

Emerging and Reemerging Infectious Diseases: A Multidisciplinary Perspective

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ABSTRACT: Predictions that infectious diseases would be eliminated as a major threat to human health have been shattered by emerging and reemerging infections, among them acquired immunodeficiency syndrome (AIDS), hemorrhagic fevers, marked increases in infections caused by antimicrobial-resistant bacteria, and the resurgence of tuberculosis and malaria. Understanding the dynamics of emerging and reemerging infections is critical to efforts to reduce the morbidity and mortality of such infections, to establish policy related to preparedness for infectious threats, and for decisions on where to use limited resources in the fight against infections. In order to offer a multidisciplinary perspective, 23 infectious disease specialists, epidemiologists, geneticists, microbiologists, and population biologists participated in an open forum at Emory University on emerging and reemerging infectious diseases. As summarized below, the group addressed questions about the defini-

tion, the identification, the factors responsible for, and multidisciplinary approaches to emerging and reemerging infections. **KEY INDEXING TERMS:** Infectious diseases; Microbiology; Population biology; Emerging pathogens. [Am J Med Sci 1998;315(2):64-75.]

Defining the Problem

What Are Emerging and Reemerging Infectious Diseases? The predictions¹ that infectious diseases would be eliminated as a major threat to human health have been replaced by a clear awareness of the threat of microbial pathogens. Fueled by the acquired immunodeficiency syndrome (AIDS) pandemic, the 1992 Institute of Medicine (IOM) report "Emerging Infectious Microbial Threats to Health in the United States" refocused attention on emerging and reemerging infectious diseases.² In the IOM report and in public health responses to the report,³⁻⁷ emerging and reemerging infectious diseases (Table 1) were defined as those whose incidence in humans has increased within the past two decades or that threaten to increase in the near future. While the quantitative part of this definition is appealing, its utility is very often restricted by inadequate data on the incidence of many infectious diseases and by new advances in our understanding of infections. Often, emerging and reemerging infections have come to be designated by the second part of the definition and include newly recognized infections ("new threats") or "old" infections which may appear to be increasing. Clustering of infections with unusual clinical features or unexpected virulence (eg, Ebola hemorrhagic fever,⁸ hantavirus-induced pulmonary syndrome,⁹ and the discovery of infectious agents for well-defined illnesses such as peptic ulcer disease¹⁰ and hepatitis C¹¹) are examples of infections designated as emerging for which clear documentation of increasing incidence is not available.

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Table 1. Examples of Emerging and Reemerging Infectious Diseases

Disease	Distribution	Reservoir Hosts	Probable Factors in Emergence
Influenza (Orthomyxoviridae)	Worldwide	Aquatic birds	Integrated pig-duck farming, genetic recombination
HIV (Retroviridae)	Worldwide	Humans (originally from primates)	Sexual transmission; intravenous drug use; medical technology (blood transfusion); travel, mutation frequency
Marburg, Ebola (Filoviridae)	Africa	Unknown	In Europe and USA, monkey importation
Dengue (Flaviviridae)	Throughout tropics	Mosquitos, humans	Urbanization; factors favoring increased mosquito populations
Rift Valley Fever (Bunyaviridae)	Africa	Mosquitos, ungulates	Dams, irrigation
Junin (Arenaviridae)	South America	Rodents	Agriculture
Hantaan (Bunyaviridae)	Asia, Europe, USA	Rodents	Agriculture
Hantavirus (Bunyaviridae)	Southwestern USA	Rodents	Climate-mediated increases in rodent populations
Morbillivirus	Australia	Horses	Unknown
Hepatitis C	Worldwide	Humans	Transfusions, sexual transmission
Legionnaire's diseases (<i>Legionella</i>)	Worldwide	Natural component of water flora, free-living amoeba	Technology: air conditioning, water cooling towers, water storage units
Lyme disease (<i>Borrelia</i>)	Worldwide	Deer, rodents, birds	Reforestation
Toxic Shock Syndrome (<i>Staphylococcus aureus</i> , <i>Streptococcus pyogenes</i>)	Worldwide	Human nasal passages; skin, mucosal surfaces	Technology: high-absorbency tampons, toxin production
Rheumatic fever (<i>Streptococcus pyogenes</i>)	USA	Humans	Unknown
<i>E coli</i> O157:H7	USA, Europe, possibly worldwide	Cattle	Food production
Plague (<i>Yersinia</i>)	Worldwide; mostly southeast Asia	Rodents	Urban environments
Antibiotic-resistant bacteria (eg, enterococci, <i>S pneumoniae</i>)	Worldwide	—	Human and nonhuman use of antibiotics
Tuberculosis	Worldwide	Humans, cattle	Drug resistance, breakdown or lack of control programs, HIV infection
<i>Cryptococcus neoformans</i>	Worldwide	Bird feces, environmental	Immunocompromised patients (HIV-infected)
Cyclospora	Worldwide	Unknown	Food importation (eg, raspberries)
Cryptosporidium	Worldwide	Water sources	Contaminated water supplies
<i>Helicobacter pylori</i>	Worldwide	Humans	Unknown
Malaria	Worldwide	Mosquitos, primates	Drugs and insecticidal resistance
<i>Vibrio cholerae</i>	Worldwide	Unknown	Genetic change, travel, sanitation
Salmonella	USA	Reptiles	Reptiles as pets

Information on viral diseases is based on Tables 2.1 and 2.2 in Morse SS (ed), *Emerging Viruses*, Oxford: Oxford University Press 1993:10-28; references to bacterial diseases in Schrag SJ and Wiener P, *Trends in Ecology and Evolution*, In Press.

