Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Emerging Diseases: Overview

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Introduction

Emerging and re-emerging infectious diseases have been major features of contemporary societies. Indeed, there is evidence that history has been characterized by the constant interplay of humans and pathogens (McNeill, 1977). However, it is impossible to say when the terms 'emerging infection' or 'emerging infectious diseases' were first used to describe new infectious diseases, or diseases that meet the criteria that are described in this article. The belief in the 1960s that the threat of infectious diseases had been eliminated in developed countries was unfounded. A broader view of history would have demonstrated this. One possible reason for the optimism is that the 1960s was a decade of optimism in general. In the United States, social programs were instituted to address inequities; humankind had not only orbited the Earth, but landed on the moon; the gains of science and technology were impressive; economic expansion was equally impressive; poliomyelitis had been all but eliminated in the United States; and the sense of 'control' was widespread.

Beyond the borders of the United States, however, in Africa, Asia, Latin America, and elsewhere, malaria proved to be a huge challenge to life, although its prevalence was decreasing, and diarrheal diseases continued to take their toll, particularly among the young. Transportation links created the potential for transmission of infection between tropical regions and developed countries such as the United States. The potential for new diseases to emerge in the United States was there, and it took just a few years until this happened, catching the medical and public health communities by surprise.

Definitions of 'Emerging' and 're-emerging' Disease

In discussions of emergence, both 'emerging infections' and 'emerging infectious diseases' are commonly found. While the two are closely related, they are not synonymous. An infection does not necessarily represent a state of disease. 'Infection' suggests that an agent (usually a microbe) has become resident in the host. Usually that agent is replicating in the host. However, the host need not show any sign of disease, in the sense that it can conduct its normal activities without hindrance. 'Disease' is a state in which the normal functioning of the host is impaired, and both signs and symptoms are present – indeed, they are what limit normal function. An infectious disease is therefore a disease that is due to a pathogen.

Emerging Diseases

What, then, is an emerging infection, or an infectious disease? There has been some implicit variation in the literature. However, a general definition was articulated by Morse in the first volume of a then-new journal, *Emerging Infectious Diseases*:

> We can define as emerging infections that have newly appeared in the population, or have existed but are rapidly increasing in incidence or geographic range. (Morse, 1995: 7)

Thus, emerging infectious diseases are clinically significant diseases that are due to pathogens that have either

appeared *de novo*, or are being experienced in a region with greater intensity, or for the first time.

Some authors have used a more specific definition of emerging to diseases and have specified five types of emerging diseases: (1) diseases that arise *de novo*, (2) diseases that are newly recognized, (3) diseases that have not previously existed in a specific area, (4) diseases that had not yet made a species jump to humans until the present, and (5) diseases that are increasing in prevalence. There are other definitions as well. The simplest definitions are frequently the most useful, and thus Morse's definition will be used in this article.

Resurgent (Re-emerging) Diseases

Re-emerging infectious diseases are frequently thought of as being closely related phenomena to emerging infectious diseases. Whereas emerging diseases denote diseases that are being experienced for the first time in a given location, re-emerging diseases are diseases that are reappearing in regions from which they have disappeared. Usually eradication is due to deliberate efforts on the parts of government and public health agencies. For example, malaria control programs following the end of World War II were instrumental in the elimination of malaria from some areas of the world, such as Italy and Spain. Sometimes, malaria eradication was eliminated as part of multisector development programs. For example, the Tennessee Valley Authority, created during the 1930s primarily for flood control, hydroelectric power, and economic development, also had an explicit aim of malaria control. This resulted in the drainage of most swamps, and the elimination of malaria from this part of the United States.

Just as malaria was disappearing from many regions in the 1950s, the next decade saw the resurgence of malaria, and the global prevalence of malaria has been increasing ever since. There are multiple reasons for this. These include anopheline spp. resistance to DDT, banning of DDT because of suspected environmental effects, and the development of resistance to chloroquine. Malaria, then, is a re-emerging disease. Another is tuberculosis. In many societies, TB had been nearly eliminated, but with the appearance of HIV/AIDS, immunocompromised individuals were much more susceptible to TB reactivation. TB, therefore, is also considered to be a re-emerging disease.

The New Realization of the Threat of Infectious Diseases

The public and the medical and public health communities gradually came to realize that their complacency over the potential threat of infectious diseases was misplaced, and that new and emerging diseases constituted one foci of concern over health threats to the public. This change in attitude came gradually, and can be thought of as a series of historical 'moments,' each of which refocused attention on infectious diseases. While it is impossible to be exhaustive here, this section takes a roughly chronological approach in describing the events that led the public and professional communities to realize that infectious diseases had not been 'conquered.'

Legionellosis (Legionnaires Disease)

The Bicentennial of the United States was celebrated in 1976, and there were many gala events around the nation in July. One was the meeting of the Pennsylvania Chapter of the American Legion. The events surrounding this meeting were the first to bring the attention of both the population and the broad scientific and medical communities to the argument that infectious diseases in the United States had been 'conquered,' and both alarmed the public and aroused the curiosity of the scientific and medical communities because this appeared to be a new disease. Indeed, before legionellosis was identified and antimicrobial treatment identified, legionellosis was called a 'monster disease.'

Over 220 members of the American Legion who had attended the meeting developed an unusual respiratory illness, and it became clear that it was of bacterial etiology, although it was initially thought to be viral, due to its close clinical resemblance to influenza. Approximately 34 people died as a result of this outbreak. However, two things remained unclear. First, the pathogen could not be identified with conventional methods, and second, no common source of exposure could be identified initially, although the fact that the number of incident cases followed a typical epidemic curve suggested very strongly that there was some sort of common exposure to the pathogen. The news media seized upon this medical 'mystery,' and the public knew that they were dealing with an unknown infectious disease. This constituted a historical moment in contemporary American history, because it had been decades since something like this had happened. Six months later, the bacterium was finally identified.

