

Emerging and re-emerging zoonoses

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INTRODUCTION

After world war II it was widely believed that human-kind was winning the battle with the microbial world due to the advent of safe and antimicrobial compounds against diseases, such as tuberculosis and typhoid; vaccines against polio, diphtheria and pertusis; vast improvements in public sanitation and water/food quality; and effective chemical pesticides to control insect vectors of disease. In 1969, an American surgeon (William H. Stewart) even declared to the congress that: "it is time to close the book on infectious diseases, declare the war against pestilence won..."(1).

However, world wide infectious and parasitic diseases still cause untold suffering and enormous physical, economic and social toll on human existence, causing 33% of deaths world wide, with more than half of the victims under the age 5 years. But the figure is much higher in developing countries. For example, in Africa it is estimated that 68% of all deaths are as the result of infectious diseases (2). The actual burden of infectious disease deaths and illness may even be higher as an increasing body of evidence indicates that infectious agents may play a significant role in the etiology of a wide range of chronic disease

conditions, including cardiovascular diseases, chronic pulmonary disease, arthritis, and cancer.

In 1992, "new, reemerging or drug-resistant infections whose incidence has been increased within the past two decades or whose incidence threatens to increase in the near future" were defined as "Emerging Infections" (3). Previously, zoonoses were defined as "diseases and infections which are naturally transmitted between vertebrate animals and man". Thereafter, WHO noted zoonotic diseases caused either by totally new or partially new agents, or by microorganisms previously known, however, now they are appeared in places or in species where the disease was previously unknown, called emerging and re-emerging zoonoses.

While the burden of human illness due to infectious agent is the result of well-known infectious agent with human reservoirs, the majority of infectious agents known to afflict human are zoonotic. Zoonoses are diseases of animals that can also infect humans. Taylor et al catalogued 1709 species of infectious agents reported to cause disease in humans, including viruses, prions, bacteria, rickettsia, fungi, protozoa and helminthes among which 832 (49%) were considered zoonotic, 156 (9%) "emerging" disease while 114 (73%) were zoonotic (4). One year later, he and his colleagues reclassified the human infectious agents and noted 1415 species, of which, 868 (61%) were considered zoonotic, 175 (12%) "emergent" diseases, while 132 (75%) were

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zoonotic (5). Thus, while a majority of infectious agents affecting humans are zoonotic, an even greater majority of emerging agents are zoonotic. Animals would not only serve as a significant reservoir for infectious agents, but also serve as a wellspring of new infectious agents introduced into the human population.

In general, an emerging disease is either new to science or is an existing disease with incidence increasing in a given place or population, such as West Nile Virus (WNV) in north America (an agent which gains the ability to infect new hosts), the highly pathogenic H₅ N₁ avian influenza (which has caused hundreds of human cases in several countries since 1997 and 2004), or agents which evolve into new strains, such as the various antibiotic resistant strains of staphylococcus aureus (1). In the past four decades, emerging disease episodes have been increased worldwide. Examples of emerging diseases include the human immunodeficiency virus (HIV), Ebola virus, severe acute respiratory syndrome (SARS) virus, the highly pathogenic H₅N₁ avian influenza virus, bovine spongiform encephalopathy (BSE-mad cow disease), antibiotic resistant staphylococcus aureus, and antibiotic resistant mycobacterium tuberculosis. A preponderance of these agents are either directly zoonotic or, like HIV, have zoonotic origins. The list of important emergent diseases is impressive. Nearly all of these emerging disease episodes have involved zoonotic infectious agents, while, they have involved the transmission of the etiologic agent to humans from an ongoing reservoir life cycle in animals or arthropods, without the permanent establishment of a new life cycle in humans. Fewer episodes have involved species-jumping by the etiologic agent. They derive from an ancient reservoir life cycle in animals but have subsequently established a new life cycle in humans that no longer involves an animals reservoir (6).

