*, **365**, 1983.
75. AbouZahr, C. and Vaughan, J.P. (2000) Assessing the burden of sexual and reproductive ill-health: questions regarding the use of disability-adjusted life years. *Bull. World Health Organ.*, **78**, 655–666.

76. Anand, S. and Hanson, K. (1997) Disability-adjusted life years: a critical review. *J. Health Econ*., **16**, 685 – 702.
77. Mont, D. (2007) Measuring health and disability. *Lancet*, **369**, 1658 – 1663.
78. Bloom, D.E., Canning, D. and Weston, M. (2005) The Value of Vaccination. *World Economics*, **6**, 15 – 30.
79. Niehaus, M.D., Moore, S.R., Patrick, P.D., Derr, L.L., Lorntz, B., Lima, A.A. and Guerrant, R.L. (2002) Early childhood diarrhea is associated with diminished cognitive function 4 to 7 years later in children in a northeast Brazilian shantytown. *Am. J. Trop. Med. Hyg*., **66**, 590 – 593.
80. Dillingham, R. and Guerrant, R.L. (2004) Childhood stunting: measuring and stemming the staggering costs of inadequate water and sanitation. *Lancet*, **363**, 94 – 95.
81. Guerrant, D.I., Moore, S.R., Lima, A.A., Patrick, P.D., Schorling, J.B. and Guerrant, R.L. (1999) Association of early childhood diarrhea and cryptosporidiosis with impaired physical fitness and cognitive function four-seven years later in a poor urban community in northeast Brazil. *Am. J. Trop. Med. Hyg*., **61**, 707 – 713.
82. Edmunds, W., Dejene, A., Mekonnen, Y., Haile, M., Alemnu, W. and Nokes, D. (2000) The cost of integrating hepatitis B virus vaccine into national immunization programmes: a case study from Addis Ababa. *Health Policy Plan*, **15**, 408 – 16.
83. Miguel, E. and Kremer, M. (2004) Worms: identifying impacts on education and health in the presence of treatment externalities. *Econometrica*, **72**, 159 – 217.
84. Mendez, M.A. and Adair, L.S. (1999) Severity and timing of stunting in the first two years of life affect performance on cognitive tests in late childhood. *J. Nutr*., **129**, 1555 – 1562.
85. Pritchett, L. and Summers, L.H. (1993) *Wealthier is healthier* (Office of the Vice President Development Economics World Bank, Washington, D.C.).
86. Bloom, D.E. and Canning, D. (2000) Policy forum: public health. The health and wealth of nations. *Science*, **287**, 1207, 1209.
87. Bloom, D.E., Canning, D. and Sevilla, J. (2004) The effect of health on economic growth: a production function approach. *World Development*, **32**, 1 – 13.
88. *World Health Organization. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003*. : access on June 9, 2007 at http://www.who.int/csr/sars/country/table2004_04_21/en/index.html
89. Smith, R.D. (2006) Responding to global infectious disease outbreaks: lessons from SARS on the role of risk perception, communication and management. *Soc. Sci. Med*., **63**, 3113 – 3123.
90. Barreto, M.L. (2003) Science, policy, politics, a complex and unequal world and the emerging of a new infectious disease. *J. Epidemiol. Community Health*, **57**, 644 – 645.
91. Blendon, R.J., Benson, J.M., DesRoches, C.M., Raleigh, E. and Taylor-Clark, K. (2004) The public’s response to severe acute respiratory syndrome in Toronto and the United States. *Clin. Infect. Dis*., **38**, 925 – 931.
92. Calvin, L. In: *International Trade and Food Safety: Economic Theory and Case Studies*, Busby, J.C. (ed.) (2003) United States Department of Agriculture, Economic Research Service (AER-828).

93. Belton, D.J. (2004) The macro-economic impact of a foot-and-mouth disease incursion in New Zealand. *Dev. Biol. (Basel)*, **119**, 457–461.
94. Garner, M.G., Fisher, B.S. and Murray, J.G. (2002) Economic aspects of foot and mouth disease: perspectives of a free country, Australia. *Rev. Sci. Tech*., **21**, 625–635.
95. Krystynak, R.H. and Charlebois, P.A. (1987) The Potential Economic Impact of an Outbreak of Foot-and-Mouth Disease in Canada. *Can. Vet. J*., **28**, 523–527.