Legionella was not a new bacterium. Stored samples from outbreaks as early as 1943 tested positive for *Legionella* spp. However, the bacterium had not been identified in these outbreaks because it had not yet been described and characterized. In retrospect, most renowned is an outbreak that occurred in Pontiac, Michigan in 1968, although the symptoms were milder than in the *Legionella* outbreak in Philadelphia. In fact, mild legionellosis with a nonpneumonic form is often called 'Pontiac fever.'

This is not the place to review the epidemiology, pathophysiology, and clinical aspects of legionellosis in

depth. Briefly, though, it usually has an acute onset, and is usually caused by *Legionella pneumophila*, although other species are also pathogenic. In fact, there are 40 species of the genus, and numerous serotypes. Epidemiologically, *L. pneumophila* is by far the dominant species in human disease. The major reservoirs are bodies of freshwater, and the main mode of transmission is through small droplets that are inhaled from the environment. In the Philadelphia outbreak, the source was finally traced to the air conditioning system in the hotel in which most attendees were lodged; the attendees were inhaling small particles in certain parts of the building. Dozens of subsequent outbreaks have been traced to similar mechanisms. These have been not only air conditioners but also shower heads, aerosolizers in sinks, and whirlpools. Virtually anything that aerosolizes fresh water is a potential mechanism by which legionellosis may be transmitted.

Symptoms of classic legionnaires disease are nonspecific and include fever, malaise, headaches, and myalgias. Frequently, rigors will develop, as will a productive cough (in about half the cases). Dyspnea (shortness of breath) is almost invariably present, and chest pain is common, as is a relative bradycardia for the elevated temperature. There are a number of abnormalities in laboratory tests, and chest films are markedly abnormal. A urine antigen test is available for one serotype, so laboratory diagnosis must frequently rely on more complex and time-consuming laboratory methods such as DFA. Sputum cultures or cultures from bronchoalveolar lavage have been the mainstay of laboratory diagnosis.

Since laboratory methods do not show a definitive diagnosis until a minimum of 3 days following onset, diagnosis is usually made on clinical grounds, and treatment is initiated based upon index of suspicion. Erythromycin proved to be effective in 1976, and other macrolides (azithromycin, clarithromycin) are highly effective. Tetracycline and doxycycline are frequently used, as are the fluoroquinolones, such as levofloxacin. In hosts who are not immunocompromised, the prognosis is generally positive.

There is no doubt that legionellosis was an emerging disease when it was first identified. Its particular significance lies in its historical context – in the fact that this was the first occurrence that began shaking the optimism of the 1960s and early 1970s that infectious diseases had been conquered, and also in the fact that the etiology of an obviously infectious syndrome with a reasonably high case fatality ratio remained unknown for a number of months.

Toxic Shock Syndrome

Chronologically, the next event to bring infectious disease to the attention of the public was another emerging infectious syndrome. In late 1979 and 1980, a number of women in the United States became seriously ill with a syndrome characterized by high fever, shock, rash, hypotension, and capillary leak. This syndrome had been first described as such 2 years earlier, although in retrospect it had been noted in the medical literature in the 1920s. The 1978 paper identified toxic shock syndrome in males, females, and children – and the females were both menstruating and not menstruating. The 1980 outbreak was associated with menstruating women, many of whom were using superabsorbent tampons. Although this was a major risk factor in the 1979–80 outbreak, much of the public and many physicians were under the erroneous impression that toxic shock syndrome (TSS) was necessarily associated with menstruating women who were using superabsorbent tampons. Although TSS is not necessarily associated with menstruating women, this does remain a risk factor in the epidemiology of TSS.

As with legionnaires disease, TSS was a rare disease, yet the public's perception of it was out of proportion to its true prevalence – the risk was exaggerated. This is something that social scientists have called the 'social amplification of risk' in the context of new events that are potentially dangerous, but that nonetheless carry with them a low risk. Amplification takes place as a result of media coverage, and as a result of intrapsychic processes that tend to amplify the threat of novel threats when the locus of control over the event is external to the individual. During the outbreak of toxic shock syndrome, newspapers were full of stories about TSS and the sometimes deadly consequences of developing the syndrome. These were frequently on 'page 1 above the fold' and necessarily caught the attention of the public. The same was true of television news.

Once this outbreak of TSS appeared to be concentrated in one single group – menstruating women using superabsorbent tampons – the general public's fear of TSS began to diminish, and the federal government mandated the withdrawal of those tampons from the market. The number of incident cases began a rapid decline, and was back to baseline of about 100 cases per year by 1985. Some reports demonstrated that there was a decrease in the use of all tampons – not just superabsorbent tampons.

It was already known in 1980 that toxic shock syndrome was caused by staphylococci (specifically, *S. aureus*). In these cases, treatment is threefold: removal of the tampon, indwelling tampon, or other hypothesized environmental cause; aggressive fluid resuscitation; and rapid use of antistaphylococcal antibiotics.

Other bacterial species can cause toxic shock syndrome. In rare cases, other *Staphylococcus* species have been associated with toxic shock syndrome, and because they are coagulase-negative, they are difficult to treat. At this time, coagulase-negative staphylococci constitute the most common cause of hospital-acquired bacteremia. This sometimes results in endocarditis, and usually the only effective treatment is surgical valve replacement, particularly in the

case of those who have had earlier valve replacement. Aggressive antibiotic therapy is occasionally effective.