Also important in the definition of emerging infections is the human population under study, including demographic and socioeconomic factors, the background rates of disease in the population (which can vary locally and globally), and changes in how a particular infectious disease is diagnosed. Each of these factors will influence calculations of incidence. For example, the resurgence since the late 1980s of tuberculosis in the United States was due to increases in the disease among homeless, HIV-infected, new immigrant, drug-abusing, minority, and institutionalized populations, while the incidence of tuberculosis in other populations in this country continued to fall.¹²

The definition of emerging and reemerging infections should address these concerns. Maintaining a broad working definition is appropriate, but should not decrease efforts to assess emerging infections in quantitative terms. Thus, emerging (newly defined) and reemerging (previously recognized) infectious diseases are infections which are increasing or, when prior incidence in specific human populations is uncertain, appear to be increasing or threaten to do so.

In considering how infectious diseases emerge or reemerge, a division of infections into those that are resident within a species and those that are new to a species is useful. For infections resident in a species, determining what factors increase the incidence or

change the characteristics of the infection in order to cause more disease is important. For example, what changes in host ecology or genetics result in shifts from an endemic to an epidemic state, and what genetic changes in the pathogen result in differences in virulence or transmission? For infections that are new to a species, understanding the factors conducive to a successful host-shift and the genetic changes needed to achieve such a shift is essential. These factors may include enhanced contact opportunities, immigration, or changes in social structure, the relatedness of the species, and the characteristics of the new disease (eg, respiratory, diarrheal). Emergence and reemergence of infectious diseases can result from changes that affect the environment, the pathogen, the host, or a combination.

While the focus of this report is on infections in humans, lessons can be learned from emerging and reemerging infections that occur in other animals and in plants. Studies of evolutionary and ecological models of infections in animal and plant populations can provide considerable insight into disease dynamics and may provide approaches that are relevant to the management of emerging infections in humans.

How Are Emerging and Reemerging Human Infections Identified? Emerging and reemerging infections are identified by the reporting of sentinel cases, by passive or active surveillance networks of physicians, other healthcare providers, and public health officials, and, uncommonly, by changes in vital statistics such as death rate. A critical element of these methods is the detection threshold or sensitivity of detection, which varies according to the kind of method and the sophistication of the public health infrastructure. A major goal of public health policy directed at infectious diseases should be the development and maintenance of high sensitivity and specificity detection systems to permit early identification of emerging and reemerging infections, and to implement early prevention strategies.

Sentinel Cases. Cases or case clusters reported to public health officials which, in the view of reporting healthcare providers represent unusual, unexplained, or excessive morbidity and mortality, are designated as sentinel cases. Sentinel cases are the most common means of identifying emerging and (to a lesser extent) reemerging infections. Emerging infections identified by sentinel cases include Legionnaire's disease,¹³ Ebola virus hemorrhagic fever,⁸ Lyme disease,¹⁴ Hantavirus pulmonary syndrome,⁹ Kaposi's sarcoma and HIV infection,¹⁵ the resurgence of rheumatic fever,¹⁶ and drug-resistant tuberculosis. However, the detection threshold of sentinel cases is quite variable. Reports may be serendipitous and are likely to be generated only because of close clustering, unusual morbidity and mortality, novel clinical features, or the chance availability of medical expertise. Thus, recognition

of emerging infections by sentinel cases often depends on chance and the insight to identify and report unusual cases. Development of sentinel case surveillance systems through groups of practitioners and enhanced reporting of sentinel cases, as implemented recently by the Centers for Disease Control and Prevention (CDC)³ should be a major step in the early detection of emerging infections in the United States and can be expanded worldwide.

Passive Surveillance. Passive surveillance systems are based on the routine reporting by healthcare agencies of the laboratory identification of specific agents or, much less often, of clinically diagnosed infectious diseases. Passive surveillance systems may identify emerging infections, but have the greatest sensitivity for reemerging pathogens (eg, tuberculosis), and can provide warnings or information about infectious disease outbreaks or trends (eg, meningococcal outbreaks, antibiotic-resistant trends in bacteria). However, inferences from passive surveillance systems are limited. The basis of these systems, notifiable infections, most often requires isolation of the pathogen and relies on passive reporting, resulting in a wide range of reporting sensitivity (3% to 99%; personal communication from R. Berkelman, CDC, 1995). Thus, the incidence of infections using passive surveillance systems is often underestimated and may vary with the diagnostic tools or the current perception of threat. In addition, passive surveillance systems of notifiable diseases are not uniform among states or developed countries and do not exist in much of the developing world. In some settings, the only passive surveillance systems for detecting emerging infections are crude methods of detecting increased morbidity (increased hospital admission or clinic visits) and mortality. Efforts should be made to improve passive surveillance systems through reporting requirements, uniformity of case definitions, and education of healthcare providers and laboratories.

