Chapter 3

Old and New Pestilences

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INTRODUCTION

There has been much popular interest in, as well as technical concern over, newly emerging diseases, and there is a fear that heretofore unknown virulent pathogens will create new, global epidemics. At the time of this writing, two such pathogens are active, warranting such concern: a) cases of SARS (Severe Acute Respiratory Syndrome, caused by a coronavirus) appeared in China in November, 2002, and has spread to Western and Central Europe and North America; b) a strain of Avian Influenza Virus (N5H1), first identified in Hong Kong in 1997, reemerged in 2002 in Southeast Asia. Other avian flu strains found simultaneously in poultry in North America have underscored the concern of local and international health authorities. Both SARS and avian flu demonstrate high mortality rates, but, to date, the number of cases has been only in the hundreds. So, are these pestilences? What constitutes a pestilence? Is the term synonymous with newly emerging diseases? Two definitions of pestilence have near unanimity, but are not very specific:

a) *"Any fatal epidemic disease, affecting man or beast, and destroying many victims."* The Oxford Universal Dictionary, 3rd edition, 1955, Oxford Press, 2515 pp.
b) *"A contagious or infectious epidemic disease that is virulent and devastating."* Webster's Seventh New Collegiate Dictionary, 1965. G. & C. Merriam Co., Springfield, Mass., 1221 pp.

Accordingly, a pestilence should be an infectious disease, devastating (killing) a large number of people (or animals).

The truly epidemic diseases are usually of viral or bacterial origin (although we will make a case for some other types of pestilences). The classification of

'old' and 'new' pestilences requires us to take a brief historical tour of the bio-epidemiological sciences.

- Reports of epidemics of many of the pestilent diseases are found in Greek, Egyptian, and Chinese literatures, and go back as far as 2,500 years, but most are hard to identify as currently known diseases, except for those with very characteristic symptoms (e.g., plague, measles, smallpox, cholera, etc.). These are the classic 'old' pestilences, some of which have been controlled, in part; others remain active today.
- There was no science of infectious diseases, no germ theory, until Louis Pasteur, Koch, and Lister (among others) began their work in the late 1800s—only 125–130 years ago.
- The cycles of vector-borne diseases (malaria, plague, yellow fever, dengue, and filariasis, to name a few) were only elucidated around 1900, which clarified the etiology of some 'old' pestilences while describing the first of those we might consider 'new' (e.g., arenavirus or filovirus outbreaks). The first virus, foot and mouth disease, was isolated in 1898 by Loeffler and Frosch.
- Immunological diagnostic tools used to identify, describe, and classify pathogens and 'new' diseases have become more specific and widely available in the past 50–60 years.
- More specific and effective preventive and treatment measures (vector and environmental control, vaccines, antibiotics, et al.) have been developed and made available in the past 50–60 years since World War II.
- The past half-century, in which most 'new' pestilences have occurred, is marked by large human population increases and densities, changes in natural habitats, and encroachment of human populations into sylvatic areas with their natural populations of active and potentially active pathogens and their vectors, or other routes of transmission.
- There has been a development of local, regional, and global surveillance systems to facilitate rapid response measures.

OLD PESTILENCES (TABLE 1)

Plague

Plague, in both its bubonic and pneumonic forms, is the quintessential pestilence. A myriad of books have been written on the classical plagues, from the Decameron to Camus' La Peste. Although earlier epidemics around the Mediterranean may have actually been plague, the first epidemic historically accepted as the plague was the Plague of Justinian (A.D. 542–43, with intermittent outbreaks

Table 1. **Old Pestilences:** Examples of some of the pestilences that fit into this category are shown below: This is not a comprehensive list and some were known and reported on before others, but all were known prior to, or about, the time of the development of microbiology.

Disease	Etiology	Comments
Plague	Bacterial, flea-borne	Global, but focal; reservoirs in sylvatic rodents
Yellow Fever	Arbovirus, mosquito-borne	Africa and South America, focal; primate reservoirs
Malaria	Protozoal parasite, mosquito-borne	Global; most severe in Africa
Smallpox	Virus, personal contact	Previously global, eradicated by intensive vaccination program: last naturally occurring case, 1977.
Measles	Virus; air-borne, personal contact	Global; number of cases reduced by vaccination; most severe in developing countries
Polio	Virus; personal contact, oral-fecal route common	Formerly global; continued reduction by ongoing vaccination programs in developing countries
Influenza	Virus; air-borne	Global; immunization available annually, virus highly variable
Cholera	Bacterial *(vibrio)* food/water, fecal contamination	Potentially global; SE Asia remains high risk, often associated with civil strife and/or in disaster areas

that may have been bubonic plague continuing until A.D. 750). The "Black Death" of the fourteenth century, which continued to appear in chronic pockets of Europe and the Middle and Near East for centuries thereafter, is by far the best-known plague, and the one that produced the greatest mortality and social impact on the affected populations. Consider that as a conservative estimate, 25—33% of the European population died, and maybe more. This death rate reduced the available work force so that, for the first time, peasants and landless people could sell their labor, which introduced freedom of movement and resulted in economic changes that eventually contributed to the decline of the feudal system.

