

Emerging Infectious Diseases¹

HV Fineberg and ME Wilson

Institute of Medicine
fineberg@nas.edu

Harvard School of Public Health
mewilson@hsph.harvard.edu

I. Introduction: the evolutionary context

Emerging infectious diseases are one category of emerging risks that could have important consequences for human populations – microbial predators are as threatening to human survival and wellbeing as the macro-scale predators. The microbial world is defined by its tiny scale, invisible to the naked eye, and embraces viruses, bacteria, archaea, fungi, prions, and protozoa, each analogous to the more familiar macro-scale kingdoms of plants and animals. Although the evolutionary origin of viruses is uncertain (no fossil record), bacteria have been evolving for 4 billion years. The animal kingdom—including the recent arriviste, *Homo sapiens*, which first appeared about 50-100,000 years ago—has co-evolved with the microbial world from the outset of its existence.

Whenever living organisms co-exist in the same ecological space, they may have one of three types of relationship:

- i. Independent co-existence
- ii. Symbiosis (mutual, benign exploitation)
- iii. Dependence (unidirectional exploitation, with one benefiting and the other experiencing varying degree of harm from none to mortal: feed on or be fed upon)

Mutual or unidirectional exploitation generally serves one or both of two biological processes: (1) nourishment, to obtain energy to survive, grow, and reproduce; and (2) reproduction, the point of the evolutionary exercise.

Most human interaction with the microbial world is either independent co-existence or benign mutual exploitation. The gut of every human being contains thousands of microbial species (many uncharacterized) and billions of organisms -more individual microbes in each human gut than there are humans on the face of the planet. The microbiome resident in the human gut confers nutritional and immunological benefits and aids resistance to some pathogens. These intestinal organisms illustrate the difference between colonization (presence that is not harmful) and infection (disease-producing). The same organism may in one location of the body (gut, skin) be a colonizer, while in another location (bloodstream, heart valve) a source of infection.

In this co-evolutionary light, infection represents an exception to the usual interaction of humans (and other animals and plants) with the microbial world. To infectious viruses, human (or other host) cells provide the machinery for reproduction. To infectious bacteria and fungi, the human or other host is a source of nourishment.

¹ This paper accompanies the IRGC report “The Emergence of Risks: Contributing Factors” and is part of phase 1 of IRGC’s project on Emerging Risks. More information can be found online at <http://irgc.org/Project-Overview.219.html>

Animals and humans have evolved a series of mechanisms to defend against infection, including physical barriers (skin) and a sophisticated immune system that can detect, disable, and destroy invading organisms. The various microbial kingdoms can also threaten one another, and, to help protect themselves, bacteria, fungi and plants may develop and express microbial toxins. The term “antibiotic” applies to such naturally produced substances, which are a subset of the more inclusive category of “antimicrobials.” Some antibiotics, such as penicillin, have been utilized for treatment of infection in humans and animals.

Although this paper focusses primarily on the direct adverse consequences of microbes to humans, infections of food crops can indirectly threaten human health and wellbeing. A rapidly spreading infection of a major food crop, such as rice, wheat, or cassava, could threaten the food security of large populations, especially those who have marginal resources and are already vulnerable. Pathogens and vectors that spread plant diseases can be dispersed long distances by trade (e.g., movement of seed, produce, contaminated products) and travel (e.g., accompanying humans in contaminated soil on shoes or in luggage). Whiteflies, an important vector for plant diseases, can be transported in trucks, airplanes, and other vehicles.

Diminished food production can lead to malnutrition, which makes individuals more susceptible to many infections, and to death by starvation. Famine can precipitate migration of populations, economic instability, political unrest, and conflict.

Today many of the plants grown for food are genetically similar, bred for high yield in a broad range of environments. Because of lack of genetic diversity in food groups, large areas of crops would be at risk from a competent, new pathogen or newly well-adapted form of an old pathogen.

II. Emerging infectious diseases: definition, source, and spread

An emerging infection is one that is newly recognized as occurring in humans (they can also affect animals and plants), newly appearing in a different population than previously affected, (though previously recognized) is newly affecting many more individuals, or has evolved new attributes (e.g., resistance or virulence). Perhaps it would be more precise to describe these as “emerging, re-emerging, and recrudescing” infections. From the risk point of view, all are relevant.

