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Emerging and Re-Emerging Infectious Diseases: Influenza as a Prototype of the Host-Pathogen Balancing Act

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DOI 10.1016/j.cell.2006.02.010

To respond to emerging and re-emerging infections, it is necessary to understand the interactions between microbial pathogens and their hosts and the impact of environmental and social factors on these interactions. The importance of understanding host-pathogen interactions is underscored by the emergence of virulent H5N1 avian influenza viruses and their transmission to humans, and the potential pandemic threat they pose.

Infectious diseases have always afflicted mankind and always will. New infectious diseases emerge and old diseases re-emerge as microbes adapt to new hosts and new environments. To remain one step ahead of our pathogenic microbial foes, we must understand in detail how pathogens interact with their hosts, and how biological, environmental, and social factors combine to allow pathogens to infect new organisms. Deciphering each step in the different processes by which microbes adapt to new hosts is critical to developing effective countermeasures to detect, prevent, and treat infectious diseases. Our current efforts to prepare for the unpredictable event of a possible global influenza pandemic and to minimize the burden of highly predictable, seasonal influenza epidemics exemplify the challenges of trying to keep up with and hopefully stay ahead of the influenza virus, a constantly evolving pathogen.

A Delicate Balance

Infectious diseases are the second leading cause of death throughout the world. In 2002, according to the World Health Organization (WHO, 2002), more than a quarter of approximately 57 million deaths worldwide were caused by infectious diseases. Millions of additional deaths are due to the secondary effects of infec-

tions. Among people under the age of 50 years, infectious diseases are the leading cause of death and account for nearly one-third of all healthy years lost to illness (Morens et al., 2004).

An estimated 75 percent of emerging infectious diseases in humans are zoonotic in origin, that is, they arise from microbes that infect other animals (Taylor et al., 2001). Most microbes have evolved to reach an equilibrium with their natural hosts without causing disease. However, factors such as economic development and land use leading to perturbations in the natural microbial environment, human demographics and behavior, and international travel and commerce can create an imbalance in the established microbe-host equilibrium and trigger the emergence of new infectious diseases. Human intrusion into settings such as rainforests has led to exposure of humans to viruses and other microbes that otherwise would not have occurred. For example, the practice of butchering nonhuman primates for “bushmeat” may be in part responsible for the “jumping” of HIV from its natural animal hosts to human hosts, as well as for the recent Ebola virus outbreaks in Central Africa. The flow of rural populations into cities, urban poverty, and weakening of traditional family and social structures have

led to increased sexual promiscuity, prostitution, and other practices that undoubtedly fueled the spread of HIV/AIDS in Africa. An outbreak of Nipah virus in Malaysia occurred when pigs penned near fruit orchards contracted the virus from the droppings of bats, whose habitat had shifted as a result of deforestation. The infected pigs readily transmitted the virus to their handlers. The spread of bovine spongiform encephalopathy (BSE), or mad cow disease in cattle, and variant Creutzfeldt-Jakob disease in humans, primarily in the United Kingdom, resulted from the practice of feeding cows grain containing the remains of scrapie-infected sheep (Morens et al., 2004).

New diseases do not emerge or re-emerge in a vacuum—they do so against a background of established infectious diseases and host-microbe interactions that have existed for centuries. The diseases that make up this matrix were at some point emerging diseases that had never been previously observed in human populations but eventually became so entrenched in the population that they became part of the background infectious disease burden. For example, in the late 1970s and early 1980s, HIV/AIDS clearly was an emerging disease, but now it is an endemic matrix (background) disease. More recent examples of