The 3rd pandemic of plague began in the 1850s and continues to this date, although reduced in more recent years. A major characteristic of this epidemic has been the dissemination of plague from its traditional homes in Africa and Asia into areas previously plague free, especially North and South America, by the inadvertent transport of rats and their fleas by boat. The infection is now well established in Africa (gerbils); Central Asia (gerbils, ground squirrels or "susliks," and marmots); Southeast Asia (various *Rattus* species); North America (ground squirrels and some native field mice); and South America (introduced *Rattus*). The

last major urban outbreak was in Surat, India in 1994: More than 6,500 cases and 56 deaths were reported. However, the impact of this outbreak was also seen in the number of people who fled the plague zone, and the over two billion dollar loss that ensued.

Only a few outbreaks are reported to WHO each year. Indochina and Burma frequently report, as well as sites in Africa (Ovamboland on the frontier between Namibia and Angola); the United States has a vast infected area in the west of the country, but only 8–10 cases per year are reported, with 1–2 deaths on average every 10 years. Many other sites of infection are known and should be monitored, as some rodent species are highly susceptible to serving as effective amplifying reservoirs, whereas others maintain low-level infections for long periods of time, allowing much time to pass between outbreaks. Environmental measures (rat-proofing, rodent and flea control, etc.,) are the first measures of control. Surveillance, prompt diagnosis, and treatment with antibiotics (e.g., streptomycin and tetracycline) are recommended.

Yellow Fever (YF)

Yellow fever is the best known of the arboviral (arthropod-borne virus) diseases. There are some 500 known arboviruses, of which about 100, produce disease in man. Both the yellow fever virus and the primary mosquito vector, *Aedes aegypt,* are of African origin - the species name, '*aegypti,*' refers to classical Africa in general, not, specifically, modern Egypt. Most cases in Africa occur East to West along the transition zone (ecotone) between the savannas and the rain forests inhabited by numerous aedine vectors as well as *A. aegypti.* The disease has two cycles: a 'jungle' cycle involving various tree dwelling mosquitoes and non-human primates as reservoirs, and an 'urban' cycle, with A. aegypti as the vector and humans as reservoirs. The last reported major African outbreak vectored by *A. aegypti* occurred in Nigeria and involved some 20,000 cases and over 4,000 deaths between 1986 and 1991.

Yellow fever was introduced into the Americas one or more times most likely during the age of sail: The virus can be transmitted vertically (transovarian passage) in *A. aegypti.* The mosquito's eggs can easily be laid in water barrels and withstand desiccation for months, only to hatch and develop when submersed at a later date. Epidemics of YF raged throughout the Caribbean and tropical America until the end of the 1800s, when the transmission cycle was elucidated by the team led by Walter Reed, confirming the role of *A. aegypti* which had been proposed by, but not confirmed by, Carlos Finlay. Epidemics occurred as far north as Philadelphia in the United States and the last epidemic in North America occurred in New Orleans as late as 1905, with over 3,000 deaths. Cases (with 25–50%) mortality continue to occur sporadically in Brazil and in the foothills of several Andean countries (Bolivia, Peru, Ecuador, and Colombia). Often the victims are young, indigenous

males from the highlands who were temporarily working in the coca processing plants in the forests. These infected areas are only kilometers from large cities (with populations of more than 1 million people) such as Santa Cruz, Bolivia, which are accessible by public transportation and are heavily infested with *A. aegypti*.

Although the YF vaccine is one of the oldest, safest, and most effective available, and immunological protection is rated for at least 10 years, vaccination coverage in many of the affected areas of Africa and South America is low.

Cholera

The Cholera pathogen, *Vibrio cholera*, originally described by Robert Koch, was one of the first human pathogens (along with anthrax and tuberculosis) to be identified, in the late 1800s, shortly after Pasteur's publication of the "germ theory." Koch and his students studied material they collected in Alexandria, Egypt, during an 1883 outbreak. It was difficult to determine the origin of cholera and/or to distinguish it historically from other diarrhetic diseases except by the severity and rapidity of onset. Health historians such as McNeill suggest an origin on the Indian sub-continent, associated with dense populations, poor hygiene, and certain religious practices such as communal bathing; thus the term "Asiatic cholera," by which the disease became known in Europe in the 1800s. The disease's appearance in Europe and the Americas (London and New York in 1832, and again in 1854) were clearly associated with intercontinental traffic. It was during the 1854 epidemic in London that a physician, John Snow, noted the clustering of cases and deaths in people using the same water source, and proposed what turned out to be the correct action to stop the epidemic ("Take the handle off the Broad Street pump!!"), although he had no idea of the actual cause of the disease. However, it was such observations, along with structural, hygienic, and administrative changes in major cities, particularly in Europe and North America, that established the public health measures that we tend to take for granted in this early part of the 21st century.

Cholera is still with us: various serotypes of the vibrio have spread since the early 1960s, affecting over 25 countries in Asia, 21 in the Americas, and into the West Pacific. In 1993, approximately 400,000 cases and 6,800 deaths from cholera were reported. In 1991, the El Tor strain of cholera was reported in Lima, Peru; by 1994, almost a million cases had been reported in the Western Hemisphere.