Should toxic shock syndrome be considered to be an emerging disease? It certainly was in 1980, when the public was so concerned with its appearance. Now, in 2007, 29 years after it was first described, this label is more questionable. What was most significant about toxic shock syndrome, however, was its historical significance. It followed the outbreak of legionnaires disease so closely that it turned the public's attention, once again, to infectious diseases, and to infectious diseases that had been unknown. It also reminded the biomedical community that infectious diseases had not been conquered. The issue at the time was whether legionnaires disease and toxic shock syndrome were anomalies, whether the assumption of the conquest of infectious diseases had clearly been erroneous, or whether these two outbreaks were harbingers of a new stage in 'epidemiologic history' – a historical period during which emerging infections would become common and would catch the attention of the public, the public health community, the medical community, and government agencies. The public health and medical communities were divided on this. It would soon become clear, however, that the latter would hold true – that emerging infectious diseases would come to the forefront of public health, epidemiology, and the medical community. In the cases of legionnaires disease and TSS, the social amplification of risk exaggerated perceived threats. Nonetheless, the public became more attentive to infection. Two other phenomena would solidify this attention. One was the appearance of HIV/AIDS in the United States, and the other was public attention that was drawn to hemorrhagic fevers, mostly in Africa.

HIV/AIDS

The details of HIV/AIDS are covered elsewhere in this encyclopedia, and there will be no attempt here to duplicate this material. Rather, this discussion concentrates on the significance of HIV/AIDS.

When HIV/AIDS first appeared in several urban areas in the United States in 1981, it appeared to be an anomalous syndrome. It was not called 'AIDS' until 1982, when the Centers for Disease Control (CDC) gave the syndrome that label. In the same year, researchers at CDC also linked one of the pathways of transmission to blood and blood products, causing a great deal of public concern – if it was possible to contract AIDS through a frequently used medical practice, it had the potential of affecting millions of people. Until then, AIDS was thought to be restricted to the gay community. In 1983, blood banks were warned by the CDC that blood and blood products could definitely transmit AIDS, and surgeons and other medical personnel began rethinking the criteria necessary for transfusion. By 1983, it was clear that the exponential increase in the number of incident cases was a definite trend. In 1983 and 1984, two teams discovered that the pathogen causing AIDS was viral, and although it had a different nomenclature at first, there was a great deal of relief that the causal agent had been discovered. It is an interesting study in the sociology of science to analyze the competing claims by Luc Montagnier at the Institut Pasteur and Robert Gallo in the United States concerning their respective claims that they discovered HIV. It is now clear that Montagnier discovered the virus.

Shortly after the virus was discovered and characterized, an antibody test was developed to detect HIV *in vivo*. This was quickly used to screen blood products as well as to detect HIV in individuals. Whereas some people decried the slowness of the U.S. government's response to HIV, the time from the first presentation of a group of males with Kaposi's sarcoma or oral thrush until the antibody test for a recently identified virus was only 3 years. Granted, the president of the United States, Ronald Reagan, had not even mentioned AIDS, and funding was less impressive than it could have been, but the time was quite short. The real challenge with HIV has been to find an effective vaccine, or to find a 'cure,' although antivirals have been effective in suppressing viral load in the majority of cases since 1995–96.

The prevalence and mortality data are well-known. The best estimates are that globally, over 40 million people are living with HIV/AIDS, and approximately 22 million have died of HIV/AIDS. Currently, about 19–20 million of those living with HIV/AIDS are women, and in developing countries, particularly in sub-Saharan Africa, HIV/AIDS is becoming, increasingly, a disease of women. Currently, approximately two-thirds of those living with HIV/AIDS are in sub-Saharan Africa, but the increasing prevalence and incidence of HIV/AIDS in Asia – and particularly, in India and China – are making East Asia and South Asia regions of tremendous concern. This is because each country has over 1 billion people, and the prevalence rates do not have to be high to result in large numbers of infected people.

The global significance of HIV/AIDS is that it, by itself, has altered demographic trends, and the political economy of nations and regions, not to mention the human suffering that this disease has exacted. In Botswana and Swaziland, for example, the gains in life expectancy during the 20th century have not only been completely reversed, but the life expectancy at birth is lower now than it was at the beginning of the 20th century. In the context of this article, HIV/AIDS is an emerging infectious disease *par excellence*. A generation ago, it was literally unheard of. Now in all developed countries and in many developing countries, HIV/AIDS shapes many behaviors, is responsible for significant stigma, is feared, and causes a significant percentage of deaths. Globally, HIV/AIDS is

the fourth leading cause of death, although in many parts of Africa, it is the leading cause of death.

HIV/AIDS is an emerging infectious disease because of the historical rapidity with which it moved from an unknown localized zoonotic complex in West and Central Africa to the most prevalent infectious disease in the world. While the scientific evidence suggests that there were a number of species jumps of both HIV-1 and HIV-2 that occurred in Africa, these were so localized and the societies isolated enough from the rest of the world that HIV went unnoticed. Thus, it appeared as though the disease went from nonexistence to a major pandemic in a matter of a few years. And there is another major significant dimension. Since HIV/AIDS appears to have originated in Africa – 'out there,' away from Northern Europe and North America – some have argued that HIV/AIDS acquired a certain nefariousness – a disease emerging from the dark, foreign, isolated jungle – the stereotypical cauldron of new diseases.

Hemorrhagic Fevers

Viral hemorrhagic fevers have been in the public eye since 1969, when there was a major outbreak of a hemorrhagic fever in the Jos Plain of Nigeria. The disease came to be called Lassa fever, caused by an arenavirus (Lassa) that seemed particularly undesirable to the public. The virus is named after the town in which this outbreak occurred. Like all hemorrhagic fevers, including dengue in some cases, one of the characteristics of Lassa fever is that it can disturb the clotting/coagulation mechanism, resulting in disseminated intravascular coagulation (DIC) and diffuse hemorrhage. The 1969 outbreak was publicized in the United States through the news media, perhaps because it was an 'exotic' or newsworthy event, and once again, the social amplification of risk was responsible for exaggerated fears of 'what if it spreads here?' That this outbreak occurred in sub-Saharan Africa, which, in the eyes of the North American public, may have been thought to be all 'jungle' (the Jos Plain is not rain forest) probably also contributed to the amplification of risk.