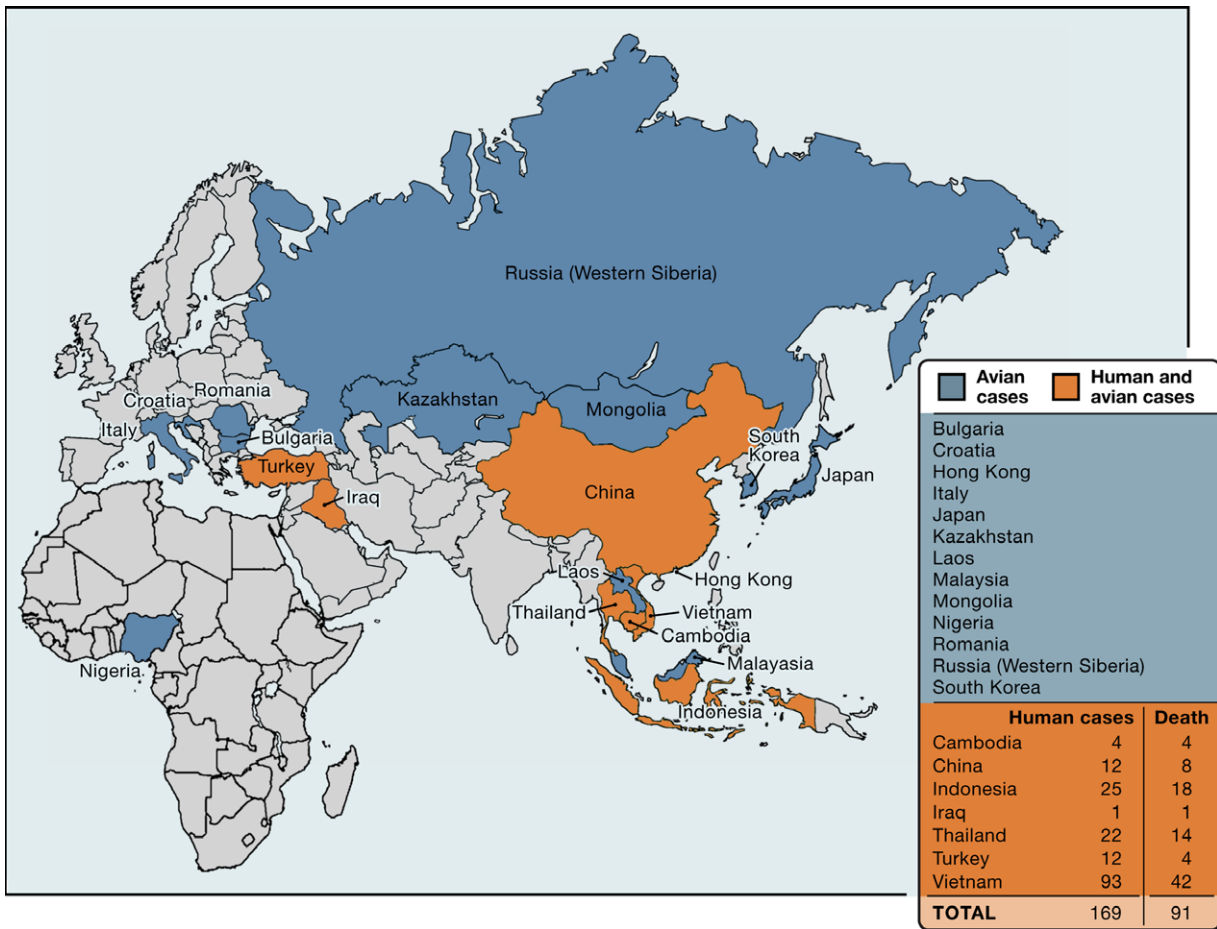


Figure 1. Documented H5N1 Influenza Cases among Birds (Blue) and Humans (Orange) 2003–February 9, 2006

newly emerging infectious diseases include Severe Acute Respiratory Syndrome (SARS), Nipah virus encephalitis, Lassa fever, and most recently, human disease caused by the H5N1 strain of avian influenza virus. Infectious diseases that have previously occurred in humans also can re-emerge or resurge in different forms or in different environments. Examples include West Nile virus in the western hemisphere; monkeypox in the United States; dengue fever in Brazil, other parts of South and Central America, and even the Caribbean; and multidrug-resistant tuberculosis throughout the world (Morens et al., 2004).