Measles

Measles is one of the oldest known and most widespread infections of man: Epidemics ascribed to measles appear in the oldest literature, although they are often confused with smallpox. However, in 622 A.D., Ad Ahrun, a Christian priest living in Alexandria, Egypt, described the pox lesion, and in 910 A.D. the Arab

physician Al-Razi distinguished between the two diseases. Prior to widespread immunization, measles was common in childhood—more than 90% of people were infected by age 20. Although endemic in large communities, measles became epidemic every several years, with the severity of infection decreasing with the frequency of the epidemics. In his study of the history of plagues, McNeill makes mention of the importance of animal husbandry and zoonotic diseases in the area. Measles, he claims is probably related to both rinderpest (in hoofed-mammals) and canine distemper. Because dogs, sheep, and goats have been domesticated for at least 10,000 years, measles may have been among the first viral diseases to have "jumped the species barrier." As we will see, most, if not all, of the new pestilences are, or may be, derived from animal wild or domesticated reservoirs. To support this thesis, McNeill lists as follows the number of diseases human populations share with domestic animals, with numerous overlaps between the species:

Poultry	26
Rats and mice	32
Horse	35
Pig	42
Sheep and goats	46
Cattle	50
Dog	65

Measles was responsible for (or contributed to, along with smallpox) the decimation of the indigenous Amerindian populations, first in Central and South America at the time of the Spanish conquest (1500s), and later (1700s and 1800s), in North America. Amerindian populations lacked immunological protection from these and other imported infectious diseases. Some attribute this immunological naïveté to the comparatively small number of domesticated animal species—dogs, ducks and turkeys, guinea pigs, and cameloids (llamas and relatives) in the Andes, and few, if any, in large number prior to the European invasion. In any case, the attack and mortality rates were staggering. By one estimate, a pre-conquest Amerindian population of perhaps thirty million by 1556 was reduced by 90%, down to only 3 million. This catastrophe occurred in less than 50 years after the Spanish entered the American mainland.

Influenza

Influenza is another viral disease that has many unstable varieties infecting a host of mammalian and avian species, both wild (sylvatic) and domestic. Epidemics with symptoms similar to modern influenza were noted by Hippocrates as early as 412 B.C., and later, in Rome, by Livy. Various medieval and Renaissance writings

describe influenza-like illnesses. Robert Johnson of Philadelphia is credited with the first "modern" description of an influenza epidemic, which occurred in that city in 1793. His description was applied to subsequent epidemics in 1833, 1837, 1847, 1889–90, and 1918.

Antigenic shifts in the structure of the influenza virus may change the virulence of the strains, increasing the likelihood of epidemics. The most severe flu epidemic ever recorded (1918–1919)—also known as the Spanish flu (although it did not originate there)—first struck World War I troops of all combatant nations while in northern France, and it continued on to become a global pandemic. Conservative estimates of mortality range between twenty and forty million persons, and other estimates more than double these figures.

The ease with which the various influenza strains infect domestic mammals, pigs, and poultry (chickens and ducks) producing huge reservoirs of potentially infectious material, often proximate to human habitations, is a major public health concern. Especially worrisome are the conditions under which millions of such animals are raised and brought to market.

Other Pestilent Diseases

The 'old' diseases examined above are only a few of those which might be used as examples of the old pestilences: others might prefer to include schistosomiasis, typhus (murine and/or louse-borne), and several of the classic childhood diseases (diptheria, pertussis, tetanus, rubella), as well as leprosy, yaws, the leishmaniases, and, certainly, smallpox. Fortunately many of those mentioned here (schisto and others) are being controlled rather well in some areas by vaccines, specific drugs, and/or antibiotics when applicable, at least in the more developed countries. Even polio, which had been a major epidemic threat for centuries, has been virtually eliminated as a threat in areas where the politics and health infrastructure allow the efficient application of this very effective vaccine.

Much of the fear engendered by specific diseases depends on the time, place, and severity of the local outbreaks, as well as the knowledge and perception of the community. For example, I was raised in New Orleans, in the Southeast of the United States, during the 1930s. Although I and my brothers were normal, well nourished children, our parents were fearful of dogs (rabies), cuts on unshod feet (tetanus), and any summer colds or stiffness/weakness of the extremities (polio), and they preached cleanliness as a means to prevent anything bad happening.

Special "Old–New" Pestilences (Malaria, Dengue, and Tuberculosis)

These diseases are old, but at present each has developed certain new characteristics that make their modern expression different from their historic ones, and decreases our ability to control them.

In the last 50 years, malaria parasites have developed resistance to chloroquine, the most common, globally used anti-malarial drug; at the same time, the anopheline mosquito vectors of malaria have progressively developed a parallel resistance to the insecticides used to control them. Dengue, and Dengue Hemorrhagic Fever (DHF), have spread globally, infecting vast new areas, especially urban areas where the human living conditions are substandard, but readily suited for vector breeding. Finally, tuberculosis, whose incidence was slowly reduced in the late 1800s and early 1900s by improved public health, housing conditions, and nutrition, has again surfaced as a secondary infection to immuno-compromised persons, especially those suffering from HIV infections. At the same time, the causative agent, *Mycobacterium tuberculosis,* continues to develop resistance to the most economic and readily available antibiotics.

Malaria

Malaria is caused by blood parasites of the genus *Plasmodium* and vectored by anopheline mosquitoes. There are four species of human malaria parasites: *P. falciparum, P. malariae, P. vivax, and P. ovale,* as well as a number of related species infecting other mammals (non-human primates, rodents, etc.). Historians note that malaria-like symptoms were discussed in the Chinese Canon of Medicine (2700 B.C.) and malaria-like illnesses were described in 6th-century B.C. cuneiform literature from Nineveh (now part of Iraq). Hippocrates made a connection between stagnant water and fevers in the local population. It is estimated that there are still several hundred million unreported cases each year resulting in 1–2 million deaths per annum, mostly children. Although malaria is still endemic in Asia, Latin America, and Africa, 90% of the cases are found in Africa, where *P. falciparum* is the most common malaria parasite.