Emerging infections in humans tend to be caused by microbes that are established in vertebrate animals and have crossed the species barrier to infect humans. Such animal to human transmission is termed a zoonotic infection or zoonosis. Typically, there may be a number of instances of cross-species events before an organism becomes established in the newly infected species. For our purposes, the potentially newly infected species of greatest concern is the human. Wildlife (e.g., bats, nonhuman primates) and food animals (e.g., poultry, swine, and cattle) have been sources of zoonoses. Some animal microbes only occasionally spill over into the human population under an unusual confluence of circumstances (e.g., Nipah virus from bats); others have become well adapted to the human host (e.g., the retrovirus, human immunodeficiency virus) and now are sustained by human-to-human transmission without the need for reintroduction from the animal reservoir (e.g., primates). Many well known human pathogens, such as the measles virus, emerged from related animal viruses in the remote past.

Infections described as emerging recently are caused by many classes of agents (bacteria, fungi, protozoa, helminths, prions, viruses) and have many different routes of transmission. The most prominent emerging pathogens globally have been viruses that spread from person to person, typically by inhalation, sexual exposure, or direct contact to mucous membranes (e.g., HIV/AIDS, SARS, influenza viruses. Infectious disease deaths globally by mode of transmission include: person-to-person 65%; food/water/soil 22%; insect/vector 13%; directly from animal <1%. [WHO, 1996]).

For an infectious disease to emerge in the human population, something has to change in the ecological balance, and these changes constitute the principal contributing factors to risk emergence. In general, these factors deal, directly or indirectly, with changes in the relationships of humans, animals, and potential microbial pathogens.

Once an infection has occurred in a human, in order for the infection to be maintained or to spread in the population, the infectious organism must reproduce (in new hosts) faster than it dies out (in already infected hosts). Epidemiologists characterize this basic reproductive rate (R_0) in numerical terms, where R_0 must exceed a value of 1.0 for an infectious outbreak to spread [Anderson and May, 1991]. In general, four features influence the value of R_0 : (1) the intrinsic infectiousness of the organism; (2) the duration of the infectious period in an infected individual; (3) the number in the population who are susceptible to infection; and (4) the extent of mixing between those infected and those susceptible. These elements are useful in that they help characterize what has changed to produce an emerging infection and point to opportunities to interdict the spread of disease, i.e., to prevent or mitigate the risk. A key feature that determines how controllable an infection will be is the duration of infectivity in the absence of overt symptoms (e.g., HIV-infected persons often have long periods without symptoms when they can transmit the virus) [Fraser et al., 2004].

III. The emergence of infectious diseases: human, animal, environmental dimensions

A recent IOM report on *Sustaining Global Surveillance and Response to Emerging Zoonotic Diseases* [IOM, 2009], characterized the main drivers of emerging infection in a matrix of features and interactions among “human,” “animal,” and “environmental” dimensions (Figure 1).

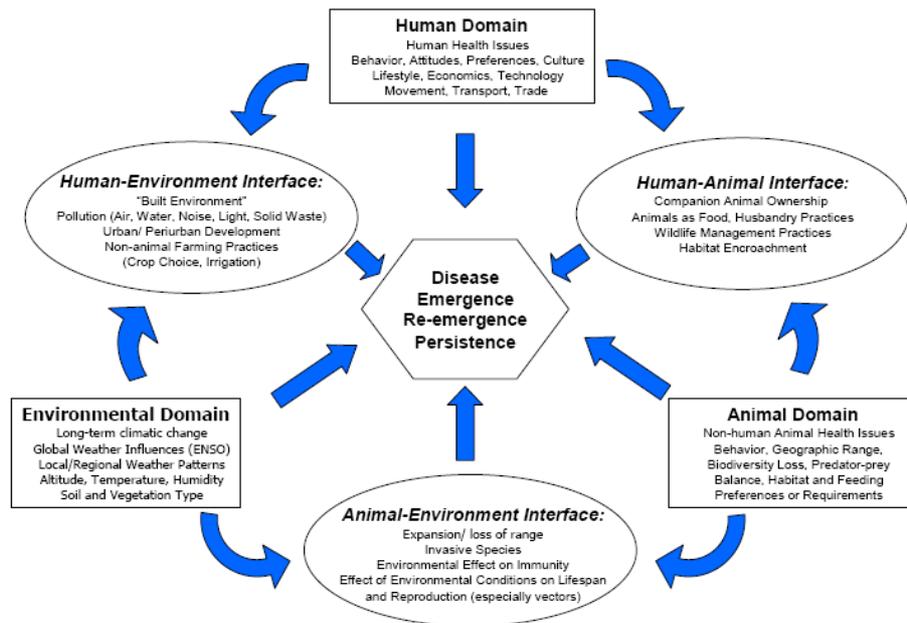


FIGURE 1. Overview of the driver-pathogen interactions that contribute to the emergence of infectious zoonotic diseases.