Active Surveillance. Active surveillance networks target healthcare providers and diagnostic laboratories to determine rapidly and prospectively the incidence of specific infectious diseases in defined populations. These systems are powerful tools for assessment of emerging and reemerging pathogens.^{17,18} However, active surveillance systems are expensive, labor-intensive, and also may have limitations with case definition (eg, the cases easiest to identify are those with growth in culture or positive serology). Thus, active surveillance systems are very effective when they are designed to monitor specific infectious agents through prospective laboratory surveillance. They are less developed for assessment of clinically defined infectious syndromes (eg, meningitis, adult respiratory distress syndrome). Efforts should be made to enhance this powerful reporting tool. Increased development of active surveillance

systems based on computerized clinical and laboratory databases could decrease cost and enhance the quality of active surveillance systems.

Ascertainment Bias. How much of the emergence and reemergence of infectious disease can be attributed to ascertainment bias, such as better and/or more consistently applied procedures to find diseased individuals and identify microorganisms responsible? Because the true incidence of an infectious disease is frequently underestimated (due to inadequate detection systems), ascertainment bias can create the illusion of the presence of an emerging or reemerging infection. However, calculating the impact of an ascertainment bias is difficult. Two important ascertainment biases are the Hawthorne effect and the evolving case definition.

Hawthorne Effect. The Hawthorne effect¹⁹ is defined as the appearance of an increased incidence of an infectious disease because it is aggressively looked-for or publicized (eg, *E coli* O157:H7,²⁰ meningococcal disease in England following the Stonehouse outbreak,²¹ group A streptococcal infections). The availability of accurate incidence figures for an infection in a population will diminish or eliminate the impact of the Hawthorne effect. Another way to address the Hawthorne effect is by use of surrogate markers such as hospitalizations for hemolytic uremic syndrome to assist in monitoring incidence of *E coli* O157:H7.

Evolving Case Definition. The best case definitions of some infections remain clinical (eg, pertussis,²² Kawasaki's disease, early Lyme disease). In these infections, laboratory diagnostic tests have low sensitivity or specificity, and/or are not available, thus making accurate calculations regarding incidence difficult. For other infections, the case definition and diagnostic criteria change as expanded clinical data and more sensitive or specific diagnostic tests become available. For example, new laboratory procedures have permitted us markedly to expand our detection of HIV, *H pylori*, and hepatitis C. This has led to case definitions of infections changing over time (eg, AIDS), and altering (almost always increasing) the calculated incidence. Ascertainment biases must be considered in defining the incidence of emerging and reemerging infections. However, they cannot a priori be assumed to be the explanation for such infections.

What Contributes to the Development of an Infection and to Severity and Spread? In addressing this question, it is important to note that our current ability to predict when a microorganism will or will not be a problem to human health is limited. What factors are needed or not needed, and the magnitude of the impact of specific factors on emergence or reemergence of an infectious disease, are often not known.

R_0 . As a theoretical construct, an understanding of the number of secondary cases produced on aver-

age by introduction of an infectious agent into a population of susceptibles is important in defining the characteristics of emerging and reemerging infections.²³ If R_0 is less than 1, the disease is unlikely to become established in the population; greater than 1, disease incidence is likely to increase over time; and greater than 10, very high levels of transmission can occur. Small changes in R_0 may generate large effects on disease spread. While an understanding of R_0 can describe the initial spread of a pathogen in a susceptible population, the immune response of the host must be considered. For example, rapid development of a protective immune response to an immunodominant strain of a pathogen with a high R_0 will allow an immunorecessive strain with a lower R_0 to increase in frequency in a population.

Long-lived Infectious Stages. The persistence of the pathogen in infectious forms between or within hosts and the persistence of the pathogen in the environment of humans will enhance the possibility of emergence and reemergence of infections.

Mechanism of Transmission. The specific mechanism of transmission of a pathogen is a key factor in R_0 and the potential of a pathogen to emerge. Certain vector-borne diseases such as malaria have values of R_0 approximately 16 to 80²⁴; measles, whooping cough, chicken pox and other viral infections spread by respiratory transmission have R_0 values of 3 to 13; and waterborne infections like cholera and cryptosporidium also have a high R_0 , whereas the R_0 for sexually transmitted diseases is low.

Capacity for Genetic and Structural Variability by the Pathogen. This capacity permits escape from immune protective mechanisms, creates functional diversity, and may change host or tissue tropisms. This characteristic also provides the pathogen with the potential to undergo rapid change in response to other selective pressures (eg, antimicrobials). A limited capacity may cause constraints on emergence (eg, the emergence of chlorine-tolerant or -resistant *Vibrio cholerae* could have a dramatic impact on incidence of cholera).

Case Morbidity and Mortality Caused by an Infection. An infection may still be a major threat even if the pathogen causing the infection has a low R_0 if it kills a large percentage of those infected.

Latency. Latency is defined as a prolonged period between infection and recognizable disease (as occurs in AIDS). Delayed onset of symptoms affects the ability of individuals to change their behavior in a timely fashion. Delayed onset of symptoms may also impair the ability of public health officials to issue alerts and manufacture vaccines.