Such huge figures mask the focal, and sometimes epidemic, nature of malaria, which may be brought about by natural or man-made environmental conditions. Some of the human activities that may enhance malaria transmission may be development projects for agriculture (e.g., irrigation schemes), other water and land use projects (as in the Amazon basin, converting forest areas through resource extraction such as mining and logging) into marginal livestock and farming areas. Often such environmental changes bring about changes in malaria transmission from 'stable' (endemic) to 'unstable' (epidemic). In highly endemic areas, severe malaria and death is concentrated in the younger age groups, whereas in the areas of unstable (epidemic) transmission, severe malaria and death is more evenly distributed throughout all age groups. Needless to say, prevention and /or case control strategies must be different for each transmission type.

In many parts of the world the anopheline vectors of malaria have developed resistance to the insecticides used for their control. Frequently, this is due to the use, often excessive, of the same or similar insecticides for control of agricultural pests

in the same geographic areas. Such resistance not only hinders control operations directly, but also indirectly, by increasing the need for greater quantities and/or more costly insecticides. Broadscale usage of insecticides has also become limited on environmental grounds, because some donors have reduced funding insecticide purchases.

By far the most serious setback to malaria control in recent decades has been the emergence and spread of chloroquine-resistant strains of *P. falciparum*, the causative agent of the most severe form of malaria, and the most common in Africa. Emerging in the 1950s in Southeast Asia and South America, resistance spread rapidly from these focal points. It was not noted in Africa until 1979–80 but spread rapidly in the ensuing ten–fifteen years. Chloroquine-resistant strains of *P. vivax* have been identified in some areas of Southeast Asia, New Guinea, and Indonesia.

Efforts to produce a malaria vaccine(s) have been under way for over 25 years. A number of candidate vaccines have been produced, but none are operational in humans as yet.

Dengue and Dengue Hemorrhagic Fever (DHF)

Like yellow fever, described earlier, dengue and dengue hemorrhagic fever are vector-borne diseases transmitted (primarily but not exclusively) by the mosquito *Aedes aegypti*. "Classical" dengue is caused by infection with one of the four serotypes of the dengue virus. DHF may occur following a subsequent infection with a different serotype. The following quotation is from an article written by the author in 1999 (R. Lennox and A. Arata, Dengue Fever: An Environmental Plague for the New Millennium. Capsule Report, Environmental Health Project/USAID. 8 pp.):

> With 2.5 billion people at risk and estimated cases in the tens of milllions, dengue is considered by many to be the second most important vector-borne disease in the world (surpassed only by malaria). Classical dengue and its more lethal form, dengue hemorrhagic fever (DHF), now circle the world with endemic illness and continuing threats of epidemics.
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> Dengue is very much an environmental disease, affecting urban and peri-urban settlements in more than 100 countries. It is characterized by seasonal outbreaks of illness carried by mosquitoes that thrive in household containers which collect water (such as flowerpots and washtubs) and in the detritus of human consumption, such as bottles, tin cans, and old bottles. Children, specially in Asia, are most frequently and seriously affected by the severe form of the infection, DHF.
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> Mosquito control is the only effective approach to prevention, although effective case management will reduce mortality. Insecticides targeted at larval mosquitoes are effective, but resistance of mosquitoes to affordable and

environmentally safe chemicals as well as declining will and infrastructure have all but eliminated this approach in most countries. Vaccines are in the pipeline, but a system which could deliver them to half the world's population is probably at least a decade away. Community action—to protect containers from becoming havens for mosquito breeding and to dispose of empty containers and trash, along with surveillance and personal protection—is the best hope for transmission risk reduction.

Tuberculosis (TB)

Tuberculosis is another ancient disease that has bridged the old to new definition: The TB bacillus, *Mycobacterium tuberculosis,* was among the first to be scientifically identified and described (by Robert Koch, in 1882). The disease is transmitted by airborne droplets from people with pulmonary or laryngeal tuberculosis. This mode of transmission is most effective in dense populations, and hence TB became widespread with the development of urban centers in the Middle Ages (Europe), and was very common from the 14th century until recently in Europe. With improvements in housing and nutrition TB rates continued to decline (except for periods of war) until the first half of the 20th century. At that time, two conditions emerged: the development of Multiple Drug Resistant TB (MDRTB) and the emergence and spread of Acquired Immune Deficiency Syndrome (AIDS) upon which TB is an opportunistic infection.

Prior to 1984, about 10% of TB bacilli isolated from patients in the U.S. were resistant to even one antibacterial drug: in 1984, 52% were resistant to at least one drug, and 32% were resistant to more than one drug. In the U.S. the cost of treatment of ten cases of MDRTB in Texas in 1990 was US$ 950,443. WHO lists TB as one of the major causes of mortality in the world. A new major funding effort (WHO and World Bank and various bilateral donor groups) is focusing on HIV/AIDS, TB, and malaria as the most serious, and intractable, causes of death.

Other forms of TB, including non-pulmonary cases and those associated with other species of *Mycobacterium* sp. (e.g. *M. bovis),* are sporadic, but suggest the possible very early animal origin of the pathogen group.

Chronic, Non-epidemic Pestilences

Diseases such as Chagas disease and schistosomiasis are examples of diseases that do not easily fit the epidemic definitions of a pestilence mentioned earlier in this chapter, but they do heavily impact the affected populations, not only through mortality rates, but especially through morbidity/disability.

