EMERGING INFECTIOUS DISEASES

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“Microbes and vectors swim in the evolutionary stream and they swim faster than we do. Bacteria reproduce every 30 minutes. For them, a millennium is compressed into a fortnight; they are fleet afoot, and the pace of our research must keep up with them, or they overtake us. Microbes were here on earth 2 billion years before humans arrived, learning every trick for survival, and it is likely that they will be here 2 billion years after we depart.” (Krause, 1998)

The 20th century witnessed both the recognition of many new infectious diseases and agents and a host of new vaccines and anti-microbial agents. By the late 1960s, the Surgeon General of the United States and one of the leading infectious disease researchers in the U.S. (who would prefer not to be identified) both declared infectious diseases conquered!

Then came HIV/AIDS, reminding us that infectious diseases would be a constant threat as new agents emerged and old agents mutated to become resistant to the cures and treatments we had developed.

TYPES OF EMERGING DISEASES

Emerging diseases can be divided into four major groups. Newly emerging diseases not previously known (e.g., hantavirus, Ebola virus, and human immunodeficiency virus/acquired immune deficiency disease (HIV/AIDS); re-emerging diseases (e.g., tuberculosis and malaria); new manifestations of known disease agents (e.g., genital, respiratory, and cardiac manifestations of chlamydiae); and introduction of known agents to new territories (e.g., the rapid spread of West Nile virus in the United States in the last decade of the 20th century).

Another strategy for classifying emerging diseases was proposed in the U.S. Institute of Medicine report on Emerging Infections (National Academic Press, Washington, D.C., 1992). This classification grouped emergent diseases by the most likely cause of their emergence or re-emergence. These are: 1) changes in human demographics and behavior (human immunodeficiency virus/acquired immunodeficiency syndrome [HIV/AIDS], dengue virus); 2) technical and industrial advances (vulnerable populations and nosocomial infections, food processing and Salmonella agoni); 3) economic development and changes in land use (reforestation and lyme disease); 4) international travel and commerce (sudden acute respiratory syndrome [SARS]); 5) microbial adaptation and change (influenza, drug-resistant organisms); and 6) breakdown of public health measures (resurgence of V. cholerae in the Americas in the early 1990s.)
CAUSES OF EMERGING DISEASES

The reasons for the emergence of new agents and resurgence of known agents are complex, and involve the many changes occurring as society modernizes and becomes more affluent. These changes are discussed below, using a modified classification strategy of that proposed by the Institute of Medicine. There is, however, considerable overlap between the two classification schemes. Examples are provided for each factor.

Changes in Human Behavior: Although people have engaged in multiple sexual partners for centuries, there were dramatic changes in sexual behaviors in the 20th century. Whereas having multiple sexual partners was socially unacceptable in the early 20th century and only covertly practiced, having multiple sexual partners had not only become acceptable by the latter half of the 20th century, but became the norm in many societies. As cures for the known sexually transmitted diseases (STDs) became available, the constraints against multiple partners were reduced. Getting an STD became a treatable inconvenience, not a life-compromising event. Multiple partners became the rule in some subpopulations, such as men-who-have-sex-with-men (MSM). An MSM going to a bathhouse could engage in oral and anal sexual intercourse with as many as 10-20 partners in a single evening. Among heterosexuals, the barrier of unwanted pregnancy was reduced by effective contraceptive methods. In many societies, recreational drug use became common. Because of rising drug costs, many users switched to injecting, which requires lower doses of expensive drugs to achieve a “high”. Because of constraints against obtaining clean needles and syringes, injecting drug users (IDUs) often share injection paraphernalia with other injectors. The increase in sexual mixing and syringe/needle-sharing promoted the rapid spread of many infectious disease agents, including human immunodeficiency virus (HIV), hepatitis C (HCV), herpes simplex type II, and genital chlamydiae, which were unknown in the early part of the century but were identified in the 20th century.

