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Preface



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Guest Editor

Infectious diseases are changing in ways that are unprecedented in scope and scale. The dynamic nature of infectious diseases has become increasingly evident in recent years, because of the appearance of new infectious diseases, the recognition of previously unidentified pathogens, the resurgence and change in the distribution of well characterized diseases, changes in resistance patterns (almost always involving increased resistance) of microbes to antimicrobial agents, and, in some instances, the appearance of more virulent forms of pathogens.^{1,2} These infections affect people, plants, and animals; the pathogens come from all classes of organisms—bacteria, viruses, fungi, protozoa, and helminths. Changes are occurring in all regions of the world and are not restricted to pathogens that are spread from person to person; they also involve pathogens with other mechanisms of transmission.

Many broad factors are contributing to the global changes in infectious diseases.^{1,3} Multiple factors contribute to each emerging infection, which is described clearly in many of the articles in this issue. Emergence of an infectious disease is typically complex. For example, one cannot single out just one factor that led to the appearance and rapid broad spread of West Nile virus infections in the United States and in the Americas. The complexity of the contributing factors also makes it difficult to anticipate and predict where and when new microbial threats will emerge. A single simple intervention usually will not suffice for prevention.

Socioeconomic, political, demographic, and environmental changes are among the many factors involved in the emergence of new microbial threats.^{1,2} Many infectious diseases (or their vectors or intermediate hosts) are sensitive to temperature, humidity, and climatic factors, so they potentially can be influenced by global climate change. Land use and alteration of the environment (including clearing forests, building roads, dams, and other structures) can affect patterns of infectious diseases. The characteristics of global populations today—size, density, mobility, and location—make the world especially vulnerable to new microbial threats.⁴ The size of the human population and that of animals raised for food is larger than ever, providing unprecedented opportunities for microbial replication, mutation, and adaptation. The size of many urban populations now is sufficient to sustain the ongoing circulation of certain viruses, such as dengue.

Mobility, as described in the article on travel, is unprecedented in volume, reach, and speed. Movement involves people, plants, and animals and allows juxtaposition of species that have never been in contact before and novel opportunities for transmission across species, especially from animals to humans.⁵ The high density of populations also facilitates the spread of microbes to large and interconnected populations. For the first time in human history, more than half of the world's people live in urban areas. Urbanization in tropical and subtropical areas and global travel have been key factors in the emergence of dengue virus infections in many tropical areas.

The expansion of concentrated food animal operations in the United States, and increasingly in other countries, means that large concentrations of genetically similar animals are living together in close proximity, a milieu that could allow the rapid spread of a pathogenic microbe.⁶ These sites also may be the setting for the emergence of resistance genes and microbes that can infect humans.

The location of the most rapid population growth today and the location with the most projected population growth in the coming decades is urban areas in low latitudes—predominantly in developing countries and often in urban areas that lack adequate infrastructure to provide clean water, sanitation, and adequate housing and nutrition. Periurban slums at the periphery of these cities are inhabited by residents who work in the city but remain connected to families in rural areas, and they provide a conduit for movement of pathogenic microbes in both directions: from rural areas into the city and from the city to rural areas.⁴ These tropical and subtropical locations are also regions with greater species richness and presumably have a greater range of pathogens that could potentially infect humans.⁷ Surveillance for infectious diseases in humans and animals often is limited in developing countries because of inadequate laboratory facilities and a lack of resources. The presence of many endemic infectious diseases, such as malaria and other infections that can cause fever, may mean that recognition and identification of a new or unusual infection in that area may be delayed or that infection may go completely unrecognized. Serosurveys of populations in tropical areas confirm the circulation of viruses and other pathogens causing infections that have not been recognized in the health care systems in those areas. Information about infections in some areas of the world becomes available through surveillance networks that use returned travelers from those areas as sentinels.⁸ Careful evaluation of returned ill travelers in developed countries where specialized laboratory support is available may help distinguish pathogens (or sequence specific strains or assess sensitivity patterns to antimicrobials) from other parts of the world.⁹

Global changes in microbial threats are possible because of the abundance, variety, and the very nature of microbes.¹ Microbes are old (existing before humans) and diverse and occupy every part of earth, including areas that are extremely hot, cold, or have other extreme environments. Humans have identified only a small fraction of microbial species that exist, and presumably, they have identified only a small portion of those that are pathogenic for humans. The vast majority of microbes are not pathogenic for humans. Many are essential for life. It is their capacity for rapid replication and evolution through a variety of mechanisms that allow them to adapt to changing environments, whether physical, chemical, immunologic, and so forth. The progressive development of bacteria's resistance to antibiotics (including *Mycobacterium tuberculosis* to anti-tuberculosis drugs), the malaria parasite's resistance to antimalarials, and influenza's resistance to antiviral agents over the past few decades are examples of microbes' remarkable capacity to adapt to human-applied antimicrobial interventions.