[Source: Institute of Medicine of the National Academies, *Sustaining Global Surveillance and Response to Emerging Zoonotic Diseases*, Washington, D.C., National Academies Press, 2009. Figure 3-1, p79. Reprinted with permission from the National Academies Press, Copyright [2009], National Academy of Sciences.]

Human factors that contribute to emerging infection include such elements as behavior and lifestyle, mobility (travel and immigration), and economic and technologic conditions of living. The size of the human population and density of habitation also affect emerging infections. Environmental factors range from soil and vegetation, weather and season, longer-term climate change, and local conditions such as altitude, temperature, humidity that influence animal and vector populations. Animal factors include geographic range, legal and illegal trade in domesticated animals and wildlife, biodiversity, predator/prey balance, habitat, and animal health.

Particularly telling are the drivers that occur at the intersections of the three core dimensions: at the human-animal interface, for example, factors such as industrial food production [see Pew Commission, 2008] wildlife management, animal husbandry practices, live animal markets, food preferences (bush meat), and human encroachment on animal habitat. At the human-environment interface appear such factors as urbanization and crowding, the nature of the built environment (window screens), water and waste management, and non-animal farming practices. At the animal-environment interface are such factors as conditions for reproduction and survival of disease vectors, and expansion or loss of species range.

IV. Contributing factors in the context of the IRGC report

Of the contributing factors outlined in the IRGC report, three in particular represent and encompass a number of the above-discussed drivers of emerging infectious diseases. These are (1) “Social Dynamics”; (2) “Technological advances”; and (3) “Varying susceptibilities to risk”. These factors operate within a complex international system, whereby international cooperation, can be a serious potential attenuator or amplifier of the risk of emerging infection depending on the degree of successful collaboration on such matters as surveillance (that includes animal populations), travel policy, trade restrictions, and enforcement.

- **Social Dynamics.** This factor embraces many of the human, human-animal, and human-environmental factors that contribute to emerging infection. Growth in the number and size of urban centres, increases in international travel and trade, a growing migrant workforce, enormous rise in farm animal production, and proximity to live animals hunted or acquired for food, are among the most powerful contributing factors. [Smolinski 2003]

The speed and scale of both the growth in international travel and the growth in animal food production and agricultural trade have been significant [Wilson 2010a].

Between 1990 and 2007, the number of international travellers (tourist arrivals) more than doubled, rising from 436 million to 903 million annually. As shown in Figure 2, revenues from international tourism have risen along with the number of travellers. In 1950, the top 15 destinations accounted for 98% of all international tourism. This fraction fell to 57% by 2007, reflecting the growing prominence of new destinations, many in developing countries [UNWTO, 2008].