Changes in the Environment: Increasingly the growth of the population and the concomitant release of pollutants in the air have modified the environment. As people seek respite from the crowding of the cities by moving into rural environments, they are increasingly exposed to zoonotic agents such as hantaviruses, not previously recognized as human pathogens. The reforestation of areas previously devoted to farming, a result of the increased efficiency of agriculture, also results in the reintroduction of animals such as deer and arthropod vectors, which introduce zoonotic diseases such as Lyme disease into new areas. During the 20th century, there has been an extraordinary number of new chemical agents developed to improve the quality of life. Eventually these agents find their way into the air and water supply, adversely affecting the increasing number of vulnerable persons in society and making them more susceptible to agents previously thought to be benign. The rapid urbanization of populations all over the world has put tremendous pressure on cities to maintain effective waste disposal systems. Often these systems cannot keep up with the demand, and breakdowns occur, exposing residents to infectious disease agents. “Global warming’ due to the promiscuous release of hydrofluorocarbons and other gases may also promote breeding of disease-bearing mosquitoes in areas previously not experiencing mosquito-borne diseases.
Promiscuous Use of Antibacterial and Antiviral Drugs: One of the great advances of the 20th century has been the development of drugs against a wide range of bacterial, viral, and other agents. Unfortunately, improper and over-use of these drugs has resulted in the evolution of drug-resistant agents of diseases that we thought we had under control, such as tuberculosis. This problem has been compounded by the widespread addition of antibiotics into the feed of livestock, including chickens and cattle, to control disease amongst them, further promoting the evolution of resistant strains of organisms.

Changes in Health Care: Advances in health care have increased the number of vulnerable persons surviving life-threatening diseases. Procedures such as bone marrow replacement for leukemia patients have produced temporarily vulnerable patients in hospitals, which tend to be repositories of infectious disease agents. The stringent procedures to isolate these vulnerable individuals are not always successful. Other changes, such as the assignment of multiple patients to a single nurse, possible because of technical advances increasing nursing efficiency, provide an opportunity for inadvertent transmission of agents between patients. Other individuals with immunodeficiency diseases such as AIDS or who are undergoing chemotherapy for malignancies are kept alive through the “miracle” advances developed in the 20th century, but are susceptible to opportunistic organisms such as Pneumocystis carinii, which do not cause disease in healthy individuals.

Antigenic Drift and Shift: Some organisms, most notably the influenza virus, respond to selective pressures such as high proportions of immunes in society due to previous epidemics or vaccination programs, by undergoing genetic changes that overcome specific human immune responses to previous influenza strains. Sometimes these agents can also undergo genetic exchange if two different strains of the agent simultaneously infect natural reservoirs such as pigs. Thus, the mixing of avian and human strains of influenza in pigs is thought to have been responsible for the lethal 1917-18 swine flu pandemic that killed millions worldwide, and is a concern regarding the recent H5NI influenza outbreak in birds and humans.

Lapses in Public Health Vigilance: Complacency with accepted public health measures can result in the resurgence of diseases previously brought under control. An example is the resurgence of measles 20 years after the implementation of an effective vaccine in Los Angeles, San Diego, and Dallas. Immunization rates had been allowed to decline, particularly in minority populations, resulting in over 1,000 cases of measles in each of these cities in 1990. Succumbing of public health professionals to public pressure by specific interest groups can also result in breakdowns of public health vigilance. Thus, MSM groups in the early 1980's successfully pressured public health officials to not screen blood donors for individuals practicing male-to-male sex. Because public health officials forgot that their first obligation was to protect the uninfected, thousands of blood recipients and hemophiliacs were infected with HIV. In 1993, there was a breakdown in the water supply to Milwaukee, Wisconsin, resulting in a huge outbreak of cryptosporidia that infected half a million people and resulted in 100 deaths, underscoring the need to avoid complacency regarding long-established public health interventions.
Advances in Food Processing: Food preparation, a time-consuming task in the early part of the 20th century, has been revolutionized with the introduction of processed foods and “fast food” restaurants. However, introduction of a disease agent into the food processing chain can occur, as happened with the distribution of frozen strawberries from Mexico through a USDA-sponsored school lunch program in 1997, which resulted in hepatitis A infection of many children from a single event. Introduction of contaminated food into a fast food restaurant can cause illness in large numbers of people served by the restaurant. An example of this was the outbreak of *Escherichia coli* 0157:H7 in Seattle in 1993.