The Environment

Role of Ecological Change in Host-Parasite Associations. What is the role of ecological change in host-

Table 2. Examples of Environmental or Social Changes Resulting in Emerging or Reemerging Infections, or the Potential for These Infections

1. Changes in sexual practice (HIV disease, other STDs)
2. Drug abuse and needle-sharing (HIV disease, viral hepatitis)
3. Population changes, growth. Increases in population density are probably among the most critical environmental factors.
4. Migration/travel, global commerce, changes in societal practices (HIV spread, malaria, occurrence of tuberculosis and other infections in refugee camps, outbreaks of O135 H7 *E coli* in fast-food restaurants, and respiratory transmission of bacterial pathogens in daycare centers.
5. Transfusion/transplants (zoonoses, eg, pig- or monkey-to-human transplants)
6. Urbanization of the developing world and developed world crowding (increased pathogen transmission, incidence of many diseases in metropolitan areas in the United States comparable with incidence in the developing world)
7. Changes such as healthcare reform in medical practice (increased empiric treatment, decreased diagnosis, increased antibiotic selection pressures)
8. Environmental changes (deforestation and reforestation, changes in land use alter vector/host populations (increases in deer population = increases in Lyme disease), introduction of new vectors, and changes in vector ecology (arbovirus infections, hantavirus, dengue)
10. Nutrition and changes in food industry (listeriosis, salmonellosis, antibiotics in animal feeds)

parasite associations in the emergence and reemergence of infectious diseases? How much of the emergence and reemergence of infectious disease can be attributed to changes in technology, social practices, population densities, migration patterns, physical environment, and biotic environment? For example, how much of the emergence of HIV/AIDS and the reemergence of tuberculosis can be attributed to social change?

The vast literature on genetic bases of pathogenicity, along with a resurgence of interest in the evolution of virulence,²⁵⁻²⁷ might suggest that genetic characteristics of pathogens lie at the heart of infectious disease emergence. However, an alternative hypothesis is that for many emerging and reemerging infectious diseases, changes in the pathogen and host ecology probably play the primary role (Table 2).^{28,29} Seemingly minor ecological changes (eg, the implementation of a new farming technique or long-distance travel of infected hosts) may significantly alter transmission and exposure patterns leading to sudden proliferation of disease. Exposure of pathogens to new environments may also result in disease emergence. For example, even if mutants with greater virulence arise frequently, if such mutations are negatively associated with the ability to survive, they will be rapidly eliminated. In addition, evolutionary changes resulting in new disease often require ecological "co-factors." A microbe that evolves an expanded host range cannot emerge in a new host unless it is able to reach that host.

Changes in population density or, for sexually transmitted diseases, changes in mating systems, shifts in climate or nutritional status, and, for vector-transmitted diseases, changes in environments affecting vector abundance, may alter host/microorganism ecologies and result in shifts from endemic to epidemic states. For example, some of the resurgence of tuberculosis¹² is related to social change. Increased crowding in metropolitan areas, immigra-

tion, and the breakdown of public health infrastructures for control of tuberculosis are among the social factors which account for the recent increases in active and latent infection with *M tuberculosis* in certain populations. The South American hemorrhagic fever viruses^{30,31} provide an example of how the development of new areas for human settlement and agriculture increase the likelihood that new infectious diseases will emerge. Other examples of emerging and reemerging diseases in which ecological changes, social changes, or changes in medical practice may play a role are shown in Table 2. New ecological and social changes and conditions will continue to arise and will be important contributors to emerging and reemerging infectious diseases.

Alternatively, changes in environment may also result in a reduction in the incidence of certain infections. The retreat of malaria from the British Isles may have been partially due to changes in cattle-raising or human exposure to cattle.³² Also, it should be noted that establishing an ecological correlate of an emerging disease is often easier than establishing a genetic correlate. Establishing causation from such correlations is even more difficult. Thus, the exact role of environmental versus evolutionary factors is often not known for most infections.

A growing number of emerging infections occur as a result of infections in natural populations of animals that come in increased contact with humans or other species (eg, hantavirus⁹ and salmonellosis³³). The conditions that influence the chance of contact with zoonoses may have common and predictable characteristics. For example, the morbillivirus group includes human measles, canine distemper, rinderpest in livestock and wild ungulates, and cetacean morbillivirus. Recently, a strain of morbillivirus caused a fatal outbreak of disease that affected 21 horses and 2 humans.³⁴ The diseases caused by morbilliviruses are known for causing sweeping epidemics in African wildlife (eg, rinderpest and distemper).

An epidemic of canine distemper caused serious mortality among lion populations in the Serengeti National Park. The lions were most likely exposed to the disease through the high density of domestic dog populations owned by tribesmen living around the park. Other potential zoonotic threats include simian immune deficiency virus (SIV) variants producing rapid death in macaque monkeys,³⁵ the widely distributed hemorrhagic fever viruses (Table 1)^{8,9,31}; B herpes virus in monkeys, and new influenza virus recombinants which may develop in animal hosts.