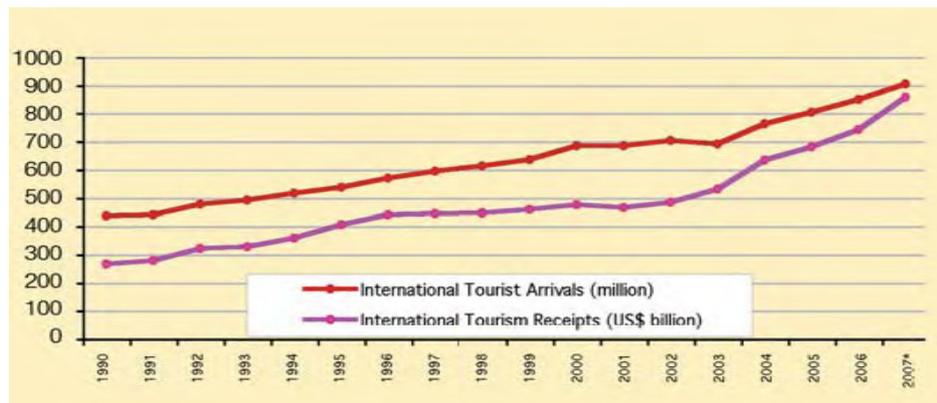
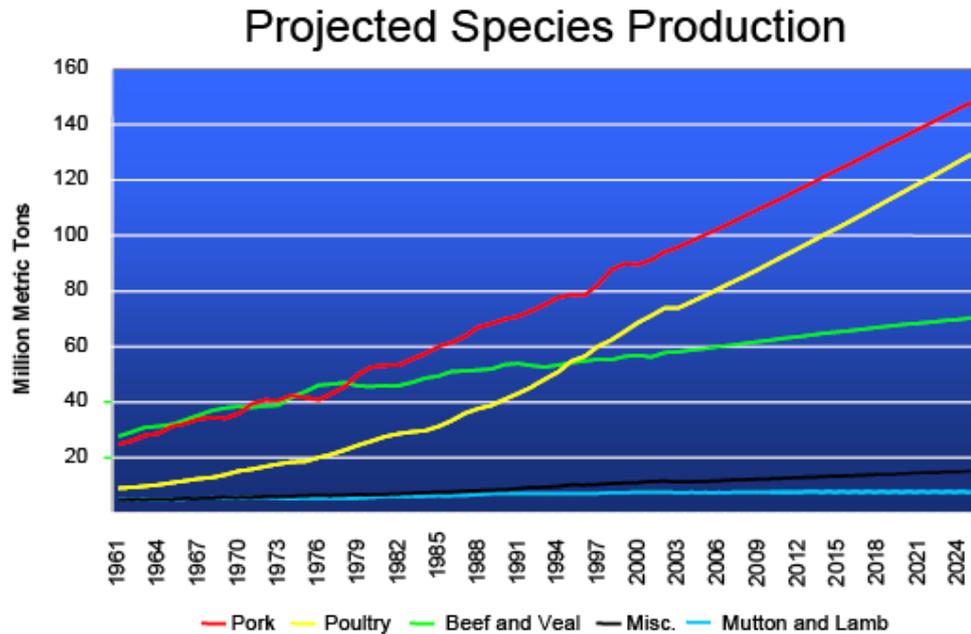


FIGURE 2. International tourist arrivals and receipts, 1990-2007

[Source: The World Tourism Organization (UNWTO), *Tourism Highlights*, 2008 edition, UNWTO, Madrid, 2008. ©UNWTO, 9284403710]

Animal food production and international trade in agricultural and animal products have similarly grown rapidly in recent decades, as illustrated in the following figure (drawn from the IOM report on *Sustaining Global Surveillance and Response to Emerging Zoonotic Diseases* [IOM, 2009]). The rise in poultry production has been especially steep in Asia. As an illustration, in China the human population increased about twofold (790 million to 1.3 billion) between 1968 and 2005. During this same period, the swine population expanded almost 100 fold (5.2 million to 508 million), and the poultry population increased more than 1000 fold (12.3 million to 13 billion) [Osterholm, 2005].



Source: Center for Global Food Issues

FIGURE 3. Projected production of animal meat by species, 1961–2025.

[Source: (Newcomb, 2004). Reprinted with permission from Bio Economic Research Associates, LLC (bio-era™). All rights reserved.]

- **Technological advances.** On the one hand, these advances have both allowed for and promoted the changes in social dynamics described above. New farming equipment plus advanced networks of infrastructure, transportation and distribution have led to larger scale animal farming and increased trade (risk amplification). This can facilitate new routes and scale of exposure to infection. However, on the other hand, technological innovation has also produced the vaccines and antimicrobials that provide specific means of prevention, diagnosis, and treatment of infection (risk attenuation).
- **Varying susceptibilities to risk.** The extent to which the various contributors to emerging infection affect a population is highly related to the *socio-economic status* of the population at risk. In the same climate and prevalence of mosquitoes, the presence of screened window openings and air conditioning in homes can make a huge difference in exposure and spread of infection. Many tropical areas with climate and weather that favour emerging infections are also regions that are crowded, economically underdeveloped, and especially susceptible. Inadequate nutrition (both macronutrients and micronutrients, such as vitamin A and zinc) affect susceptibility to infection. Access to adequate health care can dramatically affect the likelihood of contracting and the consequences of infectious diseases.