Internationalization of the Food Supply and Laboratory Animals: With the development of rapid means of transportation and better preservation of food (e.g., refrigeration), food can be imported great distances both within countries and from country to country. Thus, fresh fruits from Mexico and Chile are commonly consumed in the winter in the United States, and from Israel and other countries in Europe. Similarly, meat from Argentina, Canada, and Australia is consumed in many countries of Europe and in the United States. Thus, organisms occurring in the producing countries can cause diseases not usual in the consuming countries, as happened in October 1994 with a snack food produced in Israel, which caused an outbreak of *Salmonella agona* in both Israel and the United Kingdom. In modern research, there is an increasing need for monkeys and other laboratory animals for development of laboratory models of disease and evaluation of potential vaccines. This has necessitated the importation of these animals into those countries most actively involved in research. Thus, monkeys imported from Uganda were responsible for the introduction of Marburg virus into Marburg, Germany in the late 1960's, causing many deaths.

International Travel: Since the third quarter of the 20th century, individuals have been able to travel huge distances in a matter of hours, well within the incubation period of many infectious diseases. Thus, an individual acquiring influenza, dengue, or malaria in an endemic area can transport the causative agent to new areas with many susceptibles and, in the case of malaria, dengue, and other arboviruses, to many vectors capable of transporting the agent to new susceptibles.

War: Although not a new phenomenon, in the 20th century, war continues to promote the exposure of troops to new agents that they can introduce into their home country upon return. Further, war promotes the breakdown of public health measures and usually creates thousands of refugees who are herded into refugee camps that are crowded and lack sanitary facilities, ideal conditions for the spread of many infectious diseases. War also promotes lapses in behavioral constraints regulating disease-spreading behaviors, most notably sexual constraints. Thus, thousands of women were raped, and they and their resulting children were tragically infected with HIV during the Ruandan civil war.

As pointed out by Richard Krause at the beginning of this chapter, disease agents respond rapidly to the opportunities presented by these events and social changes that occurred in the 20th century, adapting their modes of spread, host requirements, etc., to thrive in the new
environments presented by these changes. Thus, it is reasonable to expect the emergence of even more new diseases, re-emerging diseases, and resistant agents as we progress into the 21st century. For example, we have already seen the emergence of two new threatening agents, SARS and H5N1 avian influenza, and the new century is only five years old!

EXAMPLES OF DISEASES EMERGING IN THE 20TH CENTURY

It is impossible in a single chapter to discuss all the agents and diseases that emerged in the 20th century. Therefore, enclosed in the Appendix is a list of the major emergent diseases of the 20th century, their symptoms, mode of transmission, and causes of their emergence. Two major re-emergent diseases, tuberculosis and malaria, are discussed elsewhere in this volume, and therefore will not be discussed further in this chapter. Below is a more detailed discussion of five emergent diseases as examples of the range of diseases and control strategies implemented in the 20th century. These are HIV/AIDS, Ebola, kuru, and dengue hemorrhagic fever, all new diseases, and the new manifestations of chlamydiae infection, as examples of major emergent diseases of the 20th century.

HIV/AIDS

Perhaps the most significant new disease of the 20th century was HIV/AIDS, which accounted for over 70 million cases and over 30 million deaths between its first recognition by Michael Gottlieb at the University of California, Los Angeles (UCLA) in 1980 and the end of 2004. Because it attacks primarily individuals in groups shunned by mainstream society, it is probably the most politicized disease of the 20th century.