Serologic tests demonstrate that exposure to Lassa virus is common in West Africa. For example, in parts of Nigeria, seroprevalence is positive in 21% of those tested; in Sierra Leone, the figure varies from 8–52% depending on the region (Richmond and Baglole, 2003). It is now known that humans are dead-end hosts, and that the rat species *Mastomys natalensi* is the natural host. These rats are extremely common throughout sub-Saharan Africa. People become infected by inhaling aerosols from rat excreta, and risk is increased by eating them, which is a very common practice in West Africa.

Modern modes of travel have allowed infected individuals who are either symptomatic or asymptomatic at time of entry to travel to other continents, where they require treatment for Lassa fever. These cases have not been numerous, but cases have appeared in the United States and Japan, as well as in several European countries. This has caught some clinicians unprepared, since they were not trained in tropical medicine and were unaware of how to diagnose or manage a viral hemorrhagic fever.

The prevalence rate of Lassa fever is much higher than was initially thought. In one series, Lassa fever accounted for 30% of adult deaths in Sierra Leone, and as many as 16% of hospital admissions (Richmond and Baglole, 2003). Following the outbreak in 1969, it took some time to investigate adequate treatment protocols, but now, aggressive fluid replacement and the use of antivirals – particularly ribavarin – are the treatments of choice.

Ebola hemorrhagic fever and closely related Marburg virus are both single-stranded RNA viruses, as are other viruses that cause hemorrhagic fevers. Ebola and Marburg are Filoviruses; Ebola virus is actually a genus and there are four species. It was first described in the Sudan in 1976, and estimates are that mortality from this virus has now exceeded 1000 people. The case fatality ratio exceeds 50%, and may be as high as 90% in some cases. Transmission is different than Lassa fever. It is usually through direct contact with blood and bodily secretions from individuals who are ill with Ebola fever, or from nonhuman primates who are also infected. Evidence points to bats as the natural reservoir of Ebola virus, but this is not certain. In several studies, however, bats have been shown to be infected by the virus (Leroy *et al.*, 2005). This is highly suggestive, but it is not conclusive proof.

Like so many other viral hemorrhagic fevers, the symptomatology of Ebola is very nonspecific and typical of viral syndromes in general. The clinician needs to have a high index of suspicion. At this point, the only certain treatment is supportive, and from a public health point of view, quarantine is of the utmost importance, since Ebola fever is so contagious. This was well-documented by the news media in the outbreak in Kikwit, Democratic Republic of the Congo (DRC, then Zaire) in 1995. This was so well-documented that once again it led to exaggerated perceptions of risk, with overtones of the 'exotic disease' from sub-Saharan Africa and its possible spread to the United States.

Recent advances in understanding the pathogenesis of Ebola and the role of proinflammatory cytokines has led to the use of some recombinant products that block the progression of the inflammatory cascade to DIC in some animal models. Nonetheless, this approach has not been used in humans as of 2007.

There are three notable points that need to be mentioned concerning Ebola. First is that it appears to be increasing in prevalence in Africa. This may be because detection is better and the disease has been better described, both epidemiologically and pathophysiologically. Second is that there is significant concern that

Ebola virus could be used as a biological weapon. It has thus been placed on the highest level (Category A) of potential biological weapons by the CDC. Finally, Ebola, more than any other emerging infectious disease, typifies in the mind of the public the sort of dangerous, threatening disease risk that is associated with tropical areas, the 'jungle,' and the threats that are associated with a more interconnected world.

Bovine Spongiform Encephalopathy

Bovine spongiform encephalopathy (BSE), or 'mad cow disease' in nontechnical terms, is another infectious disease that focused public awareness on emerging infections. The pathogen in this case was unusual not only in the sense that it had not been described elsewhere, but also because the whole class of pathogens – prions – have been very rare. Like another neurologic disease, kuru, BSE turned out to be due to a prion. Essentially, prions are very simple since they are just unusually folded and self-replicating proteins. They cannot even be described as organisms. The source of the prion is not known, although many speculate that it is somehow derived from sheep infected with scrapie.

In 1986, an unusual disease seemed to be affecting cattle in the United Kingdom, and by the end of the year, over 175 000 cattle had died because of spongiform encephalopathy. Since it was apparent that the disease was contagious, over 4 million cattle were intentionally slaughtered to limit contagion and ensuing effects on the cattle industry.

By the mid-1990s, there was a clear epidemiologic association between BSE and a variant of a neurodegenerative disease in humans that had been described in the middle of the 20th century: Creutzfeldt-Jakob disease (CJD). However, there were some notable differences between CJD and the disease that was affecting humans in the 1990s. The median age of this new syndrome was much younger than in classical CJD; the median duration of survival from onset of symptoms was longer than in classical CJD; and pathological differences and differences on MRI were apparent with this new variant. Accordingly, the CJD associated with BSE first was named 'new variant Creutzfeldt-Jakob disease' or 'nvCJD;' as time progressed, nvCJD was renamed 'variant CJD' or 'vCJD.'

Although there were very few cases of vCJD in the UK human population, the threat of this disease was great according to public perception. According to the World Health Organization (WHO), as of November 2002, there had been 129 cases of vCJD in the United Kingdom, six in France, and one each in several other countries (WHO, 2002). Nearly all of those with vCJD died or would die within 3 years.

Because of the realistic fear of contagion, several steps have been taken to limit the spread of vCJD. Feeding practices for cattle have changed so that it is no longer legal to feed animal protein that might contain any tissues proximal to the central nervous system to other cattle. In the United Kingdom, there was a ban on cattle over 30 months old from entering the commercial food supply. In the United States, individuals who have lived in the United Kingdom or who have spent more than 6 months in the United Kingdom are banned from being blood donors on the assumption that they might have consumed infected beef during their stay(s) in the United Kingdom. A ban was instituted on importing cattle and cattle feed from the United Kingdom, and, occasionally, from Canada, in an attempt to prevent BSE from spreading to the United States (Kuzma and Ahl, 2006). While the number of incident cases of vCJD and BSE have decreased in a typical epidemic curve pattern, the effects of the BSE 'scare' have been tremendous. The very credibility of the UK government was threatened. The whole cattle and meat industries were severely hurt. On the other hand, surveillance techniques and understanding of cattle food chains were vastly improved.