The Pathogen

Role of Microorganism (Pathogen) Evolution What is the role of microorganism (pathogen) evolution in the emergence and reemergence of infectious diseases, what are the characteristics of a pathogen that provide the potential to emerge or reemerge as an infectious disease? How important is the role of genetic change in pathogen evolution and emerging infections? The expanding tools of molecular biology (eg, nucleotide sequencing) now allow us to better evaluate how genetic change affects structural and functional properties of pathogens. However, what specific genetic changes (if any) are needed to result in an emerging or reemerging infection are often not clear. Genetic change may result in:

- *New species or tissue tropisms.* Genetic change may allow pathogens to cross species barriers to cause new human infectious diseases (eg, plague³⁶ [frame shift in Yop protein leading to pneumonic plague], HIV, swine influenza viruses) or for microorganisms to acquire new tissue-specificity.
- *Enhanced invasiveness or survival.* This results in new or more severe clinical diseases caused by previously recognized infectious agents (certain strains of *Haemophilus influenzae* biogroup aegyptius now cause an invasive and often fatal syndrome known as Brazilian Purpuric fever,³⁷ whereas most strains cause only conjunctivitis).
- *Antigenic shifts and drifts,* leading to epidemic outbreaks of known pathogens (eg, influenza A, meningococci, 0139 cholera³⁸) or within-host shifts that can occur within a patient. AIDS has been proposed to be the result of continuous selection for antigenic variants within a host, leading to gradual immune system breakdown under the weight of a wide diversity of HIV variants.³⁹ A similar phenomenon may occur in malaria.^{40,41} In these cases, the ability of a disease-causing organism to genetically change rapidly within the host may, in itself, be the factor that makes the infectious agent a threat.

Genetic change may not be required for a pathogen to emerge. As noted previously, some emerging or reemerging diseases may not be due to genetic change, but are associated with ecological or other

environmental changes leading to enhanced exposure (eg, haptavirus, Lyme disease) and transmission. The contribution of genetic versus environmental changes to an emerging pathogen is a major area for future study.

Anticipated Directions of Natural Selection on Virulence, Host-Range and Transmissibility Natural selection may create differences in virulence and transmission. How virulence evolves, if it is a by-product of other characteristics, and how virulence relates to prevalence are important questions. Infections may emerge because of decreased virulence and prolonged survival of an infectious stage in a host. Alternatively, virulence may be a pleiotropic effect of differences in transmission. Changes in transmission, the host/pathogen characteristics which predispose to increased transmission, and whether an infection is related to a specific transmission mode are thus important factors.

The identification of the conditions that favor changes in virulence requires careful studies of diseases in natural systems of plants and animals. Changes in virulence of diseases may be a result of novel combinations of hosts and microorganisms; for example, myxoma virus in domestic rabbits is much more virulent when compared to the same strains in wild rabbits native to Central and South America.⁴² However, long-term associations of hosts and microorganisms can also lead to local adaptation of infections, resulting in increased transmission and virulence in the native host species.⁴³ Studies of fig-wasps and their nematode parasites have shown that transmission is a key factor that influences disease-induced host mortality; nematodes were shown to be more virulent in cases where horizontal transmission opportunities were enhanced.⁴⁴ By contrast, diseases that are solely vertically transmitted depend on host viability and reproductive potential to enhance pathogen fitness. For example, grass endophytes that are spread through seeds or clonal reproduction in plants have been shown actually to enhance plant competitive abilities and decrease herbivory in several species of grasses.^{45,46}

A number of hypotheses have been proposed regarding the effects of natural selection on emerging and reemerging infectious diseases.^{23,26,47} Selective pressures likely to result in evolutionary changes are recognized. These include the use of antibiotic and other pharmacologic agents, chemicals such as pesticides, animal or human passage (which may yield either more or less virulent phenotypes such as pneumococci, myxoma,⁴³ varicella, measles, or Ebola virus), mutagenic environments, starvation, selection for virulence genes that increase survival of infectious pathogens, and the changing host defense and immune status of the population, including vaccine-induced changes (virulence altered by level of host susceptibility).

The conditions that create enhanced virulence (eg, toxin production) may not be obvious. Often this is due to our limited knowledge of the pathogenesis of an infection or understanding of the microorganism's ecology. As an example, genes which enhance survival of an organism in intermediate hosts may be virulence determinants in human pathogens. Cholera toxin produces diarrhea in humans, increasing transmission of *Vibrio cholerae*; however, toxin production in humans may be an incidental consequence of the selective pressure for toxin expression in marine estuaries. Cholera toxin produced by *V. cholerae* appears to be released in squids in order to facilitate nutrient availability important in the survival of the organism in an aquatic environment.⁴⁸

The presence of a toxin or virulence factor may increase a selective advantage to the microorganism's survival and propagation. This is true for both exclusive human pathogens and those with environmental reservoirs. Examples of virulence determinants which may enhance organism survival include the enterotoxins of *E. coli* which produce diarrhea and facilitate organism spread; the transmission of *Bordetella pertussis* by coughing induced by pertussis toxin; lysogeny, stimulated by hostile environments of phage carrying the erythrogenic toxin of scarlet fever; and the production of *C. difficile* toxin for survival of the bacterium in the ecological niche of the large intestine. A virulence factor is most advantageous when it enhances the probability of the microorganism encountering susceptible hosts.