There are several forms of schistosomiasis caused by different species of *Schistosoma*, a blood fluke (trematode)—this is an ancient illness, known from Egyptian antiquity. Infections occur in fresh water where people work and/or wash and

children play. Larval worms, known as cercaria, developed in a snail intermediate host, pass through the skin and penetrate diverse organs according to species. The most important effects are those that arise from chronic, and cumulative, infection.

Chagas disease has a very different etiology, mode of transmission, and pathology than does schistosomiasis. By definition it could be new because it was first described in 1907 by the Brazilian Carlos Chagas, who subsequently described the pathogen, a flagellate protozoan, *Trypanosoma cruzi,* and the vectors, blood-feeding triatomine bugs. The disease is also know as American Trypanosomiasis, and occurs only in the Western Hemisphere, from Mexico to Argentina—a few cases have been reported in North America. This form is very different from African Trypanosomiasis (sleeping sickness).

The initial (acute) phase of the disease usually occurs in children; there is then a long latent phase (~20 years or more), culminating later in life in a chronic phase which may include irreversible cardiac and/or intestinal manifestations and shortened life spans in the victims. PAHO and WHO consider Chagas disease to be the most serious parasitic disease in Latin America and the main cause of heart disease in the Region. There is no adequate medical intervention. The infection can be transmitted by vectors, congenitally, or by transfusion of blood or blood products. An estimated 100 million persons in the Region are at risk, and in some countries (e.g., Bolivia) 25% of the 8 million inhabitants have been shown to be seropositive. In addition, in Bolivia, one study demonstrated that the burden of Chagas disease, in terms of Disability Adjusted Life Years (DALYS), was 4 million DALYS, or estimated loss of 494 million Bolivianos: equal to more than 100 million US dollars at the time of the report (1994).

The purpose of this brief segment is to emphasize that pestilences need not carry with them only high mortality. Very high morbidity and sustained disability with all the concurrent social and economic implications can be a tremendous burden on a population—or a nation.

Puerperal Fever

Puerperal fever, a forgotten pestilence, is caused by a streptococcal infection and is an iatrogenic disease (induced by a physician) that was once the scourge of pregnant women, before physicians learned to wash their hands before examining pregnant women and/or assisting at childbirth. Improved hygiene in hospitals was concurrent with the development of the germ theory and mortality rates dropped quickly. This disease, also called childbirth fever, was never reported as one of the great pestilences, however a few figures reveal the state of scientific knowledge regarding any infectious diseases, both endemic and epidemic.

1833–1842 London Lying-in Hospital (no hand-washing): average mortality per year = 587/10,000.

1830–1840 Paris Maternitée (no hand-washing): average mortality per year = 547/10,000.
1825–1834 Dresden Maternity Hospital (no hand-washing): average mortality per year = 305/10,000.

Same general period: home delivery with midwife : estimated mortality per year = 40–50/10,000.
1831–1843 London's Royal Maternity Charity (home delivery): estimated mortality = 10/10,000.

It is frightening that not only was the incidence of puerperal fever higher in the hospitals, but so was the associated mortality: 35 % of the patients died if the disease occurred after a home delivery, but 80–90 % died if the disease was contracted in a hospital.

POTENTIAL NEW PESTILENCES (TABLE 2)

Although we have no crystal ball to predict what, if any, new pestilences are in store for mankind in the future, several groups of zoonotic viruses include likely candidates (Table 2). Also included is HIV/AIDS, truly a new pestilence that already, in a relatively brief period, has taken its place among the worst pestilences ever known to man.

Arboviruses

As mentioned above, there are over 500 **arboviruses** isolated and characterized—about 100 are capable of infecting humans, from nonapparent infections to very severe ones. Two of these have already been mentioned above (dengue and DHF and yellow fever), but the arboviruses as a group represent the source of many potentially new diseases—or, put more correctly, existing zoonotic diseases that emerge when humans accidentally become involved in their cycles. A good example is the recent outbreak of **West Nile encephilitis** in the U.S. In 1999 and 2000, the virus was isolated from/around New York City from large numbers of dead birds (especially crows and jays): 21 human cases and two deaths were confirmed. By 2001, the disease moved west toward the Mississippi River, infecting 55 people and killing nine. In 2002, there were over 2,400 cases (117 fatal); by 2003, the virus, and human cases, were found in all 48 contiguous states (excepting Alaska and Hawaii). The virus has been found in mammals, birds, and mosquitoes throughout the U.S.

But is this a new disease, or just a disease new to us? West Nile virus has been found in over 50 countries since its discovery in 1937 in Uganda, and has been

Table 2. **New Pestilences:** Examples, not comprehensive, of diseases that have become pestilent since the early 1900s, or the beginning of microbiology. This does not mean that all these diseases did not exist earlier but, rather, were not described at that time. Note that the first four listed are groups of related pathogens/diseases: the fifth (SARS/Asian flu) are placed together for convenience rather than etiology.