Some instances of emerging infections arise as a by-product of socio-economic, scientific, and technological development. These include, for example, hospital-acquired infections, microbial resistance secondary to the use and overuse of antimicrobials, microbes conveyed by blood transfusions and tissue transplantation, Lyme disease related to human habitation in suburban and rural areas, and Legionnaire's disease facilitated by contemporary water handling systems. However, a much larger number of emerging infections and their consequences are related to overcrowding, poor living conditions, and lack of resources, including clean water and adequate sanitation. The common feature—whether as a function of affluence or of poverty—is a new ecological milieu juxtaposing microbes and humans. Individual susceptibility to particular infections or to infections in

general, may depend on a number of biological and environmental factors, including genetic predisposition, previous exposures, nutritional status, and diseases or treatments that affect the immune system. Low latitude (tropical) areas are characterized by high biological diversity, including a greater array and abundance of potential pathogens. These areas coincide with large and growing populations in developing countries [Guernier, 2004].

Other *environmental forces* of weather and climate, changes in vegetation and habitat, and shifts in ecological balance also affect microorganisms, vectors, animals, and human exposure [Wilson 2010b].

In addition to these three key factors, two other factors can be construed as bearing on the likelihood, frequency and consequences of emerging infectious diseases. These are:

- **Scientific unknowns.** Scientific knowledge about microorganisms, vectors, and disease is an extremely strong contributor to averting and reducing the effects of emerging infections. Terminologically, the “health” goals of prevention, treatment, and rehabilitation have their “risk” counterparts in avoidance, management, and mitigation. Scientific understanding of the roles of microorganisms and vectors in disease has led to preventive strategies (behaviour adjustment, mosquito control, vaccines, and bed nets) and effective treatment (antimicrobials) against many emerging and established infections.
- **Conflicts about interests and values.** While not a primary driver of emerging infection, these factors can powerfully influence the response to certain diseases. For example, in the case of HIV, which is spread by sex and initially prominently affected homosexuals, ideological and religious convictions strongly influenced the response to the epidemic. Opposition to vaccination with poliovirus vaccines has hampered elimination of poliovirus in some parts of Africa.

Different emerging infectious diseases illustrate specific examples of contributing factors that act on their appearance and dissemination (see Table).

Table: Selected Attributes of Illustrative Emerging Infectious Diseases

Infectious Disease	Class of Organism	Main Modes of Transmission	Examples of contributing factors
vCJD [variant Creutzfeldt-Jakob disease (form of spongiform encephalopathy)]	Prion	Ingestion of contaminated meat	Animal rendering and feeding practices; economic incentives and interests
Dengue	Virus	Vector-borne (mosquito)	Urbanization and population growth; International travel and trade; Poor infrastructure
<i>E. coli</i> O157	Bacterium	Ingestion of contaminated food or water	Industrial food animal production; Food distribution networks

HIV/AIDS	Virus	Person-to-person (sexual; mother-to-child transfusion/injection)	Primate contact (bush meat); sexual practices; social stigma; travel and migratory workers; intravenous drug use and injection practices
Influenza	Virus	Person-to-person (respiratory)	Multiple zoonotic reservoirs; international travel
Monkeypox	Virus	Animal-human contact	International trade in wild animals
SARS	Virus	Person-to-person (respiratory)	Cultivation of wild animals (civet cats) for food; bat-civet cat interface; international travel

To illustrate the variety of factors and specific features that pertain to any one emerging infection, consider the case of dengue fever:

- The mosquito-transmitted dengue virus has expanded in geographic reach and is now found in tropical and subtropical areas where 2.5 to 3 billion people reside. An estimated 50 to 100 million cases occur annually leading to more than 20,000 deaths. Explosive outbreaks plague major urban centres in Asia and the Americas and are increasing in frequency and severity. Because four distinct dengue virus serotypes exist, humans can be infected up to four times. In fact, prior infection with one serotype predisposes to more severe infection, dengue hemorrhagic fever and dengue shock syndrome, if a person is infected with a different serotype. This means as background infections with dengue virus increase in a region, the population becomes more vulnerable to severe disease, if a new serotype is introduced into the human population (*varying susceptibilities to risk*).
- Although the dengue virus originally was passed from primates to humans, the primate-human cycle is now rare and virtually all human infections today result from dengue virus in one human being transmitted to another by a competent mosquito vector. The primary vector mosquito for dengue virus, *Aedes aegypti*, is well adapted to the contemporary urban landscape and prefers human to animal blood. It breeds easily in debris littering cities—discarded plastic cups, used tires, other trash—and in flowerpots, eaves, and water storage containers. It enters houses, rests in closets and corners; if its feeding on one human is interrupted, it will complete its blood meal on one or several other humans. This nervous feeding habit means that one infected mosquito can infect several humans (*social dynamics > urbanization*).
- The dengue virus spreads by being carried from one geographic area to another, within a city or region, or more distantly by ground transport or by long distance air transport. A person infected with the dengue virus will carry the virus in the bloodstream for up to 5-7 days, during which the virus can be picked up by a mosquito. If, after the virus multiplies in the mosquito and reaches the mosquito's

