



## Reviews

### Emerging Infectious Diseases: A Cause for Concern

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#### Abstract

As the twenty-first century begins it becomes increasingly apparent that the twentieth century, which opened with the promise of the eradication of most infectious diseases, closed with the specter of the reemergence of many deadly infectious diseases that have a rapidly increasing incidence and geographic range. Equally if not more alarming is the appearance of new infectious diseases that have become major sources of morbidity and mortality. Among recent examples are HIV/AIDS, hantavirus pulmonary syndrome, Lyme disease, hemolytic uremic syndrome (caused by a strain of *Escherichia coli*), Rift Valley fever, Dengue hemorrhagic fever, malaria, cryptosporidiosis, and schistosomiasis. The reasons for this situation are easily identified in some cases as associated with treatment modalities (permissive use of antibiotics), the industrial use of antibiotics, demographic changes, societal behavior patterns, changes in ecology, global warming, the inability to deliver minimal health care and the neglect of well-established public health priorities. In addition is the emergence of diseases of another type. We have begun to characterize the potential microbial etiology of what has historically been referred to as chronic diseases.

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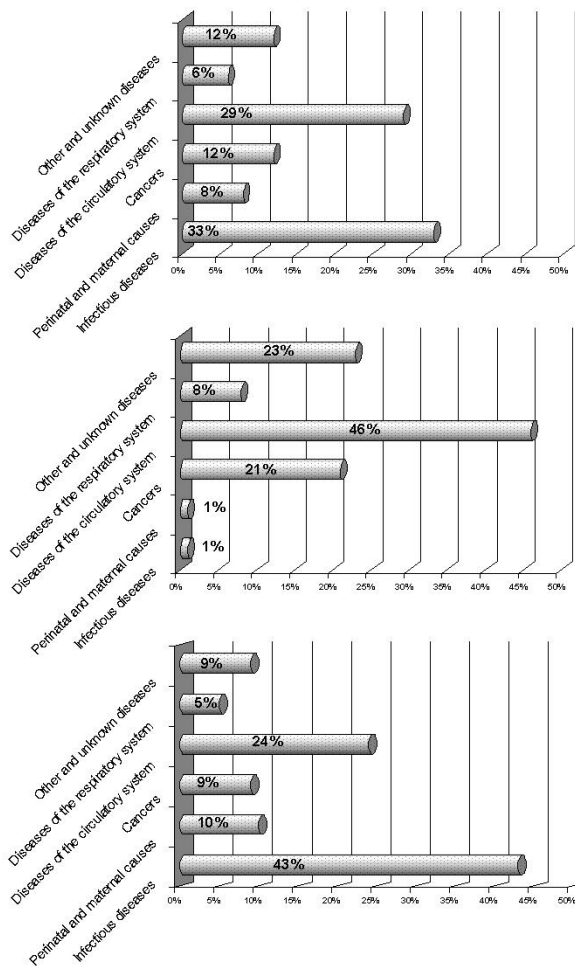
A common desire of all people in all generations is the existence of a healthier and a better world in which to live and raise our children. During the past 50 years we have witnessed astonishing improvements in health as the result of socioeconomic advances, the wider provision of safe water, sanitation facilities, better personal hygiene and the expansion of national health services. Spectacular advances in the development of vaccines and medicines, and countless other innovations in medical investigations, diagnosis and treatment of illness have ameliorated much suffering.

Some infectious diseases have been conquered by modern progress, such as smallpox, poliomyelitis, measles, tuberculosis and leprosy. And until the mid-1980s we hoped that most infectious diseases would be eradicated or at least

treatable. But as we enter the twenty-first century we are confronted by the sober reality that requires a different message: *Beware of infectious diseases. Infectious diseases are hitting back. Infectious diseases are unpredictable.* We even call them by another name; we now term them "emerging or reemerging infections."