SARS

Severe acute respiratory syndrome (SARS) proved to be of great import in both the public awareness of emerging infectious diseases and in the testing and real-time construction of both domestic and international systems of public health surveillance and response. It was particularly important in terms of public awareness because it spread very rapidly on the international and intercontinental scales.

SARS apparently began as a few cases of a viral pneumonia in Guangdong province in southeastern China in late 1992. However, this was not immediately apparent to the global public health communities because it was not publicized by the Chinese government. What catapulted SARS to international attention in the media and in the public health community was the appearance and rapid increase of incident cases in Guangdong in February 2003 (Zhao, 2007).

SARS spread rapidly to Hong Kong, where contact tracing eventually identified one night in a specific hotel where the index case stayed as being the epidemic focus. The index case infected at least 16 others who were in the hotel at one time or another during that night.

SARS spread from Hong Kong to other areas of Hong Kong and to Singapore, Vietnam, and Canada (Toronto, Ontario). The spread of all these cases has been traced to airplane travel, followed by localized spread by an index case.

A case definition was developed based upon clinical presentation, which typically consisted of fever, initially, followed by lower respiratory signs and symptoms, sometimes resulting in acute respiratory distress syndrome

and respiratory distress typical of acute lung injury as a response to the inflammatory cascade.

Just over 8000 cases were identified worldwide, and 774 died, for a case fatality ratio just <10%. A disproportionate degree of contagion occurred in intensive care units and areas of hospitals in which hospital personnel were exposed to respiratory excretions; close proximity – within 1 m – to an infected patient who was undergoing endotracheal intubation was the single greatest risk factor for contracting SARS.

Local measures to control the spread of SARS consisted largely of quarantine and containment. In China, for example, separate quarters for SARS patients were constructed very rapidly. In Singapore, arriving and departing passengers were required to pass through automated temperature detectors, and anybody with a fever was required to undergo further medical evaluation. The same was true at most points of entry in most developed countries. Since most cases were contracted in hospitals and health facilities, rigorous contact control procedures were instituted, and in some cases, hospitals were closed to visitors and new admissions.

The identification of the pathogen causing SARS constitutes a textbook example of how international cooperation in science and public health may occur when the willpower is there and the scientific capability exists. By mid-March 2003, many leading laboratories with advanced virologic capabilities had agreed to cooperate in a network that was coordinated by the World Health Organization. Within 2 weeks, a pathogen was identified as a novel coronavirus, using a combination of methods: molecular polymerase chain reaction, culture, and electron microscopy, and shortly thereafter, the criteria of Koch's postulates were met. Thus, the evidence was quite clear that the new coronavirus was the pathogen. The virus was named the SARS coronavirus, or, almost always, SARS coV.

The ecology of SARS was not understood as quickly as the pathogen was identified. Some features were identified within a number of months. First was the phenomenon of superspreaders, which is a concept that previously had received scant attention. In this case, it became apparent that a small number of individuals spread SARS to a disproportionately large number of people. It is not clear whether this is because of behavioral factors, host–pathogen interaction, or environmental factors. What is fairly clear is that were it not for superspreaders, the epidemic would not have affected nearly as many people as it did. This is because the R_0, or number of people who one individual could infect, was inflated by superspreaders. Thus there was a domino effect of contagion.

In 2007, bats were identified as the reservoir of SARS coV. There had previously been some speculation about bats being the reservoir, but there was no solid evidence, and the reservoir had been a mystery. Some had suggested that proximity of people to avian species could possibly be a factor in the pathogenesis of SARS, because of the importance of this process in avian influenza. However, this turned out not to be the case with SARS.

SARS is a prototype of an emerging infectious disease (Berger *et al.*, 2004). There is no evidence that SARS coV existed in the human population prior to the outbreak of late 2002–03. The specific syndrome surprised the public health and medical communities, yet its general features did not, and the emergence of new diseases had been a familiar concept since the U.S. Institute of Medicine report of 2002. At the same time, the rapidity of the appearance of SARS and its very rapid spread at every scale fueled public apprehension, and even hysteria in some cases.

Avian Influenza

Evidence exists that history has been punctuated by relatively regular influenza epidemics and pandemics. The rapidity of epidemic spread, leading to pandemics, is largely determined by the velocity of the prevailing transportation modes. Severe epidemics and pandemics are caused by genetic shift, whereby the viral genome expressing surface antigens (hemagglutinin and neuraminidase) undergoes relatively major change. Relatively minor epidemics occur because of genetic shift, in which the surface antigens undergo minimal yet detectable changes in their configuration. Following genetic shift, people have minimal immunity to the virus, and are susceptible.

In one sense, each year influenza constitutes an emerging infection, because the precise genome of the influenza viruses and the surface antigens undergo change. Similarly, whenever a pandemic occurs, influenza represents a more significant emerging infection. On the other hand, influenza represents a disease entity that is not new to the population. Thus, it is a matter of semantics whether to consider influenza to be an emerging infection.

Avian influenza may constitute the next serious pandemic threat. It has been known for decades that genetic reassortment occurs in southeastern China because of the proximity of humans, avian species, and swine. An unusual number of influenza epidemics appear to arise there. However, the concern over avian influenza arises from a slightly different situation.

It has been known for some time that no less than 24 influenza subtypes – different configurations of surface antigens – can infect aquatic bird species. It has been well-established that several of these subtypes can infect humans, although recent experience suggests that all subtypes that circulate in avian species may have the potential to infect humans. This is one of the reasons that has given rise to concern over the possibility of an avian influenza pandemic. This theoretical concern moved

closer to reality in Hong Kong in 1997, when one influenza strain (H5N1) was transmitted directly from poultry to humans. This took place in 'wet markets' – markets in which live poultry are densely packed, and where people co-mingle with their intended purchases. The transmission in 1997 appears to have been limited: Only 18 cases were confirmed. However, the case fatality ratio was high. Six of the 18 people died.