Host

Hospitalized and Immunocompromised Humans as "Breeding Grounds" for Evolution of New Pathogens. Are hospitalized and immunocompromised humans "breeding grounds" for the evolution of new pathogens and changes in host-range or increase in the virulence of old pathogens? Are infections acquired in hospitals more virulent to uncompromised hosts than infections with the same microorganisms acquired in the community at large? Certainly, hospitals and medical treatment create environments for antimicrobial selection pressures that have led to the emergence of resistant clones.⁴⁹ These resistant clones (eg, vancomycin-resistant enterococci) are increasingly difficult to treat in any host. Hospitals are also sources of enhanced contact of diseased and healthy individuals, leading to increased transmission opportunities (eg, tuberculosis, Ebola spread in Africa). In addition, there are concerns about greater recombination opportunities between virulent strains in hospital environments, the occasional genetic linkage of virulence factors and antibiotic resistant determinants, and the acquisition of new infectious agents in hospitals and medical practices (eg, cadaver transplants,⁵⁰ xenotransplants,⁵¹ infections

such as HIV acquired by artificial insemination⁵²). Currently, however, there is limited evidence that hospital environments select for microorganisms that cause a new clinical syndrome or enhance the host range. An exception may be certain strains of *Staphylococcus aureus* of the 1950s and 1960s.⁵³ The penicillin-resistant 80/81 *S. aureus* strain was first identified in hospital nurseries but rapidly spread and produced severe community outbreaks, including enterocolitis, before disappearing in the late 1960s. The combined effects of lysogenization, transduction, and selection in these *S. aureus* strains appeared to affect not only the phage type and antibiotic resistance, but also properties more directly connected with pathogenicity, such as lipase production.⁵³

Anticipating Changes in the Transmissibility of Virulent Microorganisms in Immunocompromised Patients. Based on what is known about the mechanisms of microparasite virulence and its evolution, what reasons are there (if any) to anticipate changes in the transmissibility of virulent microorganisms in immunocompromised patients? Immunocompromised patients, whose numbers are rapidly increasing in both developed and developing populations, have higher rates of transmissible infections and may serve as reservoirs for infectious agents. Such reservoirs may cause increased disease in other immunocompromised patients and in normal hosts. Examples include *Varicella zoster* and respiratory syncytial virus infections among hospital workers and other pediatric patients, tuberculosis in healthcare workers, possibly increased *Mycobacterium avium-intracellulare* infections in normal hosts, and *Pneumocystis carinii* infections in immunocompromised hosts.⁵⁴ Immunocompromised patients, whether hospitalized or not, may represent an expanding intermediate habitat, that is, they provide an opportunity for adaptation of a pathogen to aspects of host biology that it would normally not get a chance to encounter, allowing the subsequent circumvention of the immune system in normal individuals to be easier.

In a related perspective, the release of laboratory-grown microbes has been raised as a potential source for emerging or reemerging infections. The release of anthrax in the former Soviet Union and during World War II,^{50,55,56} the studies of *S. marcescens* in San Francisco,⁵⁷ concerns over storage of smallpox virus,^{58,59} and the possibility of biologic warfare during the Persian Gulf war indicate the potential for this to occur.

Approaches to Emerging and Reemerging Infections

Anticipating, Preventing, and Limiting Emergence and Reemergence. The goals of such efforts should be first to predict when and where infections will emerge or reemerge; secondly, to recognize infec-

tions in the early stages of emergence; and thirdly, to control their spread once they emerge. Each of these goals is associated with financial, social, and environmental costs. The process should involve the development of general and mathematical models to predict and evaluate infectious disease dynamics, the development of improved surveillance systems for the detection of infectious pathogens, and the selection of strategies for limiting the spread of an emerging or reemerging infection (eg, sanitary measures, quarantines, distribution of antibiotics or vaccines, distribution of treatment protocols, education). Each of these steps requires a thorough understanding of the pathogenesis of the infection and such efforts should involve a multidisciplinary team including clinicians, epidemiologists, microbiologists, statisticians, immunologists, veterinarians, entomologists, vector-borne disease experts, population biologists, evolutionary biologists, behaviorists, anthropologists, and sociologists.

It is clear that both ecological and evolutionary changes are likely to be important in disease emergence and that they are likely to interact. We need to be able to predict the effects of environmental change, to know what kinds of traits change genetically, and whether some environments favor genetic change more than others.

Role of Models in Understanding Emerging Diseases. The development of general and mathematical models* (Table 3) to address emerging and reemerging infections allows the creation of testable hypotheses. Modeling may provide a conceptual framework for integrating relevant information and identifying deficits, as well as answering practical questions in clinical medicine (eg, given pathogen X, what drug regimen is best) and public health (eg, optimum vaccination program, outbreak response, potential for emergence).