Disease	Etiology	Comments
Arbovirus Dengue, W. Nile, YF	Arthropod-borne mosquitoes, ticks, etc.	Any of over 500 viruses of several families that are transmitted by arthropods: approx. 100 implicated in human illness: global
Arenavirus Lassa, AHF, BHF	Rodent-borne: aerosol inhalation of rodent excreta	A family of rodent-borne viruses, (*Arenaviridae)* one each from Asia (LCM); Africa (Lassa) and several ($\sim$ 10) from the W. Hemisphere, 4 of which have been implicated in severe human illnesses.
Hantavirus	Rodent-borne: aerosol inhalation of rodent excreta	A series of viruses producing pneumonic (New World) or hemorrhagic symptoms (Old World)
Filovirus Marburg Ebola	No reservoir or vector identified to date: secretions, contaminated syringes	"Natural" cases found only in Africa; first two outbreaks were in 1976 in southwestern part of Sudan and central Zaire (Democratic Republic of the Congo)
SARS/avian flu	SARS—coronavirus; and, influenza strain H5N1: both aerosol, respiratory secretions	These two listed together only because of synchrony (2002) and location (SE Asia) of their initial occurrences
HIV/AIDS	HIV, a retrovirus: sexual contact and/or contact with other infected body fluids	Syndrome first reported in 1981, but cases in the 1970s in various parts of the world: Worldwide, WHO estimates that 4.2–5.8 people were infected with HIV in 2003: overall, Between 34–46 million are living with HIV/AIDS, of which more than 50% live in Africa, south of the Sahara

isolated from horses, bats, birds, and mosquitoes. Human disease is reported from the former USSR, the Near East, India, Indonesia, and parts of Europe.

Using North America as an example (because we have relatively good information from this area), we find numerous other arboviral—related diseases, for example:

Eastern and Western equine encephalitides,
St. Louis encephalitis,

La Crosse encephalitis,
Venezuelan equine encephalitis,
California virus encephalitis,
Colorado tick-borne fever,
and others.

Most of the above are mosquito-borne, and the major mosquito vector genera, *Culex, Aedes,* and *Anopheles,* have global representatives from which a competent vector might be found. The same is true of ticks, sandflies, and other potential vectors. Rodents, or other local vertebrates, may serve as reservoir hosts while infected migratory birds may provide distribution of the infection. Although many arboviral infections have broadly similar transmission cycles, the ecology and dynamics of each may differ widely. Arboviruses do not belong to a single viral family, but rather, to several,which increases their diversification.

Although the potential for increased arboviral epizootics or epidemics is high, the most recent episodes have not been high on the pestilence scale; rather, the most severe arboviral epidemics have been **YF** and **dengue/DHF,** the oldest of the group.

Arenaviruses

The **arenaviruses** were thought for years to be monotypic, a single species, *lymphocytic choriomeningitis (LCM),* occurring primarily in the house mouse/ laboratory mouse, *Mus musculus.* The virus (first described in 1933) has been isolated in numerous locations, but human disease is known only from Europe and the Americas. A second arenavirus was isolated from a phyllostomatid (fruit-eating) bat from Trinidad, but there was no associated human disease. Severe hemorrhagic cases in Argentina and later in Bolivia in the 1950s and 1960s resulted in the discovery of new viruses and diseases in these countries—Junin virus/**Argentine Hemorrhagic Fever** (AHF) and Machupo virus/**Bolivian Hemorrhagic Fever** (BHF). More recently, additional arenaviruses found in **Brazil (Sabia virus) and Venezuela (Guanarito virus)** produce similar hemorrhagic symptoms. AHF is the most common, 200—4,000 recorded annually between 1958 and 1995—the others are only sporadic, but mortality rates are high in all these diseases. In each of these, transmission is by contact with infected rodent excreta, dust, and other substances associated with grain harvesting and storage.

There are another five arenaviruses in the Americas that are not known to cause any illness in humans or their rodent hosts. All of the rodents associated with these viruses belong to only one of the 13 rodent families currently inhabiting South America. These rodent genera (*Calomys, Sigmodon, Oryzomys, et al),* are very closely related, and share a common ancestry. Paleontological evidence indicates that the Isthmus of Panama was a bridge connecting North and South America

more than 2–3 million years ago, allowing a faunal interchange. The sigmodont rodent progenitors entered South America at that time, and rapidly evolved into the modern genera and species. Presumably the "ancestor virus" tagged along, co-evolving into the situation that now exists.

By far the most important arenaviral disease is **Lassa Fever:** discovered in Nigeria in 1970, it is known from 15 African countries, mostly in West and Central Africa, but also Zimbabwe and Mozambique. The natural host of Lassa virus is the multi-mammate rat, *Mastomys natalensis,* one of the most common and widely distributed African field rats. Like their South American counterparts, the AHF and BHF hosts, *Mastomys,* is basically a grassland species, easily adapting to the man-made grasslands of maize, sorghum, millet, sugarcane, and other cultivated grasses. Cases of Lassa are generally associated with agricultural activities and food storage: transmission is by contact with excreta of infected rodents.

Without laboratory facilities for confirmation, it is difficult to distinguish Lassa fever from Ebola, YF, or even severe cases of malaria. There are an estimated 500,000 cases a year, with more than 15% mortality rate in hospitalized cases. The disease is more severe in pregnancy, with fetal mortality reported at more than 80%. In the early 1970s (and before Ebola outbreaks occurred), Lassa caused great consternation in Europe and the Americas over the possibility of introduction of this disease. These concerns still exist and have been heightened after the appearance of these other groups of viral hemorrhagic diseases.