96. Paarlberg, P.L., Lee, J.G. and Seitzinger, A.H. (2002) Potential revenue impact of an outbreak of foot-and-mouth disease in the United States. *J. Am. Vet. Med. Assoc*., **220**, 988–992.
97. Perry, B.D., Gleeson, L.J., Khounsey, S., Bounma, P. and Blacksell, S.D. (2002) The dynamics and impact of foot and mouth disease in smallholder farming systems in South-East Asia: a case study in Laos. *Rev. Sci. Tech*., **21**, 663–673.
98. Perry, B.D., Kalpravidh, W., Coleman, P.G., Horst, H.S., Dermott, J.J., Randolph, T.F. and Gleeson, L.J. (1999) The economic impact of foot and mouth disease and its control in South-East Asia: a preliminary assessment with special reference to Thailand. *Rev. Sci. Tech*., **18**, 478–97.
99. Perry, B.D. and Rich, K.M. (2007) Poverty impacts of foot-and-mouth disease and the poverty reduction implications of its control. *Vet. Rec*., **160**, 238–241.
100. Randolph, T.F., Perry, B.D., Benigno, C.C., Santos, I.J., Agbayani, A.L., Coleman, P., Webb, R. and Gleeson, L.J. (2002) The economic impact of foot and mouth disease control and eradication in the Philippines. *Rev. Sci. Tech*., **21**, 645–661.
101. Hall, C. (2004) Impact of avian influenza on U.S. poultry trade relations-2002: H5 or H7 low pathogenic avian influenza. *Ann. N.Y. Acad. Sci*., **1026**, 47–53.
102. *Spread of Avian Flu Could Affect Next Year's Economic Outlook*. In: *The World Bank. East Asia Update – Countering Global Shocks*, accessed June 9, 2007 from http://www.worldbank.org/eapupdate.
103. Bramhmbhatt, M. (2006) *Economic Impacts of Avian Influenza Propagation*, In: *First International Conference on Avian Influenza in Humans*, June 29, 2006; Paris, France.
104. (2006) Economic and social impact of epidemic and pandemic influenza. *Vaccine*, **24**, 6776–6778.
105. International Monetary Fund. Avian Flu Working Group. *The global economic and financial impact of an avian flu pandemic and the role of the IMF* (International Monetary Fund, Washington, D.C., 2006).
106. Brundtland, G.H. *Health brings wealth, in BBC News Online: Business, Friday, 23 March, 2001*: BBC, London.
107. Folch, E., Hernandez, I., Barragan, M. and Franco-Paredes, C. (2003) Infectious diseases, non-zero-sum thinking, and the developing world. *Am. J. Med. Sci*., **326**, 66–72.
108. *United Nations Millennium Declaration Resolution 55/2 adopted by the General Assembly in Millennium Summit*. 2000. accessed from http://www.u-n.org/millennium/ on June 9, 2007.
109. Shiffman, J. (2006) Donor funding priorities for communicable disease control in the developing world. *Health Policy Plan*, **21**, 411–420.

110. Wagstaff, A. (2001) Economics, health and development: some ethical dilemmas facing the World Bank and the international community. *J. Med. Ethics*, **27**, 262–267.
111. (2007) Millennium development holes. *Nature*, **446**, 347.
112. Bloom, D.E. (2006) Education in a globalized world. *World Economics*, **7**, 87–109.
113. Hawkes, C. and Ruel, M. (2006) The links between agriculture and health: an intersectoral opportunity to improve the health and livelihoods of the poor. *Bull. World Health Organ*., **84**, 984–990.
114. World Bank (1998) *Assessing aid: what works, what doesn't, and why Assessing aid*. World Bank policy research report. Washington, D.C.: Oxford University Press. xii, 148.
115. Wagstaff, A., Claeson, M. and World Bank. (2004) *The millennium development goals for health: rising to the challenges*. Washington, DC: World Bank. xv, 186.
116. Lewis, M. (2006) *Governance and Corruption in Public Health Care Systems. Working Paper Number 78*. Center for Global Development (www.cgdev.org).
117. Gayle, H.D. and Hill, G.L. (2001) Global impact of human immunodeficiency virus and AIDS. *Clin. Microbiol. Rev*., **14**, 327–335.