Below some major bacterial etiologic agents of new zoonoses identified since 1976 are listed:

1976: *Capnocytophaga canimorsus*
1977: *Campylobacter* Spp.
1982: *E. coli* O157: H7
1982: *Borrelia burgdorferi* (Lyme disease)
1983: *Helicobacter pylori* and other Spp.
1986: *Ehrlichia chaffeensis* (Human Monocytic Ehrlichiosis-HME)
1992: *Bartonella henselae* (cat scratch disease-CSD)
1994: *Rickettsia felis* (murine typhus like)
1994: *E.equil A.phagocytophila* (HGE:Human Granulocytotropic Ehrlichiosis)

Meanwhile, some major viral etiologic agents of new zoonoses identified since 1990 are presented below:

1991: Guanarito virus (Venezuelan hemorrhagic fever)
1993: Sin Nombre virus (Hantavirus pulmonary syndrome)
1994: Sabia virus (Brazilian hemorrhagic fever)
1994: Hendra virus (Equine morbillivirus)
1996: Anstralian bat lyssavirus (Rhabdovirus)
1997: Menangle virus (Paramyxo virus)
1997: Influenza virus H₅ N₁ (Hong Kong)
1998: Nipah virus (Paramyxo virus)
1999: Influenza virus H₉ N₂ (Hong Kong)
2002: SARS virus (Corona virus) (Severe Acute Respiratory Syndrome)

Disease Emergence

Many factors may contribute to the emergence of a new zoonotic disease, including microbial/ parasitological/virologic determinants such as mutation, natural selection, and evolutionary progression; individual host determinants such as acquired immunity and physiologic factors; host population determinants such as host behavioral characteristics and social, commercial, and iatrogenic factors; and environmental determinants such as ecologic and climatologic influences (6).

In a book published by The Institute of Medicine (IOM), a "Convergence model" of

infectious disease emergence was proposed that consists of four broad domains of factors that influence pathogen-host interactions and the resulting emergence of new diseases. They were:

- 1-Genetic and biologic factors
- 2-Physical and environmental factors
- 3-Ecologic factors
- 4-Social, political, and economic factors

Within these 4 broad domains, the IOM identifies 13 more specific factors that belong to one or more of these domains. These specific factors consist of:

- 1-Microbial adaptation and change
- 2-Human susceptibility to infection
- 3-Climate and weather
- 4-Physical events
- 5-Changing ecosystems
- 6-Economic development and land use
- 7-Human demographics and behavior
- 8-Technology and industry
- 9-International travel and commerce
- 10-Breakdown of public health measures
- 11-Poverty and social inequity
- 12-War and famine
- 13-Lack of political will

In addition, the harm by bioterrorism (such as the 2001 anthrax terrorist attacks in the United State) should be added (7).

Emergence of new zoonotic pathogens seems to be accelerating for the following several reasons: global human and livestock animal populations have continued to grow, bringing increasingly larger numbers of people and animals into close contact; transportation has advanced, making it possible to circumnavigate the globe in less than the incubation period of most infectious agents; ecologic and environmental changes brought about by human activity are massive; and bioterroristic activities, supported by rogue governments as well as organized amateurs, are increasing, and in most instances the infectious agents of choice seem to be zoonotic (6).

In general, there is no way to predict when or where the next important new zoonotic pathogen will emerge or what its ultimate importance might be. A pathogen might emerge as the cause of a geographically limited curiosity, intermittent disease outbreaks, or a new epidemic. No one could predict the emergence or zoonotic nature of the BSE prion in cattle in the UK in 1986, the emergence or zoonotic potential of Sin Nombre Virus as the cause of hantavirus pulmonary syndrome in the southwest USA in 1993, and certainly not the species-jumping emergence of HIV as the cause of AIDS in 1981. Consequently, investigation at the first sign of emergence of a new zoonotic disease is particularly important, although the investigation usually resembles a field- and laboratory-based research project rather than a typical case-control-based outbreak investigation. This reality must drive strategic planning for dealing with new zoonotic diseases.

The factors and mechanisms discussed above have likely affected the emergence, distribution, and prevalence of zoonotic diseases in the world. The following factors may also play roles in this regard: human demographic and behavior, international travel and commerce, complications of modern medicine, microbial adaptation and change, and the breakdown of public health measures. Some emerging diseases are associated with environmental changes that occur with economic or agricultural development or changes in land use patterns (8). Certainly, the development and growth of cities fueled by an influx of migrants can foster the establishment of a new infection in a population. Once established in a crowded urban area, a disease can easily take root and can be extremely difficult to eradicate. Other human activities that disturb natural ecosystems, including road-building, logging, and irrigation projects, can also bring humans into new areas while displacing microbes that must then seek out new hosts. Changes in local climate, such as drier, wetter, or

warmer periods, can extend the range of mosquitoes and other disease vectors (9).