Hantaviruses

The **hantaviruses** are comprised of two large groups of viruses, all transmitted by rodents and producing a range of hemorrhagic, renal, and/or pulmonary complications. The **Old World Hantaviruses** are comprised of over 20 different viruses, several known for some time under a different classification (e.g., Hanta virus is the cause of Korean hemorrhagic fever with renal syndrome, an important military disease in the 1950s). Most cases still occur in agrarian and military populations and occur in over 50 countries in Asia, Africa, and Europe: each year approximately 200,000 cases occcur in Eurasia, with more than 50% of these reported in China. Case fatalities range from 0.1% to 10.0% depending on the virus. The 15 or so **New World Hantaviruses** produce a pulmonary, rather than a renal, syndrome. Since being described as a group in 1993**,** approximately 1,000 cases have been reported in the Americas, with a high case fatality rate (45–50 %).

The natural hosts/reservoirs for the hantavirus groups are mostly muroid rodents (Old World Group), and cricetid rodents (New World Group). This is not surprising, as these two are amongst the largest and most widely distributed mammalian families. However, the manner and zones of transmission are similar—rodent contamination of grain crops in the field and storage where people come in contact with rodent excreta.

Filoviruses

The two closely related **Filoviruses (Marburg and Ebola)** are among the most virulent viruses yet described with an overall fatality rate of more than 75%, and higher in several outbreaks (possibly augmented by use of dirty syringes and needles to give injectable chloroquine (an anti-malarial drug) to the patient's friends who carried him/her to the hospital. **Marburg virus** was first described (1967) among monkeys sent from East Africa to European laboratories, there killing laboratory technicians. Subsequent outbreaks have occurred in Africa. **Ebola virus** appeared in 1976 in simultaneous outbreaks in Zaire (Democratic Republic of Congo). (Barry, 2004) One Ebola strain was implicated in an outbreak in an animal holding facility in Reston, Virginia, U.S.A. Several humans seroconverted but showed no disease symptoms.

The repeated outbreaks of Ebola and Marburg virus, mostly in Central Africa, have been described as commencing with "rapidity and devastation." During an epidemic, transmission is generally by contact with contaminated blood or other tissues from infected persons. Most outbreaks have been in rather remote areas with poor health care facilities, so that patients are seen only with advanced symptoms. We have not been able to find reservoir organisms (there have been subsequent, better equipped expeditions than the one described in the footnote, but none have been successful), nor do we know the mechanism(s) of transmission in the wild. One distinct Ebola virus strain from Ivory Coast was isolated from a chimpanzee: primates are hunted and eaten by humans in parts of Africa and this may serve as the 'link' at which the virus(es) are able to "cross the species barrier" and enter the human population.

(Barry, 2004) The Government of Sudan requested WHO assistance, and the Government of Zaire requested the same from the U.S. Government (CDC). Representatives of WHO and CDC met in the next few days at the London School of Hygiene and Tropical Medicine to work out details and coordination (WHO was represented by Dr. Paul Bres and the author, and CDC by Dr. Karl Johnson). We had all thought of Lassa and Marburg viral fevers, and were surprised when Dr. Johnson said it was neither: He then showed us electron photomicrographs of tissue taken from an early case—the stringlike "6 and 9" figures were just like Marburg. But, he explained, this one was serologically distinct from Marburg, and they proposed to name it after a river in the area, the 'Ebola'.

We agreed that I (AAA) and a virologist (Dr. Bruce Johnson) from the LSHTM would go to the site in Sudan to sample potential reservoirs and/or vectors. Bruce would bring the supplies needed for taking tissue samples and the liquid nitrogen containers needed to return the samples to the UK. I was to gather the animal collecting materials. WHO had no such equipment in Geneva, of course, so I borrowed 'mist' nets for collecting bats from the British Musum (Natural History) and the Museé d' Histoire Naturelle in Geneva and borrowed sample rodent traps from the Swiss Agricultural Research Station in Nyon, near Geneva. We had the traps made in Nzara, one of the sites of the outbreak in Sudan. To autoclave the dissecting instruments we purchased two household 'pressure cookers' at the local super market (Migros) in Geneva. Placed on stones over an open fire, they served well.

An experimental Ebola vaccine has been reported to be successful in trials with non-human primates. Human trials will be conducted soon.

SARS and AAI

Two previously unknown and unrelated human viral infections, **Severe Acute Respiratory Syndrome** (SARS) and an **Asian Avian Influenza (strain H5N1),** originating in Southeast Asia, have received a great deal of popular attention and public health concern. In November 2002, cases of a respiratory illness, subsequently labeled **SARS**, appeared in China. A delay in timely reporting of the initial cases allowed it to spread to other Southeast Asian countries, Australia, the Americas, and at least 10 European countries. Reports of the actual number of persons infected varied, but cases numbered in the thousands, and mortality rates of up to 15% were indicated. Surveys of wild animals captured for human consumption quickly showed that ferrets, civets (related to mongooses), and raccoon dogs (shaggy fox-like carnivores) were positive for harboring the virus, but it is not known if any of these are the true reservoir in nature. The WHO has reported that the chain of transmission may have been broken (no new cases reported in a period of time equal to two consecutive 10 day incubation periods). This is clearly a case of a virus "species jumping". In the world's largest, most densely populated country this could spell disaster, especially if the reporting network is compromised.

The **Asian Avian Influenza** strain initially appeared in poultry in Hong Kong in 1997, when it jumped the species barrier and killed 6 out of 18 infected persons. This recent outbreak spread to Korea (December, 2003), then Japan and Vietnam (January 2004). Hong Kong reportedly slaughtered 1.4 million chickens and ducks, and as many as three million slaughtered through the Southeast Asia region, but other reports indicate that there are nonspecific wild variants of this strain in wild birds that serve as natural reservoirs.