Modeling has played an important role in evaluating the factors responsible for observed patterns of infections in natural systems of plants and animals. Examples include predicting outbreaks of disease in gypsy moth populations,⁶⁰ modeling Anther-Smut disease in perennial wildflowers,^{61,62} and modeling the dynamics of parasitic nematodes in red grouse⁶³ to identify strategies for conservation biology of animal populations. Mathematical models have also been used successfully to design human vaccination programs—particularly in the United Kingdom,^{25,64} but also in the United States⁶⁵—to predict the

spread of rabies,⁶⁶ and more recently, to explore the dynamic consequences of HIV transmission early in the course of infection, long before AIDS is manifest.⁶⁷

Models and comparative studies help address the question of whether or not there are unifying principles that help us to understand the ecology and evolutionary biology of different classes of pathogens. Modeling generates probability arguments as well as a framework and process for the assessment of emerging infections. Models have the potential to help us predict the rate of increase of an emerging disease. However, in cases where key facets of the pathogen's life history are not understood, models are likely to give unreliable results. In this regard, it is critical to determine when a modeling approach will be appropriate and when it will not. Allaying misgivings about details that may be important for some purposes but are extraneous for others requires multidisciplinary collaboration. Some areas where modeling may help are:

- Predicting the opportunities for host shifts in different groups of pathogens (this could mean either taxonomic groups or different classes of pathogens);
- If different kinds of dynamical situations lead to qualitatively different dynamics (either genetic or numerical), predicting how these differences relate to the problems of when, where, how and if an intervention should be used; and
- Predicting the long-term evolutionary implications of different kinds of emergence (eg, with respect to evolution of virulence or drug resistance).

Given often pressing needs to assess threats and evaluate means of controlling infectious disease, available information should be modeled as simply as possible. Transmission of pathogens via contact or airborne particulates depends on the time courses of morbidity and infective particle (propagule) production (Table 3). Some directly transmitted pathogens begin disseminating propagules before illness incapacitates their hosts, others do so only late in illness, while still others disseminate them throughout milder but more protracted illnesses, all with different dynamic consequences.

To evaluate the influence of parameters in simple models, sensitivity analyses should be performed, and to evaluate their structures, increasingly complex alternatives should also be considered. While age may be an important factor, age-structured models are less tractable than unstructured ones, complicating some issues unnecessarily. Latency and immunity can introduce additional complexity to model structure. Similarly, deterministic models in which distributed quantities are represented by non-parametric statistics will suffice for some purposes, while actual distributions must be employed in sto-

* The subject of models for emerging and reemerging infectious disease was vigorously debated at the meeting, and this section summarizes the various viewpoints that were expressed with respect to the value of models. While there is a discordance in perspective, all agreed that communication between medical practitioners, modelers, and those studying nonhuman disease could be productive and exciting.

Table 3. Steps to Modeling of Emerging and Reemerging Infectious Diseases

1. Articulate question
2. Make simple, heuristic models using available data. In simple models for directly transmitted pathogens in a human population subset (eg, daycare, military recruits, nursing homes, college students), factors contributing to the rate of increase of a pathogen are:
 - a. Morbidity and mortality rates, ie, degree to which illness incapacitates an infective person and hence, transmission, or removes infected individuals from the population.
 - b. Duration of infectiousness and persistence of infective propagules (infective particles) in environment
 - c. Infective propagule production rate and its temporal variation
 - d. Mode of transmission (eg, contact, sexual vector-borne or airborne propagules)
 - e. Recovery rates
 - f. Degree of acquired immunity and loss of immunity
 - g. Probability of transmission with contact
3. Complex models. Models for pathogens with free-living stages or intermediate hosts or vectors may require more complicated models that account for relevant aspects of the environment or biota, but the art of modeling is identifying factors that have the most notable impact on rates of disease spread.
4. Perform sensitivity analyses, not just of parameters given structure of model, but evaluate alternative structures (eg, must age be considered and if so, what are the relevant classes; do we need to consider the latent period; how can we simplify expressions for transmission process?)
5. Expand sensitive parameters of structurally sound models into functions and obtain information required to parameterize them.
6. Observe and evaluate empirical data to test the validity of model predictions.
7. Data needed for modeling may include: % with mortality (time from onset of disease), % with morbidity, % asymptomatic, length of latent period, length of asymptomatic period, periodicity of infection, total span of infectious period, progressive stages (degree and length), specificity and duration of immunity, modes of transmission, host range and co-infections. For many infectious diseases, a systematic effort to gather such information often has not been made.

chastic models for others. This decision effectively determines if analytical solutions are possible or if simulations are required.

Then, sensitive parameters of structurally sound models should be expanded into functions, and the information required to parameterize them obtained. Does immunity wane, and if so, is the rate constant, or does it depend on age and whether acquired via infection or immunization? Details of the environment or other biota may be required to model pathogens with free-living stages, intermediate hosts, or vectors. The suspicion that much of the requisite information will prove inaccessible, if not unavailable, for many infectious diseases leads us to anticipate the need for surveillance and other means of learning whatever needs to be known, and for interdisciplinary interactions whereby already collected information can be accessed. This process should continue while additional data are collected, such that models always embody current knowledge, facilitating its communication and guiding further research.