PEOPLE, PIGS, AND POULTRY: THE THREAT OF AVIAN INFLUENZA

Avian influenza is an emerging microbial threat that illustrates the complex factors involved in an evolving disease and the dynamic nature of an infectious disease over time. Although avian influenza brings to mind H5N1 (which was first identified in Hong Kong as a cause of deaths in humans in 1997), multiple avian influenza viruses exist.¹⁰ The H5N1 virus is remarkable not only for the high mortality it causes when it infects humans, but also the rapidity of its spread and its extreme lethality in poultry populations. Because of the potential threat that it poses to human populations, poultry populations have been killed when they have been infected with H5N1 in an attempt to eliminate the virus. Despite the slaughter of hundreds of millions of chickens over the past decade, H5N1 persists in parts of the world and has continued to spread in avian populations. Although chickens infected with H5N1 have high mortality, the virus can infect ducks and other avian species without causing death, allowing the virus to persist and potentially spread. Mallard ducks, for example, can be infected with H5N1 and excrete abundant virus without clinical or pathologic evidence of disease.¹¹ Migratory bird species can be infected and can carry viruses into new areas, though their precise contribution to the global spread of the virus is uncertain. Global movement through trade (legal and illegal) of poultry, their parts, and materials contaminated with H5N1 virus also clearly plays an important role in the movement of the virus. In one instance, two crested hawk-eagles smuggled by a traveler in hand luggage from Thailand to Brussels via Vienna were placed in overhead compartments on commercial airplane flights. The birds were seized in Brussels because they were arriving from an area with H5N1 infection. Although the birds appeared healthy, after necropsy and further testing, both were found to be infected with H5N1.¹²

Because the H5N1 virus is shed in feces, it can contaminate water, straw, feathers, cages, and other materials that come into contact with infected poultry. Although infection of poultry has been widespread and dramatic, the influenza virus also can infect nonhuman mammalian species. Feline species in zoos were infected fatally when they were fed carcasses of poultry infected with H5N1. The wide host range of H5N1 also includes dogs and cats, animals that potentially have close contact with humans.

Infection of humans with H5N1 has been infrequent but has produced disastrous outcomes. As of June 19, 2008, 385 human infections had been confirmed from 15 countries; of these infections, 243 were fatal.¹³ Approximately 90% of confirmed infections have been in persons 40 years of age and younger. Most of those infected were previously healthy individuals. The overall case fatality rate exceeds 60%. Serologic surveys in areas with human cases suggest that asymptomatic and mild infection with H5N1 is rare. Most deaths from H5N1 follow fulminant viral pneumonia, but evidence of disseminated infection has been found by autopsy in some people who died from H5N1.¹⁰ The virus also has been found in feces and the intestine, suggesting replication may occur in the gastrointestinal tract. Tissue damage in infected individuals appears to be caused by high levels of viral replication and severe inflammatory responses to infection. Treatment with high doses of antiviral agents is recommended, but resistance to antiviral agents has been documented.

Most human infections appear to be the result of close contact with live or dead poultry or their products. Transmission might result from contact with contaminated fomites or material containing poultry feces. Although a few instances of person-to-person spread likely have occurred in settings where individuals had close contact, this virus has not caused sustained person-to-person spread or airborne transmission to date.¹⁴ Given the number of billions of replication events that have occurred with this virus in avian and other hosts, it appears that changes (via mutation, recombination, or reassortment)

that would allow the virus to become easily transmissible from person to person have not occurred in a setting where the virus could sustain spread. Because the virus persists and now is entrenched ecologically in many parts of Asia, it still could undergo such changes. Some investigators are working on a methodology to use when interpreting surveillance data in real time that would have predictive capacity to better allocate interventions.¹⁵