118. UNAIDS (2006) *Report on the Global AIDS Epidemic*. Accessed May 20, 2007 at http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp
119. Steinbrook, R. (2007). HIV in India–a complex epidemic. *N. Engl. J. Med*., **356**, 1089–1093.
120. Bertozzi, S., Padian, N.S., Wegbreit, J., DeMaria, L.M., Feldman, B., Gayle, H., Gold, J., Grant, R. and Isbell, M.T. (2006) *HIV/AIDS prevention and treatment in Disease Control Priorities in Developing Countries*. Jamison, D. T. (ed.), Oxford University Press, New York, NY.
121. Nicoll, A. and Gill, O.N. (1999) The global impact of HIV infection and disease. *Commun. Dis. Public Health*, **2**, 85–95.
122. UNAIDS (2006) *Report on the Global AIDS Epidemic*. Geneva, Switzerland, 1999.
123. Yeni, P.G., Hammer, S.M., Hirsch, M.S., Saag, M.S., Schechter, M., Carpenter, C.C., Fischl, M.A., Gatell, J.M., Gazzard, B.G., Jacobsen, D.M., Katzenstein, D.A., Montaner, J.S., Richman, D.D., Schooley, R.T., Thompson, M.A., Vella, S. and Volberding, P.A. (2004). Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society-USA Panel. *JAMA*, **292**, 251–265.
124. Zenilman, J.M. (2005) Behavioral interventions–rationale, measurement, and effectiveness. *Infect. Dis. Clin. North. Am*., **19**, 541–562.
125. Hearst, N. and Chen, S. (2004) Condom promotion for AIDS prevention in the developing world: is it working? *Stud. Fam. Plann*., **35**, 39–47.
126. World Health Organization (2004) *Tuberculosis Epidemiology* accessed July 7, 2006 at http://www.who.int/tb/hiv/faw/en/index.html.
127. Corbett, E.L., Watt, C.J., Walker, N., Maher, D., Williams, B.G., Raviglione, M.C. and Dye, C. (2003) The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch. Intern. Med*., **163**, 1009–1021.
128. Khatri, G.R. and Frieden, T.R. (2002) Controlling tuberculosis in India. *N. Engl. J. Med*., **347**, 1420–1425.

129. Okeke, I.N., Laxminarayan, R., Bhutta, Z.A., Duse, A.G., Jenkins, P., O'Brien, T.F., Pablos-Mendez, A. and Klugman, K.P. (2005) Antimicrobial resistance in developing countries. Part I: recent trends and current status. *Lancet Infect. Dis*., **5**, 481–493.
130. Frieden, T.R., Sterling, T.R., Munsiff, S.S., Watt, C.J. and Dye, C. (2003) Tuberculosis. *Lancet*, **362**, 887–899.
131. Rieder, H.L. *BCG vaccines in Clinical Tuberculosis*, Davies, P.D.O. (ed.), Arnold Publishers, London, 337–353.
132. Maitland, K., Bejon, P. and Newton, C.R. (2003) Malaria. *Curr. Opin. Infect. Dis*., **16**, 389–95.
133. Kosek, M., Bern, C. and Guerrant, R.L. (2003) The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull. World Health Organ*., **81**, 197–204.
134. Cheng, A.C., McDonald, J.R. and Thielman, N.M. (2005) Infectious diarrhea in developed and developing countries. *J. Clin. Gastroenterol*., **39**, 757–773.
135. Giaquinto, C., Van Damme, P., Huet, F., Gothefors, L., Maxwell, M., Todd, P. and da Dalt, L. (2007) Clinical consequences of rotavirus acute gastroenteritis in Europe, 2004–2005: the REVEAL study. *J. Infect. Dis*., **195 Suppl 1**, S26–S35.
136. Dennehy, P.H. (2007) Rotavirus vaccines–an update. *Vaccine*, **25**, 3137–3141. Epub. 2007 Feb. 9.
137. GAVI Alliance (2005) *GAVI alliance general information*. accessed on May 28, 2007 at http://www.vaccinealliance.org.
