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 the recognition of many new infectious diseases and agents. By 1980, however, we scientists smugly thought that infectious diseases were a threat that we had overcome.

Quote on the demise of infectious diseases

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 acquired immune deficiency disease (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 2) technical and industrial advances 3) economic development and changes in land use 4) international travel and commerce 5) microbial adaptation and change and 6) breakdown of public health measures.

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 different classification strategy than 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: Since the beginning of the 20th Century there have been dramatic changes in behavior of humans, particularly in their sexual behavior. Whereas having multiple sexual partners was unacceptable in the early 20th Century having multiple sexual partners had not only became 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 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 ten or twenty anonymous partners in a single evening. Among heterosexuals the barrier of unwanted pregnancy was reduced by effective contraceptive methods. In many societies drug use became common. Because of rising drug costs many users switched to injecting which required lower doses of expensive drugs. Because of constraints against obtaining clean needles and syringes injecting drug users (IDUs) often had to share injection paraphenalia with other injectors. The increase in sexual mixing and syringe/needle sharing promoted the rapid spread of many infectious disease agents including the human immunodeficiency virus (HIV), hepatitis C (HCV) and genital chlamydiae which were unknown in the early part of the 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, because of the increased efficiency of agriculture, also results in the reintroduction of animals such as deer and disease vectors which introduce zoonotic disease such as Lyme disease into new areas. During the 20th Century there have 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 keep up with 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 may also promote breeding of disease bearing mosquitoes in areas previously not experiencing these agents.

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 over-use and unnecessary 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. Such procedures 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 acquired immune deficiency disease (AIDS) or undergoing chemotherapy for malignancies are kept alive through the “miracle" advances developed in the 20th Century, but are susceptible to 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 which 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 epidemic which killed millions worldwide.

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 twenty 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.

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 prepared foods and "fast food" restaurants. However, introduction of a disease agent into the food processing chain as happened with ??? in 19??? can result in the infection of thousands of individuals 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 19??.

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 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 lab animals for development of laboratory models of disease and evaluation of potential vaccines. This has necessitated the importation of these animals to 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 can transport the causative agent to new areas with many susceptibles and, in the case of dengue, malaria and 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 which 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 which 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 who were raped and their resulting children were infected with HIV during the Ruandan civil war.

As pointed out by Richard Krause disease agents respond rapidly to the opportunities presented by these events and social changes which 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 ever 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, sudden acute respiratory syndrome (SARS) and H1N5 avian influenza and the new century is only 5 years old!

**EXAMPLES OF DISEASES EMERGING IN THE 20TH CENTURY**

A list of the major emergent diseases of the 20th Century, their symptoms, mode of transmission and causes of their emergence is given in the appendix. Two major re-emergent diseases, tuberculosis and malaria, are discussed elsewhere in this volume and will not be discussed further in this chapter. Below I will discuss further the emergence of HIV/AIDS, Ebola, and dengue hemorrhagic fever and the new manifestations of chlamydiae infection as examples of
HIV/AIDS
Perhaps the most significant new disease of the 20th Century was HIV/AIDS which accounted for over 60 million cases and ??? deaths between its first recognition in 1980 by a young physician at the University of California, Los Angeles (UCLA) 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 intercourse. He suggested that the disease in these young men was a new disease not previously recognized. Once he reported these cases reports of other homosexual men with a similar unexplained immune deficiency were reported from New York City and San Francisco. Within a year cases were also reported among hemophilia patients and not long after among injection drug users. 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 subsaharan African countries. However, very few of the cases reported from these countries were homosexual men or injecting drug users (IDUs). Most were heterosexual. With the recognition that the epidemic affected not just marginalized groups more action was taken by the U.S. government and funds were allocated by the National Institutes of Health to study the 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 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 users 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 Brazil government, however, has taken strong action to slow
the epidemic.

It was not until 1984 that the cause of the new disease was recognized by Robert Gallo 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.

HIV is actually a relatively non-infectious disease. It is estimated that infection in individuals without concurrent sexually transmitted diseases may occur only once in 500-1,000 exposures. Once successful infection occurs the incubation period to onset of clinical AIDS is approximately 9 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 its antigenic structure during each replication cycle. The human immune response is absolutely subtype specific and the newly replicated virus with 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 types 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 and 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 it meant that infected persons who would have died would live indefinitely, but would require continuing expensive treatment. This represented 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 a commitment by the government 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.

**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 the 1976 epidemics were first recognized among patients entering the local hospitals in the two countries. The causative agents, Ebola-Zaire and Ebola-Sudan, in the two epidemics differed slightly perhaps explaining the lower case fatality in Sudan.
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.

Fifteen subsequent outbreaks of Ebola have occurred in Gabon, Cote d'Ivoire, Liberia, South Africa and Uganda, 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 results 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 know 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 blood diarrhea. Patients are most infectious during the phase of vomiting and diarrhea. Patients die from internal 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 occurring in laboratories. The Reston virus appears to be less virulent than the other two members of the family. Recently, in 2005, Marburg has caused an epidemic of 351 known cases in Angola with a case fatality rate of 88.8%. This epidemic is 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.

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. Supportive care, primarily 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 result in protection against all four subtypes as protection against only one or two subtypes may result in more serious disease due to 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 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 the mosquito. The rapid growth of cities of Latin America and Southeast Asia has lead 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 which 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 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 7 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 have 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 which also 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 chlamydial 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 sexually transmitted disease 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 chlamydial 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 7 day course of doxycycline, but infection does not confer immunity. Thus, reinfection is common in those who are sexually active and repeatedly exposed. Another manifestation of *C. trachomatis* is lymphogranuloma venereum. The disease 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* that 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 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 atherogenic plaques and 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 has the range of diseases it causes become apparent. It is possible/likely that more manifestations of this ubiquitous agent may be discovered in the 21st Century.

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**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:

- Enhanced global watchfulness for new diseases and agent
- Develop strategies to fight new, previously unknown diseases (e.g. SARS)
- Protect the blood, food and water supplies from contamination
- Continually develop new antibiotics to organisms which have become resistant to
current drugs
- Develop new vaccines
- Prevent zoonotic diseases from spreading to humans
- Protect vulnerable population e.g. sick, elderly, pregnant women etc
- Prevent terrorist attacks with microbial agents and respond quickly and effectively when incidents do occur

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 strategies and developing new drugs to control their morbidity and spread
- **Infrastructure development** to heighten our preparedness and to sustain surveillance, applied research and prevention programs and **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 which 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 is before us.