salivary glands, the mosquito bites a susceptible human, the dengue virus can be transmitted, leading to infection, the outcome of which ranges from asymptomatic to fatal. International travellers are responsible for introductions from one region to another (*technological advances > transportation*). Today most tropical and subtropical regions of the world are infested with *Ae. aegypti*, hence vulnerable to the introduction of dengue viruses (*varying susceptibility > environment*).

Although most humans infected with dengue virus do not die, they may be incapacitated for days to weeks, interrupting education for schoolchildren and reducing societal productivity.

Many factors contribute to the increasing burden of dengue virus infections globally:

Trends in social dynamics

- Urban growth in tropical developing areas
- Increasing size of urban centres in tropical and subtropical areas (a population of 150,000 – 1 million is required to sustain the ongoing circulation of dengue viruses)
- Increasing international travel of humans
- Viral evolution and increasing size of the human population (e.g., studies show that the number of lineages of dengue virus has been increasing roughly in parallel with the size of the human population, during the past two centuries [Zanotto et al., 1996]; this signifies the potential for emergence of variants that are more virulent or transmissible)

Technological advances

- Introductions of mosquitoes competent to transmit dengue viruses by international trade (shipping thought to be the most important; e.g., mosquitoes can be shipped internationally via used tire trade; mosquitoes can also accompany flights, resting in cargo holds, wheel bays, etc)

Varying susceptibilities to risk (socio-economic status, environment)

- Poor infrastructure (e.g., poor or absent vector control programs; lack of water distribution systems, forcing residents to store water in their homes in containers that may allow breeding of mosquitoes)
- Poverty (e.g., houses that lack screens and air conditioning; abandoned construction sites where pooled water provides good breeding sites)
- Lack of access to good health care (e.g., mortality for severe dengue infections is <1% in areas with ready access to good medical care but can be >10% in areas with poor access to health services)
- Warmer temperatures (e.g., period of time for virus to multiply in the mosquito and become transmissible to another human is strongly linked the ambient temperature; higher temperatures are associated with shorter extrinsic incubation period in the mosquito)

V. Governance and emerging infectious diseases

Emerging infectious diseases are a global phenomenon. They cannot be understood in less than a global context nor managed with less than a global strategy.

Complexity and global cooperation

Governance of emerging infectious diseases is a complex undertaking involving actors at the national level (nation states), international agencies (UN, WHO) and transnational entities (multi-national corporations; global non-government organizations). Governance is complex not simply because of the multiple and interacting factors of emergence, but because economic interests (tourism, food, pharmaceuticals) are often at stake and because geo-political interests of different nations may not align (who sacrifices and who benefits from information, new products, and interventions). Even if the economic and national interests of institutional and political actors were perfectly aligned with population health needs, the task of coordination across the vast array of national, international and transnational entities that are relevant to detecting and coping with emerging infections would be daunting. The challenge goes *beyond systems thinking*, to a global capacity for communication, coordinated decision-making, scaling up to meet the general and specific challenges, and implementing with sufficient speed to make a difference, all accomplished in a sustainable way.

The heart of a global “*early warning system*” to cope with emerging infectious diseases rests on global surveillance that must include animal as well as human pathogens and diseases. While improving, global surveillance currently falls short of the resources, human capacity, and long-term commitment that would be desirable and necessary [see IOM, 2009]. The current array of reference laboratories and collaborating centres around the globe to detect and characterize emerging infections is illustrated in Figure 4.