Infectious diseases remain the leading cause of premature death among children and adults worldwide [Figure 1a]. In the developing world the situation is far worse [Figure 1b and c]. The time has arrived to recognize that infectious disease mortality and morbidity is a global issue. The start of this century should be the start of an era – one in which the availability of vaccine programs and antibiotics will minimize identifiable morbidity of infectious diseases worldwide. Unfortunately that is not the case: the role of infectious diseases in both morbidity and mortality is larger than any other factor. Eight out of 12 leading causes of morbidity are infectious diseases, while respiratory tract infections, malaria and diarrhea are among the 10 leading causes of mortality.

The first question we must ask is: Why, with the availability of such powerful tools, have we not succeeded in a greater diminution of the incidence of infectious and parasitic diseases? Part of the answer to the question of attenuating the incidence of these diseases is the lack of availability of vaccines and antibiotics in many locations that have the highest disease incidence. Examining the situation in the developed world, where there is an abundance of antibiotics, appropriate sanitation, and vaccine programs, we may well be shocked by the stark contrast [Figure 1b and c]. Nonetheless, worldwide, infectious diseases are still the dominant medical problem [Figure 1a]. Surprisingly, when we examine the last 30 years we do not see a decrease in the number and type of infectious diseases that are identified as problems by the World Health Organization [1]. On the contrary, there is an *increase* of new infectious diseases that are reported continually and older ones that are reemerging. While notable achievements are observed in disease control – such as the eradication of smallpox and the control of polio and potentially measles – the emergence of novel infectious diseases and reemergence of diseases that were believed to be essentially eradicated or of minimal incidence are more and more troubling.



**Figure 1.** The leading causes of death worldwide. [a] Number of deaths worldwide. [b] Number of deaths in the developed world. [c] Number of deaths in the developing world.

What is an emerging or reemerging disease? In 1992 the Institute of Medicine published a report prepared by a Committee on Emerging Microbial Threats to Health, which defined emerging infectious diseases as those diseases whose incidence in humans has increased within the past two decades or threatens to increase in the future. This definition could be widened to include disease of farm livestock, animals in general, and plants [2]. Why has this occurred and how can the problem be resolved? Many factors contribute to the emergence of infectious diseases. The general categories of contributing factors are summarized in the following section.

## Contributing factors to re-emerging and emerging infections

### • Microbial adaptation

Since microbes adapt to their environment, antibiotic

resistance has been a consideration since antibiotics were discovered more than 50 years ago. The permissive and inappropriate use of antibiotics by patients and physicians in primary care and hospitals has contributed to the recent escalation of antibiotic-resistant bacterial strains [3,4].

**a** Examples are strains of pneumococci, staphylococci, enterococci and *Mycobacterium tuberculosis*, among many others. The enhanced use of medical devices and prostheses has resulted in the emergence of strains of *Staphylococcus* and *E. coli* that are resistant to antibiotic therapy [5]. Microbial evolution is also responsible for the selection in the environment. Examples include the "antigenic drift" of influenza virus, and situations involving close proximity to duck and pig farming in China. Avian influenza is not generally transmissible to humans, but it can infect pigs. Variations found in virus antigens of the avian virus expressed in the pig can be included in the virus genome, which may subsequently be transmitted to humans [6].

**b**

### • Human demographics and behavioral changes

These factors generally mean significant societal changes. They include events such as population growth and migration (within countries from rural to urban areas as well as across international borders), the occurrence of war and civil unrest, the decay of cities, changes in sexual behavior, extended use of drugs, and housing facilities with a high population density. Crowded living conditions almost always lead to the emergence of tuberculosis. War and displacement of populations are synonymous with cholera outbreaks. The spread of HIV is associated with a specific sexual behavior and intravenous drug use, as are epidemics of other sexually transmitted diseases [7].