In 1980, Dr. Michael Gottlieb, then a young assistant professor of medicine at UCLA, identified three young men with severe immune deficiency without any apparent underlying cause. Dr. Gottlieb noted that all three men engaged in male-to-male sexual intercourse. He suggested that the disease in these young men was a new disease not previously recognized. Once he published these cases reports, other homosexual men with a similar unexplained immune deficiency were reported in New York City and San Francisco. Within a year, cases were also reported among hemophilia patients, and not long after, among IDUs. Because two of the major groups suffering from the disease were marginalized, there was considerable political maneuvering before the American government responded to the epidemic. The American president at the time, Ronald Reagan, did not mention the disease in public statements until 1986. It was not until late 1983 that blood banks initiated screening to eliminate blood donated by members of risk groups. Not long after recognition of the disease in the United States, reports of a similar disease were reported from Haiti and sub-Saharan African countries. However, very few of the cases reported from these countries were among homosexual men or IDUs; most were heterosexual. With the recognition that the epidemic affected not only marginalized groups, more action was taken by the U.S. government, and funds were allocated by the National Institutes of Health to study this new disease.
Although the disease was first recognized and reported in the United States, over 90% of new infections occur in developing countries and in persons 15-45 years, the most productive segment of the population. Although the prevalence in the United States has remained under 1%, in some areas of sub-Saharan African, the hardest hit area, the prevalence has reached 30% or greater among the adult population. As a result, the HIV/AIDS epidemic has had a strong negative impact on the economic and political stability of these countries. The epidemic did not take hold in Asia until the late 1980s, fueled initially by the epidemic of injection drug use, occurring primarily in the countries of the "Golden Triangle", Thailand, Myanmar, northeast India, and southern Yunnan, China. However, it was not long before heterosexual intercourse became the major mode of transmission in all of these countries. There is major concern about the spread of the epidemic in China and India, the most populous countries in the world. By 2005, there were more cases of HIV/AIDS in India than in any other country in the world. Although the potential for spread is great in China, the government has recently implemented strong intervention programs to stop the epidemic while the prevalence is still low. Russia, another large country recently experiencing the epidemic, has been slower to implement strong intervention measures. In Latin America, the epidemic has spread less rapidly, although in the mid-1980s, Brazil had the third highest number of cases. The Brazilian government, however, has taken strong action to slow the epidemic by making treatment available to those HIV-infected individuals in need of treatment.

It was not until 1984 that the cause of the new disease was recognized by Robert Gallo at the U.S. National Institutes of Health, although the causative agent, the human immune deficiency virus, was isolated from an individual with early signs of AIDS by Luc Montagnier and his group at the Pasteur Institute in 1983. Once HIV was isolated, it became possible to identify subclinical infections and to describe the natural history of HIV infection leading to clinical AIDS and death. Work began immediately on the development of a vaccine.

There has been considerable controversy over the origins of the virus. It is now accepted by most scientists in the field that HIV probably evolved from similar retroviruses infecting monkeys, probably in Africa, and spread to humans through butchering of infected monkeys for food and monkeys kept as pets. Thus, it represents a new agent evolving in the 20th century.

HIV is actually a relatively non-infectious disease agent. It is estimated that infection in individuals without concurrent STDs may occur only once in 500-1,000 exposures. Once successful infection occurs, the incubation period to onset of clinical AIDS is approximately nine years, although some infected individuals develop clinical AIDS within one year, and others may be infected for 20 years or more without signs of clinical AIDS. Once AIDS occurs, patients survive on average 6-12 months in the absence of treatment. HIV manages to evade the human immune response by changing it antigenic structure during each replication cycle. The human immune response is absolutely subtype-specific, and the newly replicated virus with the minor mutations can successfully evade the immune response to the parent virus. Thus, the immune response is always several weeks behind the HIV strain currently circulating in the infected individual.
Currently there is no cure for HIV/AIDS and no vaccine. However, by 1995, three different classes of drugs had been developed which, in combination, reduced the amount of HIV circulating in the infected individual and partially restored the level of circulating CD4+ cells, the target cell of the virus. From the perspective of the infected individual, this was a great advance, which converted a 100% lethal disease to a chronic, treatable disease, albeit with problems of side effects and development of resistance to specific drugs. On the other hand, for society, it meant that infected persons who would have died would live indefinitely, but would require continuing expensive treatment. This presents a particularly difficult burden on the health care systems of the developing countries, where the majority of cases occur.

HIV/AIDS was able to take hold and to be sustained because of the major social changes that occurred globally in the 20th century. Since the first cases were recognized, stigmatization has been a major barrier to control, and has caused some countries to attempt to ignore the epidemic. The major barrier to control was lack of a political commitment by governments at the highest levels to recognize the epidemic and to take action. In those countries where the government has made a major commitment, considerable progress towards control of the epidemic has been achieved.

Control of the HIV/AIDS epidemic presents a unique challenge to public health professionals. Unlike cholera and plague, major epidemics of the past, HIV is not manifested as clinical disease for an average of 9-10 years, and can only be recognized by laboratory testing prior to onset of symptoms. Typically, by the time the first cases of AIDS are recognized, there are usually several thousand HIV-infected individuals for every clinical case of AIDS. Thus, the epidemic is already far advanced before the need for intervention is recognized. Although HIV/AIDS is a sexually transmitted disease, unlike syphilis and the majority of the other sexually transmitted diseases, it does not present symptoms during the acute stage, and cannot be cured through treatment.