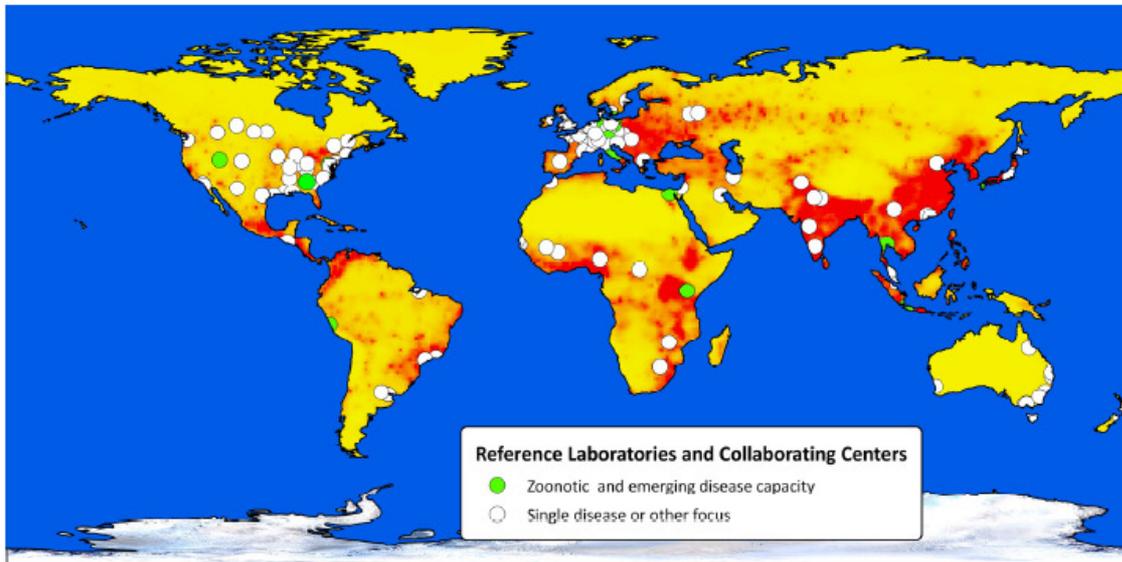


FIGURE 4. Zoonotic disease hotspots and selected reference laboratories by location.

[Source: Institute of Medicine of the National Academies, *Sustaining Global Surveillance and Response to Emerging Zoonotic Diseases*, Washington, D.C., National Academies Press, 2009. Figure S-1, p10. Reprinted with permission from the National Academies Press, Copyright [2009], National Academy of Sciences.]

NOTE: The white dots signify the location of identified World Health Organization, Food and Agriculture Organization of the United Nations, World Organization for Animal Health, and U.S. Department of Defense reference laboratories and collaborating centres, many of which have a single disease or other focus mandate. Green dots are laboratories that have a broader function in zoonotic and emerging diseases. Locations shaded

in red and orange represent hotspot regions. The map does not include university-based research and other laboratories working in the area of emerging disease detection and characterization.

Particular instances of emerging infections, such as the current H1N1 influenza outbreak, illustrate some of the difficulties that can arise from public misunderstanding of science or mistrust of technology, such as suspicions about the safety of vaccines. The development of vaccine in response to a particular, emerging influenza strain also illustrates the inter-related issues of research strategies (new approaches to vaccine design and production), safety regulation, production standards, and considerations of speed, safety monitoring, and managing public expectations.

Better agenda setting. Beyond the usual challenge of setting priorities among competing, potential risks claiming attention, emerging infections illustrate how a risk can be differentially threatening depending on local circumstances (factor #4, varying susceptibility to risk > environment, exposure, prevalence, socio-economic circumstances, and response capacity). This makes the task not simply one of asking which potential infectious diseases deserve more attention than others from a global perspective, nor even how all infectious disease threats stack up against other sources of risk, but also expressly recognizing the differential burden of disease, scale of threat, and capacity to respond—across nations, across regions, and even across individuals within a community. This latter concern, for example, lies behind considerations of priority target groups for immunization against H1N1 influenza. It also exposes ethical questions, such as the distribution of limited supplies of influenza vaccine to different countries.

Resolving conflicts. Since emerging infections represent a naturally occurring process and a common threat to all humanity, it may seem that they should be free of conflicting interests. In some instances, this is practically the case: no domestic economic, philosophical, religious, or political interest is advanced by the spread of West Nile virus in North America or Europe. However, depending on the specific drivers and attributes of a particular infection (or affected population) emerging infections can invoke powerful and *conflicting interests* (factor #5). Consider the meat industry in the face of vCJD or *E. coli* O157, or government's initial response to the HIV epidemic in many countries. Some potential emerging infections (as in early detection of a new influenza, such as the avian H5N1 influenza) represent a class of risk that is "low likelihood-high consequence." This class is especially problematic for government leaders because the naysayers, who claim any preparation is an over-reaction, will more often prove right than wrong. That is the nature of a low-likelihood event. At the same time, if the full force of the threat does materialize, preparations will almost surely, in retrospect, appear to have been inadequate. This constitutes a political and leadership challenge in communication as much as in decision-making and conflict resolution.