138. Brenzel, L., Wolfson, L.J., Fox-Rushby, J., Miller, M. and Halsey, N.A. (2006) Vaccine Preventable Diseases. In: *In Disease Control Priorities in Developing Countries*, Jamison, D. T. (ed.), Oxford University Press, New York, NY, 2006.
139. Roberts, L. (2004) Polio endgame. The exit strategy. *Science*, **303**, 1969–1971.
140. WHO (2001) *Global prevalence and incidence of selected curable sexually transmitted infections: Overview and estimates*. Accessed on May 28, 2006 at http://www.who.int/hiv/pub/sti/pub7/en/.
141. Wasserheit, J.N. and Aral, S.O. (1996) The dynamic topology of sexually transmitted disease epidemics: implications for prevention strategies. *J. Infect. Dis*., **174 Suppl 2**, S201–S213.
142. Laga, M., Nzila, N. and Goeman, J. (1991) The interrelationship of sexually transmitted diseases and HIV infection: implications for the control of both epidemics in Africa. *Aids*, **5**, S55–S63.
143. Stephenson, L.S., Latham, M.C. and Ottesen, E.A. (2000) Malnutrition and parasitic helminth infections. *Parasitology*, **121**, S23–S38.
144. Engels, D. and Savioli, L. (2006) Reconsidering the underestimated burden caused by neglected tropical diseases. *Trends Parasitol*., **22**, 363–366. Epub. 2006 Jun 23.
145. Gubler, D.J. (2006) Dengue/dengue haemorrhagic fever: history and current status. *Novartis Found Symp*., **277**, 3–16.
146. Wilder-Smith, A. and Schwartz, E. (2005) Dengue in travelers. *N. Engl. J. Med*., **353**, 924–932.
147. Isturiz, R.E., Gubler, D.J. and Brea del Castillo, J. (2000) Dengue and dengue hemorrhagic fever in Latin America and the Caribbean. *Infect. Dis. Clin. North Am*., **14**, 121–140, ix.

148. Melino, S. and Paci, M. (2007) Progress for dengue virus diseases. *Febs. J.*, **274**, 2986–3002. Epub. 2007 May 17.
149. Herwaldt, B.L. (1999) Leishmaniasis. *Lancet*, **354**, 1191–1199.
150. Murray, H.W., Berman, J.D., Davies, C.R. and Saravia, N.G. (2005). Advances in leishmaniasis. *Lancet*, **366**, 1561–1577.
151. Pepin, J. and Meda, H.A. (2001) The epidemiology and control of human African trypanosomiasis. *Adv. Parasitol*., **49**, 71–132.
152. Smith, D.H., Pepin, J. and Stich, A.H. (1998) Human African trypanosomiasis: an emerging public health crisis. *Br. Med. Bull*., **54**, 341–355.
153. Murray, C.J., Lopez, A.D., Chin, B., Feehan, D. and Hill, K.H. (2006) Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis. *Lancet*, **368**, 2211–2218.
154. Chretien, J.P., Blazes, D.L., Gaydos, J.C., Bedno, S.A., Coldren, R.L., Culpepper, R.C., Fyrauff, D.J., Earhart, K.C., Mansour, M.M., Glass, J.S., Lewis, M.D., Smoak, B.L. and Malone, J.L. (2006) Experience of a global laboratory network in responding to infectious disease epidemics. *Lancet Infect. Dis*., **6**, 538–540.
155. Chretien, J.P., Gaydos, J.C., Malone, J.L. and Blazes, D.L. (2006) Global network could avert pandemics. *Nature*, **440**, 25–26.
156. Cash, R.A. and Narasimhan, V. (2000) Impediments to global surveillance of infectious diseases: consequences of open reporting in a global economy. *Bull. World Health Organ*., **78**, 1358–1367.
157. Bresee, J., Fang, Z.Y., Wang, B., Nelson, E.A., Tam, J., Soenarto, Y., Wilopo, S.A., Kilgore, P., Kim, J.S., Kang, J.O., Lan, W.S., Gaik, C.L., Moe, K., Chen, K.T., Jiraphongsa, C., Ponguswanna, Y., Nguyen, V.M., Phan, V.T., Le, T.L., Hummelman, E., Gentsch, J.R. and Glass, R. (2004) First report from the Asian Rotavirus Surveillance Network. *Emerg. Infect. Dis*., **10**, 988–95.