Transmission also occurred with another strain – H9N1 – in 1999, and in 2001 and 2002 there was widespread transmission and mortality among chickens in Hong Kong. Because of a concern over possible transmission to humans, and because of the devastating economic potential in the poultry industry, containment of this epidemic in poultry was partly obtained by the slaughter of millions of chickens and other poultry.

Avian influenza viruses have shown some propensity, since 1997, for transmission to humans. So far, human cases of influenza that have been identified as avian strains have been limited to approximately 200, and these have all been in Asia. Human-to-human transmission has been implicated in only a few cases. If this is the case, what is the concern over avian influenza?

Because of the tendency for influenza viruses to mutate, many virologists and epidemiologists predict that there is a high likelihood that a mutation could occur that would facilitate human-to-human transmission of H5N1 and other avian subtypes that have been transmitted to humans. If this occurs, then there is little doubt that this strain would spread rapidly among the human population, and would spread locally, nationally, and between continents in a manner similar to SARS. Other epidemiologists and virologists are more circumspect in their predictions, and argue that the probability of a mutation that would increase the propensity of avian influenza to spread from human to human is unknown. A minority of authorities argue that the probability is low. Thus, in assessing the overall threat of avian influenza, the crucial question is whether the virus will spread readily from human to human. At this point (mid-2007), it is unknown whether this will occur. However, it is prudent public health policy to bolster surveillance systems, and governments are stockpiling neuraminidase inhibitors, which are medications that can moderate the course of influenza if taken early in the course of clinical disease, or sometimes prevent the onset of symptoms if taken prophylactically. Similarly, there has been great emphasis on vaccine development and stockpiling.

Attempts to Understand Emerging Infections

In response to growing public concern over emerging infectious diseases, both domestically and internationally, as well as to both interest and concern in the medical and public health communities, a major conference on emerging viruses was held at Rockefeller University in 1989. The conference was cosponsored by several government agencies. The conference participants reached many conclusions, but two of them were that emerging infections had become a major focus for scientific research and that emerging infectious diseases had become and would remain a major public health challenge for the United States. Accordingly, the Institute of Medicine of the National Research Council of the United States took a proactive role and sought funding for a major study of emerging infections. The study was funded by a number of government units, and in early 1991, a high-powered committee met in Washington for the first time to:

> identify significant emergent infectious diseases, determine what might be done to deal with them, and recommend how similar future threats might be confronted to lessen their impact on public health. (Institute of Medicine, 1992: vi)

The committee issued a report in 1992 that quickly became a standard scientific and policy reference on emerging infectious disease. *Emerging Infections: Microbial Threats to Health* was the first major comprehensive discussion of how emerging infections arise, and how they might be addressed by the public health community. The committee also identified the six 'factors' or causes of emergence.

Briefly, the factors that this committee identified were the following: human demographics and behavior; technology and industry; economic development and land use; international travel and commerce; microbial adaptation and change; and the breakdown of public health measures. It is notable that five of these six factors are social factors that are consequences of changes in society. Even microbial adaptation and change, such as the development of antimicrobial resistance as a response to selective pressure, has a large behavioral dimension. This is partly a response to a technical innovation – the development of antimicrobials – and partly a response to a behavior – the prescribing of those antimicrobials. Of course, one dimension of this factor is the nonselective and improper prescribing of antimicrobials. This has several dimensions: The prescription of antibiotics when none are needed, the prescription of broad-spectrum antibiotics when narrow-spectrum antibiotics are sufficient, the free availability of antibiotics in many developing countries on the street and in pharmacies where no prescription is needed, and the free use of late-generation antibiotics in the food industry to promote the growth of cattle, chickens, and other animals intended for human consumption. So, in fact, all of the six factors of emergence are social and behavioral in nature.

Social Causes of Emerging Infectious Diseases

It is ironic that despite the fact that both Institute of Medicine reports concluded that the major causes of emergence have been social, there have been very few social analyses of emerging infections. For example, *Emerging Infectious Diseases*, a new journal founded in 1995 in response to the growing importance of emerging infections, has an explicit aim of including a social understanding of emerging infections in its contents, yet there have been very few articles written by social scientists in this journal, and very few articles with any social content have been published. The main point is that the overwhelming understanding of emerging infections has been 'biomedical.' This is not a criticism of either the journal or of any field in public health or medicine. In large part, this is the result of the sociology of knowledge and science. For whatever reason, few social scientists have become involved in research on emerging infections, whereas the same cannot be said about chronic diseases.

Some researchers have asked the question of why emerging infectious diseases are emerging now and in the societies where they are emerging, and have sought a more contextual understanding of emerging infections. David Bradley asks a very penetrating question:

> [A]ttaching a microbiological label to an outbreak. . .does not answer either the micro-scale questions such as "why is there an outbreak here, now, of this size, affecting these people?" nor does it answer the macro-questions such as "why are there more (or fewer) outbreaks this decade than last?" Nor does it answer the question "what drives the overall worldwide trends in such problems?" (Bradley, 1998: 1)

For example, a number of individuals have argued that emerging infections may represent another stage in the epidemiologic transition.

Our understanding of emerging infections has not been totally devoid of social analysis. Inequality and poverty have become a major focus for the social analysis of health and disease. The argument is that through a complicated series of pathways that are yet to be fully understood, both poverty and inequality result in poor health status. This has not been applied extensively to emerging infectious diseases, although Paul Farmer's (1999) insightful work has been applied to emerging infections. In his critical analysis of emerging infection, Farmer asks, "Emerging for whom?" In other words, the diseases that Westerners might label as emerging may have been present or endemic in poorer societies for a long time:

> If certain populations have long been afflicted by these disorders, why are the diseases considered "new" or "emerging"? Is it simply because they have come to afflict more visible – read more "valuable" persons? This would seem to be an obvious question from the perspective of the Haitian or African poor. (Farmer, 1999: 39)

In other words, Farmer argues, the concept of emerging infectious diseases is one of epistemology – the theory of knowledge. How do emerging diseases come to be categorized as 'emerging'? By implication, many of these diseases have been present in poorer societies for a long time.