An effective vaccine has not been developed, and is unlikely to be developed within the next decade. Thus, the major intervention strategies have relied on behavior change and harm reduction. Although the U.S. government has emphasized sexual abstinence and monogamy, it is clear that there is a major segment of the population that either cannot adopt these strategies (e.g. impoverished, powerless women driven to sex work) or will not. Thus, behavioral interventions to increase use of condoms have been emphasized. This strategy (the 100% condom program) has been successful in Thailand and Cambodia with men patronizing brothels, but has been less successful with casual partners and spouses and has not been very effective in Africa.

Before treatment became available, the fear of stigmatization caused people to avoid testing and promoted continued risky behavior and transmission of the virus. With the development of effective treatment, there is a strong rationale for persons suspecting that they are infected to get tested. Numerous studies have demonstrated that both infected and uninfected individuals reduce their risky sexual behavior once they know their status.

Health education alone has been shown not to be effective. However, early education of
children, not just about the risks of HIV/AIDS, but also about coping strategies to resist peer pressure, may be effective and have been implemented in many countries. Because in many developing countries those most vulnerable to HIV/AIDS are most likely to leave school after six years, it is important to implement these programs in elementary school. Cuba used widespread compulsory testing and ‘quarantine’ as a strategy to contain the spread of HIV. To some extent this worked, because Cuba is an island with strictly controlled and limited entry and departure of travelers. These conditions clearly do not exist for the majority of countries worldwide and, thus, are not appropriate as a major strategy for containment of the virus.

For transmission by sharing of injecting equipment, “harm reduction” strategies have been promoted. These include needle/syringe exchange programs and drug replacement therapy. Needle exchange programs have little effect on reducing drug use, but reduce the likelihood of exposure to HIV-contaminated needles and reduce the amount of HIV circulating among injecting drug users in the community. Drug replacement programs provide oral drugs, usually methadone or bupremorphine, which reduce the craving for injecting. Thus, exposure to contaminated needles is eliminated or reduced. Neither of these programs treat the drug addiction, but do reduce exposure to HIV.

Ultimately, a combination of political pressure and community involvement will likely be the most effective strategy for containing the epidemic. For example, a community intervention study that mobilized the community to recognize that injecting drug use was a problem in their community and to take the initiative to address the problem resulted in a drop of new drug-using youth by two-thirds within two years.

The HIV/AIDS epidemic has, however, also advanced the fields of epidemiology, immunology, and virology through the massive amount of research funding that has been allocated. This research has refined the strategy of sentinel surveillance, and provided opportunities to improve the “nested case-control” design used in epidemiology, the understanding of the advantages and limitations of epidemiologic modeling, and the understanding of the response of the immune system, particularly the cellular immune response, to foreign agents and the strategies used by viruses to avoid the immune system response. Thus, research on HIV/AIDS has benefited the entire field of science and the public’s health.

**Ebola**

Ebola virus disease was first identified concurrently during epidemics in Zaire (now the Democratic Republic of the Congo) and Sudan in 1976, but there is serologic evidence of an earlier epidemic in 1972 in Zaire. Both of the 1976 epidemics were first recognized among patients entering local hospitals in the two countries. The causative agents in the two epidemics, Ebola-Zaire and Ebola-Sudan, differed slightly, perhaps explaining the lower case fatality in Sudan (54%) than in Zaire (88%). The transmission in Zaire occurred primarily through reuse of unsterilized needles and syringes, whereas in Sudan, transmission was primarily through close personal contact with a patient. Both epidemics died out when strict containment procedures were implemented. Containment requires universal precautions and barrier nursing care,
including the use of latex gloves, masks, and gowns, and isolation of patients. The common practice in Africa of open-casket funerals, with extensive cleansing and preparation of the body by relatives and close friends, had to be stopped, and closed-casket ceremonies substituted.