Of major concern is that outbreaks of highly pathogenic avian influenza are increasing in frequency and severity. Reportedly, in the 40 years from 1959 to 1998, there were only 17 outbreaks, but in the past six years, from 1997 to 2003, there have been six, not including the most recent incidents.

HIV/AIDS

If bubonic plague was the quintessential pestilence of the ancient and medieval worlds, **Acquired Immunodeficiency Syndrome,** caused by the **Human Immunodeficiency Virus (AIDS/HIV)** is the chief pestilence of the modern world; and it is still growing, not receding. There is also a vast literature that will not be reviewed here, but the following 2003 data points describe the severity of the pandemic pestilence:

- AIDS is gaining a firmer foothold in the large populations of India and China;
- World wide, 40 million people are infected with HIV;
- 25–28 million of these infected people live in sub-Saharan Africa;
- 5 million persons became infected this year, 700,000 are children;
- 3 million persons died of AIDS this year, 500,000 of them less than 15 years old;
- Existence of Simian Immunodeficiency Virus (SIV) suggests animal origin.

The social damage accompanying this pandemic is not reflected in the bare figures given above; especially the orphaned children, destroyed family structures, and so forth. It has been estimated that 10 billion dollars US, per annum, is required to provide the prevention and treatment facilities and services needed: To date, less than one-half ($4.7 billion per annum) has been made available.

CLOSING OBSERVATIONS

Some of the old category diseases are still strongly with us (e.g., malaria, TB, influenza), and, by adapting traits such as drug-resistance and crossing or jumping species, they expand their reservoir-host base. As such, they could be considered new. Some other old diseases are rather well controlled in the developed countries where the surveillance systems are efficient and vaccination and other preventive services are readily available and properly used. These would include smallpox (eradicated), polio (eradicated in some areas), and childhood illnesses such as pertussis, diptheria, tetanus, measles, and so on. Even bubonic plague could be characterized as being under control—it is widespread, but also well understood, and with vector control and appropriate antibiotics, outbreaks are not severe and mortality is low.

On the other hand, some of the new (most recently discovered) diseases like Ebola and HIV/AIDS are hard to handle. We know little about the natural history of Ebola, Lassa, or the South American hemorrhagic fevers, and our knowledge of HIV/AIDS in the laboratory probably exceeds our understanding of the socio-economic impacts it is having on whole cultures.

When Lassa virus "jumped" from the field rat, *Mastomys,* to humans it was dreadfully virulent, and it seemed to come from nowhere. But, after a few years, we know that (with one exception from a bat) all arenaviruses are well adapted to particular rodent groups; most rodents are grass eaters, and lots of crops are grasses (wheat, maize, sugarcane, rice, etc.); therefore, the arenaviral fevers are seen primarily in agricultural settings and with stored grain. Yet, for the more

recently known Hantavirus group, or even less with the multiferous arboviruses, we do not have good data on ecological determinents, or even host-reservoir relationships.

At the same time, people are modifying environmental conditions rapidly and extensively, and we have little information indicating whether such changes will eliminate potential disease cycles or exacerbate them. This may be even more important for diseases like influenza. If they have obligate or opportunistic vertebrate hosts and these are coincidentily reduced in number or eliminated, what selection pressures are set in action on the virus population to select new hosts? And when it comes to modifying environments, man has no equal. Yet we know that this microbial evolution is going on at a rapid pace—just look at how fast drug-resistance develops and spreads!

In reading articles and researching references for this document, I was amazed to discover again how many human illnesses have their direct animal (zoonotic) counterparts, or were vectored/hosted by arthropods, rodents, or snails, and how an avian influenza can become a mammalian influenza very quickly, and how a bat or an oppossum can do the same for the Chagas disease trypanosome. It is in this context that I feel that we know very little of the natural history or the ecological dynamics of the disease transmission cycles we teach.

Especially disturbing is to read of a new strain of Asian avian influenza and the necessity, around the world, to kill millions of birds. If one was to dream up a model pathogen incubator and dissemination engine, the perfect model would be a modern chicken farm of 500,000 birds, defecating as birds do, and that at a constant temperature and with residues of organic chicken feed all about. And we wonder why new diseases emerge? Any farmer worth his/her salt knows that monoculture breeds pests.

This is a good place to bring up one other difficult subject—bioterrorism. It is difficult for one dedicated to public health principles to imagine why anyone would even consider using infectious diseases as a weapon, but it is being done, and we need to be able to distinguish between a natural epidemic and one orchestrated by man. Again, knowledge of the natural history of the organisms, their natural hosts and reservoirs, will help.

Already the U.S.A. is stockpiling smallpox and anthrax vaccines in large quantities.

One final point; most people concerned with new versus old pestilences work as epidemiologists, infectious disease specialists, hospital officials, and so forth. But public health work is broader than the study and treatment of infectious diseases, and the study *The Global Burden of Disease,* sponsored by the WHO, World Bank, and Harvard University, based on measuring DALYS, predicts that fewer infectious disease will be as important in the future as they are at present. For example, "The next two decades will see dramatic changes in the health needs of

the world's populations, and non-communicable diseases such as depression and heart disease . . . are replacing the traditional enemies, such as infectious diseases and malnutrition."

Maybe toxic smog and non-communicable diseases will replace pestilences, both old and new!

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