The evidence affirms this. HIV was probably present in small foci in Central Africa for decades to centuries; Ebola was similarly endemic in West Africa for an unknown period, as was Lassa fever. What is novel about the past few decades is greater interconnection between places, allowing diseases, and news of diseases, to spread; better methods of detection; and changing settlement geographies that have brought people into different forms of contact with animal reservoirs. The root cause of the infectious disease emergence is human action, both intentional and unintentional. Most of this action is the result of cumulative individual acts on a mass scale. For example, the mass urbanization of society in poorer countries is the sum of millions of individuals who move from rural to urban areas. This is largely the result of the perceived economic opportunities in urban areas, and the 'push' factor of lack of opportunity in rural areas. Yet, taken together, millions of individual moves result in urbanization, and this urbanization facilitates the spread of diseases by the respiratory route, the fecal–oral route, and many other modes of transmission.

Policy in IOM Report

The Institute of Medicine Committee also developed a set of policy recommendations. These concentrated in two areas: the need for vastly increased resources for interdisciplinary training in infectious diseases because of the depleted workforce resources in this area; and the need to develop new surveillance and public health response systems, since the committee had determined that emerging infections did, indeed, constitute a major public health threat to the United States.

This report was issued with a great deal of publicity. The U.S. public's attention was already focused on emerging infectious diseases as a result of legionnaires disease, viral hemorrhagic fevers, and toxic shock syndrome. Now there was a major quasi-governmental report by a group of the nation's leading scientists who issued the sobering conclusion that:

> even with unlimited funds, no guarantee can be offered that an emerging microbe will not spread disease and cause devastation. (Institute of Medicine, 1992: 169)

Predictions Realized

Part of the Institute's report identified specific microbes and diseases that could possibly threaten public health in the future. Three of these were *E. coli* 0157:H7, cryptosporidiosis, and hantavirus. The report was prescient, because within a few years there were serious outbreaks of all of these. In 1993, which was the year after the IOM report was issued, there was a major outbreak of cryptosporidiosis on the south side of Milwaukee, Wisconsin. It caused diarrhea, ranging from mild to severe, in over 400 000 people. *Cryptosporidium parvum* is a protozoan parasite; evidence in animal models is that ingestion of even one oocyst can result in severe gastrointestinal symptoms. In humans, as few as 12 oocysts can produce these effects (King and Monis, 2007). It is impervious to usual methods of water treatment, and only recently has an effective medication become available. The Milwaukee outbreak was probably due to groundwater absorption of cattle feces, subsequent runoff due to both heavy rains and snow melting, transport of the oocysts to river tributaries, and movement of the oocysts into Lake Michigan, which serves as the water supply for the south side of Milwaukee. The filtration plant for that water was ineffective in eliminating the oocysts. Many of these events are putative, but together they constitute a logical chain. Meanwhile, research is still proceeding on the ecology of cryptosporidiosis. Understanding is progressing, but it is still incomplete.

E. coli 0157:H7 was also mentioned in the IOM report as being an emerging disease. In January 1993, the Washington State Department of Health ascertained that an outbreak of 0157:H7 was occurring in the state, and this outbreak was associated with having eaten at Jack in the Box fast-food restaurants. Subsequently, it became apparent that the epidemic was not limited to Washington, but also included Idaho and Nevada.

The epidemiologic investigation of this outbreak was intricate, and implicated a chain of events. First, because meat inspection in the United States was inadequate, one theory is that *E. coli* 0157:H7 from the bowels of cattle had gotten into meat that was sent to market when cattle were slaughtered, and the bowel was probably nicked or severed. Another is that under stress, cattle defecate over one another, and fecal matter from one cow can contaminate the hides of other cattle. Second, when this meat was ground into hamburger, it increased the surface area of the meat by several orders of magnitude, thereby allowing the pathogen a great deal of exposure. Third, once this hamburger meat was shipped to Jack in the Box restaurants, it appears that hamburgers were being systematically undercooked, below industry standards. This allowed the *E. coli* to survive and enter the hosts' systems. The consequences of such infection can be severe, and were in 1993, with those who were symptomatic frequently suffering from bloody diarrhea, fever, cramps, and, in the worst case, hemolytic uremic syndrome. The pathogenesis of this disease was only partially understood in 1993, but understanding is more complete in 2007.

The third disease that was mentioned in the IOM report that occurred shortly after its publication was hantavirus. In May 1993, in the Four Corners area of Arizona, New Mexico, California, and Utah, several males who were otherwise in good health developed a sudden serious respiratory disease that was thought to be a rapidly progressing acute respiratory distress syndrome, since this was the immediate cause of death. However, it was noted that these cases had formed a cluster, and investigators tried to find some sort of common source to explain a possible environmental exposure to explain this serious and sometimes fatal syndrome. Though hantavirus had never been described in the United States, serologic tests in patients showed a surprising seropositivity to hantavirus. It was apparent that this was the pathogen that had caused the dozen deaths associated with the outbreak. The chain of events that led up to the outbreak is now fairly clear. Winter 1993 was unusually warm in the Four Corners area as a result of El Nino, and the spring was also unusually rainy. These two conditions led to the rapid and plentiful growth of pinon trees, which provided food for a number of rodents. There is consensus that the deer mouse (*Peromyscus maniculatus*) population increased by an order of magnitude. Testing demonstrated that about 30% of the mice that were trapped after this epidemic were infected with hantavirus, and studies demonstrate that households from which infected individuals came were far more likely to have heavy rodent infestations than were households of controls. More rigorous studies eventually showed that transmission occurred from rats to humans, and that many of the cases, in this instance, were associated with crawling under houses and other places in which rodent exposure was likely to occur.