Fifteen subsequent outbreaks of Ebola have occurred in Gabon, Cote d’Ivoire, Liberia, South Africa, Uganda, and the latest in 2004 in Sudan. There have been a total of 1848 known cases, with 1287 (69.6%) deaths. Secondary transmission occurs primarily to caregivers, hospital personnel, and immediate family members through direct exposure to blood, other bodily secretions, and infected organs. Implementation of strict infection precautions and changes in burial customs usually resulted in the containment of each of the epidemics. Fortunately, Ebola does not appear to spread via the respiratory route.

The source of the initial cases in each of the epidemics is unknown, but most cases had been in proximity to African tropical forests. Ebola has been isolated from carcasses of chimpanzees, gorillas, monkeys, forest duikers, and porcupines found dead in the forests, but it is not known whether they are the primary reservoir. Presumably the primary reservoir is a dweller of the sub-Saharan African tropical forests. The origins of the virus are also unknown.

The usual incubation period ranges from 2-21 days. The initial symptoms include sudden malaise, headache, and muscle pain, progressing to high fever, vomiting, and bloody diarrhea. Patients are most infectious during the phase of vomiting and diarrhea. Patients die from hemorrhaging of internal organs. The case fatality ranges from about 50% to over 89%, and appears to be somewhat lower for Ebola-Sudan than Ebola-Zaire.

Ebola belongs to the newly described genus, filovirus. Two other filoviruses have been recognized in the 20th century, Reston virus and Marburg virus, both initially causing outbreaks in laboratories. The Reston virus appears to be less virulent than the other two members of the family. Recently, in 2005, Marburg caused an epidemic of 351 known cases in Angola, with a case fatality rate of 88.8%. This epidemic was larger than most of the known Ebola outbreaks, and suggests that Ebola and Marburg viruses may cause more substantial epidemics in the future unless more effective prevention and containment strategies can be developed and implemented.

Kuru

In the early 1900s, a fatal neurodegenerative disease appeared in the South Fore people of the New Guinea Highlands. The disease was eight-fold more common among women than men. Children were also victims of the disease. At first the disease was thought to be a genetic disease, but further studies by Gadjusek and his colleagues demonstrated that the disease was caused by a transmissible agent. Gadjusek hypothesized that the disease was caused by a slow virus with an incubation period of 2-25 years. On the basis of these studies, he was the first epidemiologist to be awarded a Nobel prize. Subsequent studies, however, demonstrated that the causative agent was not a virus, but an abnormal protein subsequently labeled a “prion”. The discovery of the cause of kuru was important because it defined an entirely new class of infectious agents that are the cause of many neurodegenerative diseases, including “mad cow
disease” (bovine spongiform encephalitis), the probable cause of variant Creutzfeld-Jacob disease in humans, which has caused so much concern and economic loss in the last decades of the 20th century.

Ritual mortuary cannibalism was practiced by the South Fore people. When one of them died, they would be butchered, and the muscles, brain, and innards consumed by women who were in charge of preparing the body for consumption by the men, who preferred muscle over brain tissue. Gajdusek, Gibbs, and colleagues were able to transmit the disease from chimpanzees injected with tissue from kuru victims to chimpanzees never exposed to tissue from kuru victims, demonstrating that the causative agent could be transmitted. They hypothesized that the agent was a “slow virus”.

Subsequently, Prusiner was able to identify the causative agent, and to demonstrate that it did not contain nucleic acids, indicating that the agent was not a virus. Further work by Prusiner and others confirmed that the prion was a cellular protein variant of a gene found in humans called PrPc, caused by a single point mutation. The variant, labeled PrPSc, recruits normal proteins by “flipping” them into a prion-like shape that can then infect other cells and animals. Thus, the prion is able to replicate in the absence of nucleic acid genetic material through a chain reaction-like mechanism. The normal PrPc gene does not appear to be essential for humans; thus, treatment may be possible through agents targeting the PrPc and its variant prion. The biologic mechanisms of prion disease, however, are still not fully understood, and present a challenge to future scientists.

Thus, kuru and the work by Gajdusek, Prusiner, and colleagues is significant because it identified an entirely new class of infectious agents that do not depend on nucleic acids for replication and transmission. Prions have now been recognized as the causative agent of many neurodegenerative disorders, but it is possible that as the 21st century progresses, we may find other diseases caused by this new class of infectious agents.