VI. Observations and impressions

Emerging infections are the quintessential risk of “natural” origin. Even so, many of the key drivers involve the interaction of human behaviours, cultural and social practices with the natural environment.

A key to understanding, detecting, characterizing, and responding to the risk of emerging infection is the nexus of interactions among animals, humans, and infectious organisms.

The contributing factors described in the IRGC report broadly encompass many of the more specific elements, described above (e.g. urbanization, farm animal production, increased mobility of goods and populations) that drive emerging infections. But these broad categories do not reveal the *dynamics* of evolutionary biology, the microbial world, and human-animal interactions that contribute centrally to emerging infectious diseases, nor do they point to the specific lines of scientific research and knowledge, public health surveillance, and response capacity that determine the consequences of emerging infection.

Effective governance of the threat of emerging infectious diseases must simultaneously take a global, systems perspective and recognize that different localities and nations will bear disproportionate risk and burden from particular emerging infections. Thus, national interests and priorities (much less specific economic interests) do not necessarily align with global population interests in setting priorities for protecting against emerging infectious diseases. At the same time, ensuring a global capacity to cope with emerging infection serves not only a global, humanitarian purpose, but as part of a larger strategy to promote global health, can serve the enlightened self-interest of more economically advantaged nations.

References

[Anderson and May, 1991] Anderson, R.M. and May, R.M., *Infectious diseases of humans: Dynamics and control*, Oxford, Oxford University Press

[Fraser et al., 2004] Fraser, C., Riley, S., Anderson, R.M. and Ferguson, N.M., Factors that make an infectious disease outbreak controllable, *PNAS*, 101, p6146-6151

[Guernier, 2004] Guernier, V., Hochberg, M. E. and Guégan, J. 2004 Ecology drives the worldwide distribution of human diseases, *PLoS Biology*, 2(6), p0740–0746,
<http://www.plosbiology.org/article/info:doi/10.1371/journal.pbio.0020141>

[IOM, 2009] Institute of Medicine of the National Academies, *Sustaining Global Surveillance and Response to Emerging Zoonotic Diseases*, Washington, D.C., National Academies Press, 2009

[Newcomb, 2004] Newcomb, J., *One World – One Health: An Economic Perspective*, 2004

[Osterholm, 2005] Osterholm, M.T., Preparing for the Next Pandemic, *New England Journal of Medicine*, 352 (18), May 5, 2005, p1839-1842, <http://content.nejm.org/cgi/reprint/352/18/1839.pdf>

[Pew Commission, 2008] The Pew Commission on Industrial Farm Animal Protection, *Putting Meat on the Table: Industrial Farm Animal Production in America*, A Project of The Pew Charitable Trusts and Johns Hopkins Bloomberg School of Public Health, 2008,
http://www.livablefutureblog.com/pdf/Putting_Meat_on_Table_FULL.pdf

[Smolinski et al., 2003] Smolinski, M.S., Hamburg, M.A. and Lederberg, J. (eds.) *Microbial threats to health: emergence, detection, and response*, Institute of Medicine of the National Academies, Washington, DC, The National Academy Press

[UNWTO, 2008] The World Tourism Organization (UNWTO), *Tourism Highlights*, 2008 edition, UNWTO, Madrid, 2008

[Wilson, 2010a] Wilson, M.E., Global travel and emerging infections, In: *Infectious diseases movement in a borderless world*, Microbial Threats Forum, Institute of Medicine, Workshop Summary, Washington, DC, The National Academies Press, p90-104 and 126-129

[Wilson, 2010b] Wilson, M.E., Geography of infectious diseases, In: Cohen, J., Powderly, W.G. and Opal S.M. (eds.) *Infectious Diseases*, third edition, Philadelphia, Elsevier, p1055-1064

[WHO, 1996] World Health Organization, *The World Health Report, 1996: Fighting disease, fostering development*, Geneva, World Health Organization

[Zanotto et al., 1996] Zanotto, P.M., Gould, E.A., Gao, G.F., Harvey, P.H., Holmes, E.C., Population dynamics of flaviviruses revealed by molecular phylogenies, *Proc. Natl. Acad. Sci. USA*, 93 (January 1996), p548-553, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC40088/pdf/pnas01506-0013.pdf>