On the other hand, in areas where populations are rapidly expanding beyond the capacity of the local water-food supplies, waterborne and food-borne infections can be expected to create serious outbreaks of disease. Bacteria, viruses, and parasites can all thrive in untreated or inadequately treated water system by contaminated feces. In 1993, USA experienced one of the largest outbreaks of waterborne disease ever reported. An estimated of 403,000 people in the Milwaukee, Wisconsin, were stricken with zoonotic cryptosporidiosis, a parasitic infection that causes severe diarrhea and is found increasingly in unfiltered raw water. Of 44,000 people sought medical attention, more than 4,000 were hospitalized. City public health officials surmise that heavy rains, snowmelt, and run off from nearby farms may have overloaded the city's water treatment plants. Cryptosporidia are resistant to chlorine and must be removed from water supplies by mechanical filtration. Also, food-related illnesses and death in the world are increasing, in the USA, it is estimated that annually food-borne diseases cause approximately more than 76 million illnesses, 325,000 hospitalizations and 5000 deaths (10). Some of the factors that contribute to the epidemiology of food-borne diseases are: diet, commercial food service, new methods of food production, new or reemerging infectious agents, ethnic preferences, and "high-risk" populations, especially increase of immunocompromised individuals (up to 20%). Meanwhile, factors associated with the "Globalization" of food-borne diseases include: water, animal feeds and manures, workers, transportation, rodents, other wildlife, insects, and food processing (11).

Some of these diseases will be discussed in brief.

Hantavirus: Hanta virus, one of the newest diseases, causes different symptoms (hemorrhagic fever, abdominal pain, or respiratory infection)

depending on the strain of the virus. It appears in areas where litter and trash abound and rats and mice nest (12). More than 100,000 cases have been reported in China. The disease is also found elsewhere in Asia and in Scandinavia, the Balkan region, much of Europe, and recently in the United States (12).

The recent hantavirus outbreak in the Southwestern United States has been linked to a change in ecological conditions. The strain that hit New Mexico in 1999 causing a frequently lethal respiratory infection was transmitted by inhalation of airborne droplets of rodent urine and feces. Between 1989 and 1993, an unusually wet and mild winter led to increased adult rat and mouse survival and, in turn, an increased rodent population in the spring. As competition forced the rodents beyond their normal habitat in search of food, human contact with infected animals (and, hence, with the virus) increased (13).

In the United States, by June 1995, the CDC had confirmed 110 cases in 23 states, 50.9% of these were fatal. As the diagnostic tests are available for hantavirus infection, it is clear that infection is more wide spread than was initially expected and that the virus has probably been around for a long time (14). In 1997, more than 164 cases in USA and more than 400 in Americas with mortality rate of 45% had been confirmed.

Rift Valley Fever (RVF): Some infectious diseases have been linked to the ecological changes brought about by dam construction, indeed, dams change the water flow and can cause water to puddle and serve as breeding sites for mosquitoes. In Senegal, the construction and activation of Diama Dam is believed to have led to the introduction of RVF, a disease never before seen in the region. Surprisingly, one third of inhabitants were found to have antibodies to the virus. Still, near the village of Keur Mecene upstream from the dam, 1987 epidemic caused 244 human deaths and more than 1,200 illnesses, as well as spontaneous abortion in sheep and cattle (14).

Dengue: Dengue virus, which is now the most important and fastest growing insect-borne viral infection in the world, is transmitted primarily by the *Aedes aegypti* mosquito. The mosquito vector that transmits dengue multiplies in any small pool of stagnant water, especially in discarded tires or other detritus that may result from life in overcrowded urban areas. The disease, also known as "break – bon fever", produces severe headache and disabling pain in muscle and joints. A far more serious form of the disease, hemorrhagic dengue fever or dengue shock syndrome, has a 40 to 50 percent fatality rate if left untreated (15).

In 1993, some 23,000 deaths from dengue and 250,000 cases of dengue were officially reported to WHO, a substantial increase over previous years. During the 1960s, dengue typically averaged about 30,000 cases per year, from 1985 through 1989, nearly 1 million cases were reported. However, even these numbers are likely to be underestimated, for every confirmed case of dengue, officials suspect that there are four additional cases that have either not been reported or have been misdiagnosed. In poor urban areas in the tropics, where mosquito-control programs are sparse or nonexistent, dengue is becoming an enormous problem. In Southeast Asia, dengue hemorrhagic fever (and dengue shock syndrome) is one of the leading causes of hospitalization and death among children. In many parts of the Latin America, dengue has reached epidemic proportions, even though the disease was believed to be nearly eradicated in the 1960s. In addition, hemorrhagic dengue fever is increasing in incidence. Brazil has been hardest hit, with 88,039 confirmed cases of dengue and 105 cases of hemorrhagic dengue fever in the first 9 months of 1995, the year's unusually long wet season and high number of hurricanes are supposed to be contributing to the severity of the epidemic, providing fertile breeding grounds for the *Aedes aegypti* mosquito (14).