**Dengue Hemorrhagic Fever**

The first reported epidemics of dengue fever occurred in 1779-80 in Asia, Africa, and North America. The disease was described by Benjamin Rush, a Philadelphia physician, as “break bone fever” in 1780. The causative agent, dengue virus, was not isolated until 1943. Dengue virus causes an acute febrile illness with severe symptomatology, but is self-limiting and seldom results in death. The hemorrhagic complications of infection with the dengue virus, dengue hemorrhagic fever (DHF), were not described until the 1950s in the Americas and Southeast Asia. Unlike dengue fever, DHF is associated with serious morbidity and a high case fatality. Volumetric fluid replacement and supportive care can reduce the case fatality from 40-50% to 1-2%. Although an attenuated vaccine to dengue has been developed, it has not been subjected to efficacy trials in humans as yet. It is unlikely that an effective vaccine will be available for public health use in less than a decade. From a public health perspective, it is essential that vaccination results in protection against all four subtypes, as protection against only one or two subtypes may result in more serious disease due to subsequent infection with the other subtypes.
By the end of the 20th century, DHF had become a major cause of morbidity and mortality in children in many of the countries of these two regions.

There are four subtypes of dengue virus, types 1, 2, 3, and 4. Infection with a particular subtype of the virus provides lifelong protection against that subtype, but not against the other subtypes. It has been suggested by Scott Halstead that sequential infection with different subtypes may result in hemorrhagic fever. However, some epidemics of DHF have been reported to be associated with subtypes 2 and 3.

The resurgence of dengue fever and the emergence of DHF can be ascribed to the rapid urbanization that has occurred in the second half of the 20th century. The usual mosquito vector, *Aedes aegypti*, breeds in urban water sources, such as water collected in discarded tires, water containers, and other urban locales where standing water collects long enough for the breeding of mosquitoes. The rapid growth of cities of Latin America and Southeast Asia has led to the building of impromptu slums, which have inadequate housing and no water, sewerage, and waste management systems. These slums usually contain many sources of standing water ideal for breeding of the dengue vector. In the absence of an effective vaccine control, efforts must concentrate on eliminating the vector. However, vector control is essentially absent in the rapidly growing urban areas of developing countries, which are often concerned with other pressing problems. The rapid increase in international travel, possible with the introduction of jet aircraft, has allowed the transmission of dengue to new locations that may have vectors capable of transmitting the virus. Control of dengue and DHF in the 21st century, in the absence of a vaccine, will require surveillance to identify areas in which dengue is occurring and vigorous efforts to control the breeding of the vector. Health education efforts to induce the public to reduce the sources of standing water around their homes will also be a key factor.

**Chlamydiae**

Trachoma, an ocular disease caused by *C. trachomatis*, was known in ancient China and Egypt thousands of years ago, but the causative agent was not isolated until 1957 by Tang and associates in China and confirmed in 1958. Trachoma was the most frequent cause of preventable blindness world-wide. It has been estimated that there are still 500 million active cases of ocular trachoma infection world-wide, including approximately seven million people with blindness associated with conjunctival scarring and eyelid deformities. Ocular trachoma is associated with crowding and poor hygiene. Although the disease is easily treatable with tetracycline-type drugs, improving living and sanitary conditions has been the primary cause of the decline in the disease.

The other chlamydial agent known for many years is *C. psittaci*, a major cause of respiratory disease that occurs primarily among those handling infected birds, including chicken and turkey processing plants. Person-to-person spread is rare, but has been observed in some outbreaks of the disease.

With the rapid development of new laboratory technologies in the second half of the 20th
century, other manifestations of chlamydiae infection have been recognized. In the late 1960s, it became clear that *C. trachomatis* could also cause genital disease in sexually active individuals. Clinical manifestations include cervicitis, urethritis, endometritis, pelvic inflammatory disease, and proctitis. Subsequently, *C. trachomatis* has been recognized as one of the major STDs world-wide. The World Health Organization has estimated that there were 95 million new chlamydial infections world-wide in 1995. Unfortunately, the majority of genital chlamydiae infections (50-70%) are asymptomatic, particularly among women. Thus, they are seldom diagnosed and treated before serious complications occur. Current infection can be eliminated by a single dose of azithromycin or a seven-day course of doxycycline, but infection does not confer immunity. Thus, re-infection is common in those who are sexually active and repeatedly exposed. Another manifestation of *C. trachomatis* is lymphogranuloma venereum, which is five times more frequent in men than women, and is also easily treatable.