Emerging Infections Reconsidered: Second IOM Report

By 2000, many of the predictions of the first Institute of Medicine report (1992) had been realized, and understanding of emerging infectious diseases had improved. There was greater focus on globalization as a process of disease spread, and the attacks on the World Trade Center and Pentagon on September 11, 2001 focused attention on terrorism. A new Institute of Medicine committee was formed to consider the nature of microbial threats and emerging diseases, and the report of this committee was issued in 2003 (Institute of Medicine, 2003). This report represented a rethinking of the factors of emergence, and presented a more nuanced understanding of the causes of

emerging diseases, most of which were still social at one level or another. Bioterrorism ('intent to harm') was specifically mentioned as a factor of emergence, as was lack of political will. Policy recommendations for surveillance, response, and training were more detailed than in the 1992 report, and there was a more urgent tone to the need to respond to emerging threats.

In this report, the emphasis on biological and social interaction was strong:

> Genetic and biological factors allow microbes to adapt and change, and can make humans more or less susceptible to infections. Changes in the physical environment can impact on the ecology of vectors and animal reservoirs, the transmissibility of microbes, and the activities of humans that expose them to certain threats. Human behavior, both individual and collective, is perhaps the most complex factor in the emergence of disease. Emergence is especially complicated by social, political, and economic factors. . .which ensure that infectious diseases will continue to plague us. (Institute of Medicine, 2003: 2)

Antimicrobial Resistance

Increasing resistance to antibacterials, antivirals, and other antimicrobials is frequently grouped under the heading of 'emerging infections.' Resistance is certainly a constantly growing and very major public health problem, but this is of importance to emerging infections only in the sense that diseases that were once highly treatable with first- and second-generation antimicrobials are no longer treatable by them. The selective pressures exerted by antimicrobials have made numerous pathogens resistant to even the newest antimicrobials due to mechanisms that are now understood. For example, many respiratory pathogens are no longer treatable by β-lactam antibiotics since their β-lactam rings are cleaved by β-lactamases. There are fluoroquinolone-resistant strains of *Neisseria gonorrhoeae*, resistant strains of *Staphylococcus aureus*, and so on.

The problem is most severe in hospitals, where severe infections once responsive to vancomycin are now resistant to this glycopeptide. Several new antimicrobials have been developed, in part to address vancomycin resistance, but resistance to these medications developed within a few years of their introduction.

Thus, antimicrobial resistance is both a community problem and a hospital problem. There is great concern over multiple drug-resistant tuberculosis, which is defined as tuberculosis that is resistant to two first-line medications, and extensively resistant tuberculosis, which has a more complex definition specifying several medications. There is not space in this article to explore antimicrobial resistance in greater depth.

Summary

The relationship between people and pathogens has been an integral part of history, and will continue to be. The progress in the diagnosis, detection, and clinical management of infectious diseases has been substantial. Indeed, Fauci (2001) has gone so far as to argue that:

> The successful diagnosis, prevention, and treatment of a wide array of infectious diseases has altered the very fabric of society, providing important social, economic, and political benefits.

Nonetheless, infectious diseases, aggregated together, constitute the second leading cause of death worldwide, and in many regions, they account for the dominant cause. Moreover, emerging diseases will continue to emerge, because of constantly changing social and demographic conditions, as well as selective pressures. The prototypical emerging infectious disease, HIV/AIDS, has an uncertain future in the long run. Perhaps a vaccine will be developed that will be inexpensive, and perhaps distribution systems will be developed that will transport the vaccine to points of demand. Perhaps antiretrovirals will become extremely inexpensive, and perhaps the failure rate for antimicrobials of 30% will be overcome. However, it is unlikely under present conditions that all of these improvements will occur. Thus, the future of HIV/AIDS is more sobering.

The same is true of antimicrobial resistance. In an age of optimism when antimicrobials were developed and used successfully – perhaps the first 30 years of antimicrobial use – concern over resistance was minimal. However, the fact that organisms adapt to changing environmental conditions and threats is something that has not been realized only recently. The inevitability of adaptation is undeniable, and the only way to meet the challenges of resistance is through a combination of appropriate antimicrobial use (including the use of narrow-spectrum antibiotics as soon as possible in the clinical course of an individual) and the development of new antimicrobials, as well as new understanding in the physiology and genetics of microorganisms, which might lead to the development of new technologies in addressing the pathogenic basis of disease.

See also: AIDS, Epidemiology and Surveillance; Antimicrobial Resistance; Severe Acute Respiratory Syndrome (SARS); Transmissible Spongiform Encephalopathies; Tuberculosis: Overview; West Nile Disease.

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http://www.who.int – World Health Organization.

Endocrine Diseases: Overview

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Glossary

Acromegaly A condition produced by overproduction of growth hormone, leading to excessive growth of the hands, feet, and jaw in postpubertal individuals and giantism in prepubertal children.

Adrenal glands Two endocrine organs situated above the kidneys that make a series of hormones: cortisol (stress hormone), aldosterone (salt-retaining hormone), and catecholamines (stress hormones).

Autoimmunity A situation in which part of the body, often an endocrine organ, is recognized as 'foreign,' triggering an immune response that tends to lead to destruction of the endocrine gland.

Cushing syndrome Excessive production of cortisol with loss of the normal circadian variation leading to weight gain, hypertension, and type 2 diabetes mellitus.

G protein Proteins within the cell that transfer the hormone message from the receptor to specific parts of the cell.

Graves disease A combination of thyroid overactivity due to an autoimmune disorder and eye problems.

Hypothalamus Part of the brain containing control centers for appetite, thirst, and pituitary hormone secretion.

Pituitary Major regulator of hormone production. Secretion of hormones regulated by the hypothalamus.