Ebola virus: If the public needed a reminder that a deadly, infectious disease could emerge at any

moment, they got one in the spring of 1995. Reports began trickling out of the city of Kikwit, Zair, that the local hospital was being swamped with cases of hemorrhagic fever. Both WHO in Geneva and the CDC in Atlanta sent teams of experts to evaluate the outbreak, but even as the teams were arriving in Kikwit, blood samples that had been sent to the CDC confirmed that the illness was caused by the Ebola virus (16).

Although extremely deadly, the Ebola virus is not easily transmitted. Close contact with blood or other body fluids appears to be necessary. The CDC and WHO teams trained local health workers in proper infection control procedures, including the use of masks and gloves, and the need to sterilized needles and surgical instruments. Local Red Cross warned people not to perform a traditional burial ritual, which would expose them to infected body fluids. After several nervous weeks, WHO officials appeared confident that the epidemic was under control, although nearly 250 people died in the outbreak (17). Health officials were especially relieved that the epidemic did not spread to Kinshasa, the capital city of 4 million less than 250 kilometers away. But it certainly could have.

The Ebola virus outbreak appeared to begin in the winter of 1994–1995, but it was not recognized until several months later. The illness has an incubation period of up to 3 weeks, although it may often be 1 week or less. During this time, the patient has no symptom. It is easy enough to imagine a truck driver or riverboat captain becoming infected and bringing the disease into the capital before showing any symptoms and then swiftly spreading the disease to others. If the disease had not been recognized promptly when the patients began showing symptoms and were therefore most infectious, the capital could easily have had a public health disaster on its hands. And the disease could even conceivably spread to other parts of the world via air travel.

The illness caused by the Ebola virus is just one of a number of new diseases such as hantavirus that has emerged in recent years or that has "reemerged" in a new location or a more dangerous form. This phenomenon has sparked alarm among health officials worldwide. Although new diseases like that caused by the Ebola virus capture headline, the death toll from the latest outbreak fortunately remained in the hundreds.

West Nile Virus (WNV): The West Nile Virus arrived in Texas, USA, in 2002, first in the mosquito vector and avian reservoir populations, then spilled over into equine and human populations. Temperature, rainfall, human behavior and living conditions, immunologic naivety within the animal and human populations, land use, and other factors play a role in the ongoing distribution, prevalence, and incidence of the disease. For example, clogged rain gutters, storm drains, and other water-collecting items associated with urban and suburban environments create extensive breeding habitats for *Culex quinquefasciatus*, the predominant mosquito vector species of WNV in the eastern and southern parts of Texas. Irrigation canals in the El Paso area and the Texas Panhandle provide increased breeding habitat for *Culex tarsalis*, the predominant vector of WNV in those areas. Socio economic, cultural, and behavioral factors, among others, also affect the incidence of WNV infection (2,18,19).

Equine morbillivirus (EMV): In 1994, horses on a property in Queensland, developed acute respiratory distress with hemorrhagic manifestation and 14 of 21 infected horses died. A horse trainer and a stable-hand became ill after nursing a sick horse, while the trainer died. The disease was found to be caused by a previously unknown morbillivirus. Remarkably, in 1996 fruit bats (flying foxes) were found to be the natural host of the virus (6).

Venezuelan Equine Encephalitis (VEE): In 1971, as the virus of VEE crossed from Mexico into Texas, agricultural disease control authorities were

prepared to start shooting and burying horses in a massive slaughter campaign. Scientist from CDC and the Middle America Research Unit (at the time a Unit of National Institutes of Health) provided the virologic and epidemiologic base to override the sanitary rifle strategy of agricultural authorities, and the US Army provided its new TC83 vaccine. But, again in 1995, VEE epidemics had progressed from Venezuela and Colombia and jumped over the north (6).

Monkeypox virus: In 2003, a Texas animal dealer imported a large shipment of wild-caught animals, primarily rodents, from Ghana in west Africa. An unknown number of these animals were infected with Monkeypox virus, an orthopoxvirus closely related to smallpox. A second animal dealer purchased some of these animals, transporting them to Iowa in an enclosed van with wild-caught prairie dogs. The prairie dogs became infected with monkeypox and were then sold or bartered to the public throughout several states, leading to 72 probable and confirmed cases of monkeypox in humans. This outbreak illustrates the risk of disease translocation associated with the international trade in animals and animal products (2,6).