**c**

### • Ecological changes

These changes could derive from economic factors such as land utilization. These include agricultural changes, construction of dams, deforestation, drought, famine and climate changes. In our immediate area, Rift Valley fever outbreaks are associated with changes in irrigation and dams, as is schistosomiasis [8]. As already indicated, pig and/or duck farming almost certainly effects antigen drift in influenza and is an important factor in the pandemic of influenza [6]. An interesting climatic change was responsible for the occurrence of hantavirus pulmonary syndrome in the United States and other locations [9,10], while the emergence of Lyme disease in the U.S. and Europe was most likely due to reforestation, which increased the population of deer and the deer tick – the vector of Lyme disease [11].

### • Global warming

Computer models predict that global warming and other climatic changes will expand the incidence and distribution of many serious medical disorders. Heating of the atmosphere can promote, by various means, the emergence and reemergence of diseases. Diseases relayed by mosquitoes, such as malaria, and several kinds of encephalitis such as

West Nile fever or Rift Valley fever constitute the greatest concern. In addition to exacerbating the vector-borne illness, global warming increases the incidence of water-borne diseases, including cholera. Drenching rains brought by a warmed Indian Ocean to the Horn of Africa in 1997 and 1998 offer an example of how people will be affected by global warming. The flooding set off epidemics of cholera as well as two mosquito-borne infections, malaria and Rift Valley fever [12].

#### • Food industry and technology

Progress in food processing and packaging and the shipping of food supplies has been responsible for new disease outbreaks as much as the availability of antibiotics in the cattle and milk production industry [13]. Hemolytic uremic syndrome results from contamination of hamburger meat and other food products by *E. coli* O157:H7. Bovine spongiform encephalopathy (BSE/CJ) is due to contaminated beef, hepatitis B and C can originate from contaminated blood products, and Creutzfeldt-Jakob disease occurred because of contaminated corneal transplants, instruments and contaminated batches of human growth hormone [7]. Whole blood and blood products were responsible for the initial transmission of HIV virus to hemophiliacs and to significant numbers of hospitalized individuals requiring blood transfusions [14]. Enhanced biotechnology techniques and the use of organ transplantation and immunosuppressant drugs, although important medical advances, also carry with them the risk of enhancing the emergence of infectious diseases.

#### • Inadequate public health programs

Complacency can be fatal when it comes to infectious diseases. Unfortunately, there are situations in which specific minimal public health programs are not adequately implemented. In scores of refugee camps in Africa the absence of appropriate sanitation has led to outbreaks of cholera. In Russia the absence of an effective vaccination program has led to the resurgence of diphtheria. In the USA the lack of follow-through on antibiotic therapy has led to a resurgence of tuberculosis [15]. In the Middle East the absence of a coordinated vaccination program for feral animals has resulted in a situation where rabies infection is endemic in the wild animal population.

#### • International travel and commerce

The global movement of people and goods has resulted in the quick and efficient transfer of infectious agents from one ecological niche to environments more conducive to the spread of diseases. The obvious example is the infected traveler who by virtue of air transportation becomes a principal disease vector. Another example, of course, is the infamous airline steward (identified as case zero) who is most likely responsible for the efficient and quick transmission of the HIV virus between continents and within far reaches of continents.

Ebola virus has caused epizootics in *Cynomolgus macaques*, which has resulted in human infections and fatalities [16]. The continuing international traffic of primates for medical research and other purposes presents a very significant infectious disease problem. This however is a small indication of the efficiency of disease transfer by transfer of the vector.

Less obvious examples include the international trade in used tires, which is responsible for moving mosquito populations from different species throughout the world [17]. Standing water in these tires are effective transport media and all too many of these mosquito are vectors for all sorts of flavivirus infections, including Dengue, Rift Valley, and eastern equine encephalomyelitis. Even cases of malaria are occasionally encountered in non-endemic-disease areas. Another classic example is the transmission of cholera strains in the bilge water of African freighters, which introduced these strains to South America. There is little doubt that hundreds of other organisms have been transported in a similar manner [17].