A distinction between use of models for emerging and for reemerging diseases must be made. Modeling approaches will probably work better for reemerging diseases than emerging diseases. With reemerging diseases, we may have a well-established set of model parameters that can be refined to existing parameter estimates. New emerging diseases, by contrast, are much more difficult to model. Critical life-history parameters and life-history characteristics of the pathogen are often unknown. Distinguishing between models that are "predictive" (ie, too true to be good) and models that are "heuristic"

(ie, too good to be true) is also important. Heuristic models provide a basis for generalizations that then can be a launching point for investigation of specific cases. The empirical "food" for such generalizations are comparative studies of broad classes of infections. Comparative studies are needed to evaluate the possibility of general principles or classes of features that would help us to understand, first, the evolution of new diseases and transmission modes, and second, the probabilities (at least qualitative) of emergence, resurgence, evolution, and host-shifts. By gathering as much information as possible, some useful generalities have emerged for sexually transmitted diseases⁶⁸ (eg, that STDs cause less mortality, are less likely to invoke immune responses, and have narrower host ranges). Our ability to identify a set of characteristics unique to a class of infectious disease allows us to construct general models incorporating (and focusing on) those features which are relevant to infections. We can use such models to ask how combinations of features interact to influence both population and genetic dynamics, evolution of transmission (eg, under what conditions should a disease evolve to be sexually transmitted) and virulence in the pathogen, and evolution of host features (eg, resistance). Of course, for any specific disease, not all of the factors incorporated into a general model will be equally important (which is why natural history and ecological information on diseases is also important). Nevertheless, analysis of the general models will allow us to investigate how changes in model structure might affect the outcomes.

The arguments about the importance of general

principles is particularly true, for example, for computing even qualitative probabilities of a new disease emerging and expanding. At the present time, we have no way of knowing what factors are likely to influence the probability of such an event. Certainly, we have a list of factors that we *think* might be important, but we have limited evidence. In actual fact, there are data (new diseases are constantly appearing), but they are not easily accessible, nor is the kind of data needed to construct a model always collected. The cases where a new disease has not "taken off" would provide useful comparisons with the smaller number of cases in which this has happened.

Models have also not been successful (eg, the swine influenza model leading to widespread vaccination⁶⁹). The failures of modeling illustrate the danger of assuming that models equal truth. Obviously, models are only as good as the assumptions built into them, but failures can tell us (in a formal way) more about the disease and may force us to study aspects of the disease that we would not have bothered to examine in the absence of a model.

Most of the models listed above and the modeling approach outlined in Table 3 are specific models used to predict the time course of a particular infectious disease. In contrast, general models are very useful to the extent that they illustrate dynamic behaviors that defy our intuition. To give a simple example, predator-prey models predict that the equilibrium abundance of a predator or parasite will be *inversely* proportional to its search rate. This is an example of something that one might not expect in the absence of a general model. General models, however, are of little value in predicting whether a specific infectious disease will emerge.

Research Needs. Critical for new research in emerging infectious disease is the *exchange of information* between diverse scientists interested in emerging infections. A major and pervasive problem has been the gap in communication between physicians and epidemiologists, and population and evolutionary biologists. This gap is certainly understandable, as it arises from qualitative differences in training and focus. Perhaps a useful strategy would be to develop collaborative units which would involve physicians, computer programmers, theoretical and empirical population and evolutionary biologists, epidemiologists, public health officials, and others interested in emerging infections.

A coordinated effort to develop useful data bases would be invaluable. Such efforts ideally would include comparative and phylogenetic studies, theoretical models, and empirical studies to test theoretical ideas where possible. While we cannot do experiments on human populations, almost certainly the same generalities and principles will apply to diseases in wild animal or plant populations. Integ-

rative databases on diseases in natural populations of animals and plants would be useful to researchers with a wide variety of purposes. Moreover, the process of developing such databases will not only help us to identify what is known but also what is unknown about a specific infection.

Better methods and global efforts (eg, ICD9 codes of organisms associated with disease) are needed to identify emerging and reemerging infections through surveillance. Surveillance systems for the early detection, tracking, and evaluation of emerging infections are needed, including the development of effective inter-nation networks. Programs to monitor and control vector-borne and zoonotic infections should be included. New technologies such as remote sensing and geographical information systems should be evaluated for their usefulness. In addition, revision of the ICD-9 codes for infectious diseases to reflect the microorganism responsible for the disease would be useful. Surveillance encompasses risk assessment in order to recognize the increased susceptibility of populations and accomplish prevention strategies.

Emphasis should be placed on applications of new technologies to emerging and reemerging infections. For example, new techniques of the polymerase chain reaction (PCR), nucleotide sequencing, and genetic mapping can revitalize our ability rapidly to detect virulence determinants, epidemiologic markers, and infectious disease-causing organisms.

The development of modeling to offer probability arguments is an important area of research. Currently, it is often not possible to develop predictive models for either the treatment or control of specific infectious diseases. In facilitating communication, the value of identifying general principles, and consequently the value of models, must be recognized. At the same time, population biologists and the medical community must work together to determine what kinds of data can be realistically gathered. In order to construct meaningful infectious disease-specific models, we still must first understand the underlying commonalities. Population ecologists and theoreticians are a vital component of many epidemiology departments, and students interested in infectious diseases research should be exposed to classes in traditional theoretical ecology and evolution.

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