In the early 1980s, Grayston et al. and Saikku et al. identified another subtype of chlamydiae, *C. pneumoniae*, which causes mild respiratory disease. *C. pneumoniae* infection is more common in men, but antibodies are found in over 50% of most adult populations world-wide. It is one of the most common causes of pneumonia in early infancy. The onset of asthma and exacerbations of asthma have also been reported to occur in association with *C. pneumoniae* infection.

In 1988, Saikku and colleagues noted that patients with acute myocardial infarction and coronary heart disease more often had elevated levels of IgG and IgA antibodies to *C. pneumoniae*. Subsequently, *C. pneumoniae* has been linked to atherosclerosis, but no organisms have been found in atherosclerotic plaques in blood vessels. A recent trial of preventive treatment with antibiotics did not result in a lower rate of myocardial infarction in those treated.

In summary, chlamydiae is a major cause of morbidity world-wide, but only through the development of new laboratory technologies in the 20th century, has the range of diseases it causes become apparent. It is possible that even more manifestations of this ubiquitous agent may be discovered in the 21st century.

PREVENTION OF EMERGING DISEASES

The U.S. Centers for Disease Control and Prevention has outlined the objectives for preventing emerging diseases in the future. These are (including examples):

- **Enhance global watchfulness for new diseases and agents**
  
  The World Health Organization has established the *Global Outbreak Alert and Response Network*, which is a collaboration of existing institutions and networks world-wide that pool human and technical resources for the rapid identification, confirmation, and response to outbreaks of international importance.

- **Develop strategies to fight new, previously unknown diseases (e.g., SARS)**
  
  SARS was contained through a strategy of alerting the public and travelers to the early symptoms, and voluntary quarantine of exposed contacts and isolation of cases.

- **Protect the blood, food, and water supplies from contamination**
Governments in developed countries, and increasingly in developing countries, have established agencies that are responsible for maintaining the quality and safety of blood, food and water.

- **Continually develop new antibiotics to organisms that have become resistant to current drugs**
  
  A major effort continues to identify new classes of drugs that act at different points in the replication of HIV; e.g., attachment of the virus to the target cell and integration of the virus into the cell genetic material. Similar research is being conducted to overcome resistance to staphylococci and other agents.

- **Develop new vaccines**
  
  There are major efforts being made by the scientific community to develop effective vaccines to protect against malaria and HIV/AIDS.

- **Prevent zoonotic diseases from spreading to humans**
  
  A major source of SARS, influenza, and other zoonotic diseases from southern China are the live animal markets, where animals are crowded together for sale, promoting rapid spread of infectious agents among them. Traditionally, Chinese doubt the freshness of animal produce unless they kill them themselves. Hong Kong has now outlawed live markets.

- **Protect vulnerable populations; e.g., sick, elderly, pregnant women, etc.**
  
  Many countries have implemented special centers for the elderly that provide activities, exercise, and advice on maintaining health. Handicapped facilities are being mandated by law. Antenatal clinics are now found in almost all countries, although the coverage may be inadequate in some developing countries.

- **Prevent terrorist attacks with microbial agents, and respond quickly and effectively when incidents do occur**
  
  Many countries have implemented special procedures for identifying terrorist attacks with microbial agents and implementing containment procedures. The U.S. and other countries are stockpiling vaccines to likely terrorist agents such as smallpox. Unfortunately there has been relatively little attention paid to resolving the underlying causes of the terrorist attacks.

The CDC proposes four interdependent strategies:

- **Surveillance** for new diseases and agents, and monitoring of their occurrence once recognized

- **Applied research** to develop new techniques to fight emerging diseases, including identifying new agents and developing new strategies and drugs to control their morbidity and spread

- **Infrastructure development** to heighten our preparedness and to sustain surveillance, applied research, and prevention programs, as well as training of personnel to implement these activities

- **Prevention and control** through surveillance, applied research, and infrastructure development

We were only partially successful at meeting the challenge of emerging diseases in the 20th
century. The 21st century will bring new social, economic, and scientific advances and changes that will foster the emergence of new diseases and the re-emergence of diseases we thought we had controlled. The challenge to do better in this century before us.
FURTHER READING