### Infectious agents – more than the eye can see

Table 1 lists the specific microbial agents responsible for recent infectious disease outbreaks and the probable factors contributing to the events. It is by no means an exhaustive compilation. Further understanding of the conditions conducive to the spread of infectious diseases requires a consideration of the potential human encounters leading to infections, as enumerated in Table 2.

What is the relevance of each of these? Powerful diagnostic technology and the realization that the so-called natural flora that inhabit our gastrointestinal tract can produce slowly progressive chronic disease, with a wide spectrum of clinical manifestations and disease outcome, have led to the discovery of new infectious agents and new concepts of infectious diseases [18,19]. It is easy to understand the occurrence of debilitating illness from virulent strains of *E. coli* and *Salmonella* and the like, but for decades the endemic infections of *Helicobacter pylori* and its effects went unnoticed. Many physicians still ignore the infectious disease etiology of peptic ulcers and gastritis. It is becoming increasingly likely that Crohn's disease may be a similar phenomenon [20].

Consider for a moment the ever-present vectors that inhabit our skin and clothing. In our area, *Leishmania*, West Nile and Rift Valley fever are examples of disease spread by insect vector. The interaction between domestic animals in this case is important. Locally, there is tick-borne Mediterranean spotted fever and the transmission of brucellosis from infected sheep. The demonstration that the final outcome of infection is as much determined by the genetic background of the patient as by the genetic make-up of the infecting organism indicates that a number of chronic diseases of unknown etiology can be caused by one or more infectious agent.

**Table 1.** Examples of recent emerging infections and probable factors in their emergence

Microorganism	Factor(s) contributing to emergence
<b>Bacterial</b>	
Cholera	In a recent epidemic in South America, probably introduced from Asia by ship, with spread facilitated by reduced water chlorination; new strain (type O139) from Asia recently disseminated by travel (similar to past introductions of classic cholera)
<i>Helicobacter pylori</i>	Probably long widespread, now recognized (associated with gastric ulcers, possibly other gastrointestinal disease)
Hemolytic uremic syndrome ( <i>E. coli</i> O157:H7)	Mass food processing technology and inadequate surveillance, allowing contamination of meat
<i>Legionella</i> (Legionnaires' disease)	Cooling and plumbing systems (organisms grow in biofilms that are formed on water storage tanks and in stagnant plumbing)
Lyme borreliosis ( <i>Borrelia burgdorferi</i> )	Reforestation around homes and other conditions favoring tick vector and deer (a secondary reservoir host)
<i>Staphylococcus aureus</i> and <i>Staph. epidermis</i>	Medical devices (stents, catheters, grafts, orthopedic devices) and biofilm growth
<b>Viral</b>	
Argentine, Bolivian Hemorrhagic fever	Changes in agriculture favoring rodent host
Bovine spongiform encephalopathy (cattle)	Changes in rendering processes
Dengue hemorrhagic fever	Transportation, travel, migration, and urbanization
Hantaviruses	Ecological or environmental changes, increasing contact with rodent hosts
Hepatitis B, C	Transfusions, organ transplants, contaminated hypodermic apparatus, sexual transmission, vertical spread from infected mother to child
HIV	Promiscuous sexual behavior, travel, contaminated hypodermic apparatus (including i.v. drug use), transfusions, organ transplants. After introduction, vertical spread from infected mother to child
Influenza	Possibly pig/duck agriculture facilitating re-assortment of avian and mammalian influenza viruses
Rift Valley fever	Dam building, agriculture, irrigation; possibly change in virulence or pathogenicity of virus
<b>Parasitic</b>	
<i>Cryptosporidium</i> , other waterborne pathogens	Contaminated surface water, faulty water purification
Malaria	Travel or migration
Schistosomiasis	Dam building

**Table 2.** Potential encounters in humans leading to infectious diseases

- Pathogens in or on body or our immediate environment
- Vectors (insects and others) on body
- Immunological sequelae of past infections
- Susceptibility to infections (physiological and psychological)
- Genetic background
- Cultural preferences (customs, behavioral patterns, technology)

Once the infection has passed it may leave long-term effects on our immune system. With rare exception, the means by which pathogens suppress, subvert or evade defenses and establish chronic or latent infection have

received little attention. Almost certainly the etiology of juvenile diabetes is a result of autoimmune sequelae of a viral infection, as may well be the case for post-polio and post-measles neurological syndromes. In the not too distant future these examples may be supplemented by some types of heart diseases and mental illnesses. Moreover, we often encounter the phenomenon where depression has an effect on the immune system, leading to greater susceptibility to infectious diseases. Genetic make-up will increasingly become a factor in understanding greater disease resistance and prevalence.