BSE Prion: Bovine spongiform encephalopathy (BSE) was first diagnosed in the United Kingdom in 1986, as of 1997, more than 170,000 cattle had been reported to be infected, but modern statistical methods have indicated that about one million cattle had been infected, roughly half of which entered the human food chain in the UK In 1995. The BSE agent "prion" was reported to be the cause of a new human zoonotic disease, new-variant Creutzfeldt – Jakob disease (6).

CONCLUSION

In addition to examples mentioned above, many emerging and reemerging infections are zoonoses that have emerged because *Homo Sapiens* and its domestic animals are coming into contact with infectious agents that were not contacted with

before or those we haven't seen for a long time. In all cases, one of the most important points is the need for greater epidemiologic resources and better trained professionals for dealing with human and animal diseases or with the zoonotic interface. This training component requires consideration of all steps along the discovery – to – control continuum. Finally, in 1934, Hans Zinsser, an eminent professor of bacteriology at Harvard University wrote in his book "Rats, Lice, and History": "Infectious disease is one of the few genuine adventures left in the world. The dragons are all dead and the lance grows rusty in the chimney corner About the only sporting proposition that remains unimpaired by the relentless domestication of a once free living human species is the war against those ferocious little follow creatures, which lurk in the dark corners and stalk us in the bodies of rats, mice, and all kinds of domestic animals, which fly and crawl with the insects, and waylay us in our food and drink and even in our love". Which is still true.

REFERENCES

1. Nelson R. Antibiotic development pipeline runs dry. New drugs to fight resistant organisms are not being developed, experts say. *Lancet* 2003;362(9397):1726-7.
2. Fonken E. Mechanisms of disease emergence. *The Epilink* 2008;65(3).
3. Anonymous. Microbial threats to health. Institute of Medicine Press, USA. 1992.
4. Taylor LH, Woolhouse MEJ. The threat of emerging infectious diseases spreading among people and other animals. International Conference on Emerging Infectious Diseases. Atlanta, GA, USA, July 16-19, 2000.
5. Taylor LH, Latham SM, Woolhouse ME. Risk factors for human disease emergence. *Philos Trans R Soc Lond B Biol Sci* 2001;356(1411):983-9.
6. Murphy FA. Emerging zoonoses. *Emerg Infect Dis* 1998;4(3):429-35.
7. Anonymous. Microbial threats to health; Emergence, detection, and response. Institute of Medicine, National Academies of Sciences, National Academies Press, USA. 2003.
8. Stephen SM. Regulating viral traffic. *Issues in Science and Technology* 1990;7(1):84.
9. Wilson ME. Anticipating new diseases. *Current Issues in Public Health* 1995;1:90-94.
10. Anonymous. Addressing emerging infectious disease threats: a prevention strategy for the United States. Executive summary. *MMWR Recomm Rep* 1994;43(RR-5):1-18.
11. Chomel BB, editor. Control and prevention of emerging zoonoses. *Agenda for action: Veterinary medicine's role in biodefense and public health (AAVMC)*. Washington, DC. USA, 2002.
12. Leduc JW. Hantaan (Korean hemorrhagic fever) and related rodent zoonoses. In: Stephen S, editor. *Emerging viruses*. Oxford University Press, New York, 1993;p:149-58.
13. Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* 1995;1(1):7-15.
14. Anonymous. World resources 1996-97: The urban environment. World resources institute, UNEP, UNDP, and World Bank. 1997, 1-8 Nov., p:1-3.
15. Robberson T, editor. Dengue fever epidemic spreads despite Latin America efforts. *Washington Post*, 1995, October 20.
16. Centers for Disease Control and Prevention (CDC). Update: outbreak of Ebola viral hemorrhagic fever, Zaire, 1995. *MMWR Morb Mortal Wkly Rep* 1995;44(20):399.
17. WHO. Ebola hemorrhagic fever. *Weekly Epidemiological Record* 1995;70:241.
18. Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. *JAMA* 1999;281(1):61-6.
19. Reed KD, Meece JK, Henkel JS, Shukla SK. Birds, migration and emerging zoonoses: west Nile virus, Lyme disease, influenza A and enteropathogens. *Clin Med Res* 2003;1(1):5-12.