Many of the conditions that exist in southern Asia favor the evolution of new strains of influenza viruses. Asia is home to a large, densely settled human population living in close proximity to large populations of multiple avian species and swine. Many residents have chickens, ducks, and other avian species that live in and around their houses. Close contact with avian species is common and widespread. Several studies have found an association between the presence of H5N1 and the abundance of free-ranging ducks and with rice farming intensity and human population.¹⁶ This provides an ideal setting for the mixing of influenza viruses that infect humans, pigs, and avian species. As the standard of living in China and other countries improves, the population is able to afford more protein in the diet, which often comes in the form of poultry and pork. Many animals are raised in backyards, and larger animal production facilities are starting to appear in many developing countries. In China, for example, the human population increased about twofold (790 million to 1.3 billion) between 1968 and 2005, while the swine population increased almost 100-fold (5.2 million to 508 million), and the poultry population increased more than 1000 fold (12.3 million to 13 billion).¹⁷

There is evidence that the viruses that cause the seasonal influenza outbreaks globally originate in Asia. A recent study that carried out antigenic and genetic analysis of the hemagglutinin of thousands of human influenza A (H3N2) viruses from six continents assessed the global circulation of these viruses. The results suggested that, at least from 2002 to 2007, influenza H3N2 epidemics worldwide (including in temperate areas) were seeded annually by viruses that had arisen in East and Southeast Asia.¹⁸ Most of the strains in Asia descended from other Asian strains and evolved during temporally overlapping epidemics in East and Southeast Asia. In tropical areas, influenza does not show the strong seasonality that is evident in temperate areas, and transmission can occur throughout the year, presumably because transmission is more efficient in cold, dry conditions, as has been shown in a guinea pig model.¹⁹ Transmission by contact is equally efficient at high and low temperatures, suggesting that contact and short-range spread may be the predominant modes of transmission in tropical areas.²⁰

H5N1 continues to evolve, as do other influenza viruses. Another avian influenza virus, H7, has caused outbreaks in poultry since 2002 and has caused human infection in poultry workers. Although H7 influenza virus can infect humans, most of the infections so far have been mild and self limited. One lineage of this virus appears to have acquired cell binding characteristics that more closely resemble those of human influenza viruses, which could favor transmissibility.²¹ This is a reminder that scientists and surveillance systems must be alert to a broad range of influenza viruses that could cause human disease.

It is uncertain if H5N1 will undergo the changes necessary for it to transmit efficiently from person to person while maintaining its current capacity to cause severe disease, killing more than half of those infected with it. It is much more certain that we will have another influenza pandemic. Whether one will emerge with the destructive force of the 1918-1919 pandemic is not certain, but it could. The current global circumstances with large, dense, extensively interconnected populations would result in the rapid spread of influenza or another infection with efficient person-to-person spread, like severe acute respiratory syndrome (SARS). In an analysis of factors that make an infection more or less difficult to control, Fraser and colleagues²² note that

the proportion of transmission that occurs before onset of symptoms or by those who are asymptomatic is important in assessing the likelihood that the isolation and tracing of contacts could be effective in halting the epidemic spread of a pathogen. SARS was contained because almost all persons infected became symptomatic before they could transmit the virus, which is in contrast to HIV/AIDS, which is transmitted mostly by people who are asymptomatic or unaware that they are infected. Typical influenza is difficult to control, because transmission can begin before the onset of symptoms.

Ongoing research and development focused on H5N1 vaccines potentially will provide knowledge that can be used to develop vaccines against other diseases as well. Researchers are making progress, and investigators recently reported that a whole-virus H5N1 vaccine derived from cell culture was immunogenic in a two-dose regimen without adjuvant.²³

The most important emerging infection of recent decades, HIV/AIDS, originated from an animal reservoir (probably chimpanzees), and the best evidence suggests that the virus entered the human population on several occasions.²⁴ Traveling humans have effectively spread HIV-1 genetic variants globally, leading to an ongoing devastating pandemic.²⁵ We can hope that the lessons learned from the global spread of HIV and current work prompted by outbreaks of avian influenza and SARS viruses can help to avert or limit the spread of other microbial threats in the future. Given the remarkable capacity of microbes, humans should remain vigilant and anticipate that the future will continue to bring new microbial threats. By better understanding the multiple forces that lead to these events, we may be able to identify high risk geographic areas and populations, try to reduce their vulnerabilities, and develop early interventions.

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