Another factor is the presence of specific receptors to microbial invasion. Finally is the most ignored factor, cultural preferences. This is clearly a dominant factor in the spread of HIV and other sexually transmitted diseases.

A most provocative theory has been proposed by Ewald [18,21] concerning the evolution of the host-parasite relationship in the spread of infectious diseases. Selective pressure does not necessarily lead to the evolution of mildly virulent genotypes of infectious agents. Rather, it is a combination of the mode of transmission of the infectious agent and the price paid for severe host illness. This notion may aid our understanding of the emergence of infectious diseases in specific circumstances. A simple example is the spread of cholera. A

waterborne illness, it depends little on the mobility of the infected host but greatly on the quality of the water supply. Poor sewage disposal and other sanitation deficiencies are essential for the spread of the virulent host. A good water supply will induce the selection of cholera genotypes that are less virulent, since the demise of the host has a negative effect on the survival of the infectious agent. The good water supply acts against spread of the disease. Thus, the prevalent prediction is that cholera strains will be less virulent in geographical areas that have good water quality. Tentative data in support of this hypothesis have been reported for areas in South America with good sanitation [18]. This has significant implications for understanding the emergence of infectious diseases.

A further ramification of the theory proposed by Ewald reflects on our possible lack of understanding of the true prevalence of infectious diseases. The conventional wisdom on many chronic diseases is accepted – namely, that the basis for many of them is genetic. It would follow from that proposal that selective pressure would attenuate the survival probability of those phenotypes carrying this disadvantageous genetic complement. A fitness decrease in an inherited disease that results in a mere 1% decrease in its reproducibility rate will, over a not very long time, lead to a selection *against* survival of carriers of this disease. However, this is not the case – more people are diagnosed with autoimmune diseases. Therefore, we are left with the distinct possibility of an until-now hidden microbial etiology of many of these diseases. An example of such hidden microbial etiology is the link between *Helicobacter pylori* and gastritis, peptic ulcers and gastric cancer [22].

There is a case to be made from the extension of the selective pressure theory of Ewald in this regard. The attenuation of promiscuous sexual behavior and intravenous drug abuse could lead to selective pressure on the HIV virus to evolve to less virulent forms in which it can survive for longer periods with less damage to the host. The behavior patterns that resulted in the pandemic create evolutionary pressure to select the most virulent forms of the virus, since the health of the host is of no consequence for viral survival.

## Summary

In summary, the dimensions of the problems associated with emerging infectious diseases are sufficiently large to cause great concern in the medical community. In addition to the increase in morbidity, which strains an already overburdened health care system, is the appearance of novel disease syndromes that require additional vigilance and the availability of new treatment modalities. Not only do many commonly used antibiotics become less useful, but the emergence of some diseases require treatment and prevention strategies that go well beyond the dispensing of medication. Human behavior becomes an integral part of medical analysis and treatment.

We do possess the tools and the ever-expanding knowledge to deal with the problem. Most important, we function in an era of instantaneous communication necessary to optimize our response. The time has surely arrived to construct the appropriate system and interactive parts that will assure international cooperation to achieve the goal of the Twenty-First Century – Health For All.

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*I did think I did see all heaven before me and the great God himself.*

*George Frederic Handel, German-born British composer (1685-1759).*

*With tears streaming down his face, this was his comment after completing the Hallelujah Chorus of The Messiah*