Humans and microbes coexist in a delicate balance amid an ever-present tension. Microbes possess the ability to adapt naturally to their

hosts, to their environment, and to new ecological niches offered to them as humans encroach upon their territory. They are also adept at circumventing efforts to suppress them, whether as a result of internal host pressures such as innate and adaptive immune responses or in reaction to external pressure applied by antibiotics, antivirals, or vaccines. In the face of our efforts to eliminate them, microbes almost always adapt successfully, thwarting our efforts to destroy them.

Influenza

A prototypic example of the constant struggle between microbes and man is the evolutionary success of influenza viruses as they adapt to their many hosts, including humans. Research to understand how influ-

enza viruses coexist with hosts that serve as their natural reservoirs and attempts to delineate the factors that result in viruses adapting to new hosts and triggering disease serve at least two purposes. This information is crucial to controlling yearly, seasonal influenza epidemics and preventing the devastation that may occur should a global influenza pandemic emerge. In addition, research into the natural evolution of influenza viruses and their adaptation to different hosts may inform our efforts to understand other infectious diseases that emerge and re-emerge in unpredictable ways.

Influenza is fundamentally a recurring background or matrix disease that usually re-emerges each year in a slightly different form (antigenic drift). However, it occasionally

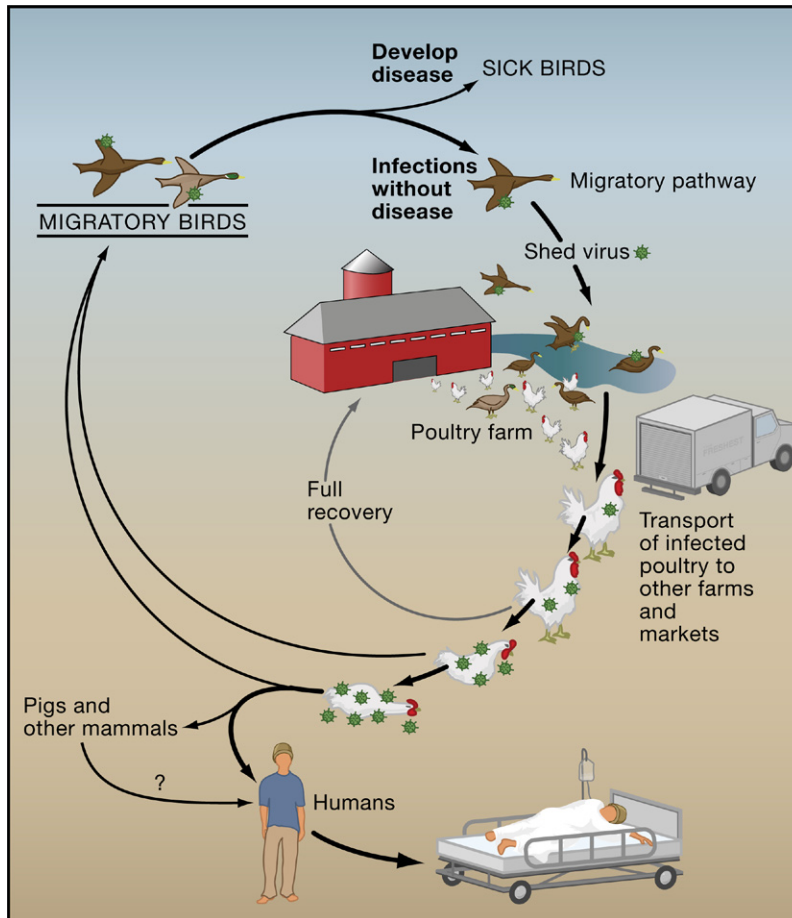


Figure 2. Possible Mode of H5N1 Avian Influenza Virus Transmission among Migratory Birds, Domestic Poultry, and Humans

Migratory birds harboring a low pathogenic strain of influenza virus are generally without symptoms of disease but can excrete virus. If a low pathogenic avian influenza A virus is transmitted to domestic poultry through direct or indirect contact or by exposure to fecal droppings, the virus can progressively mutate following passage from one susceptible bird to the next. This is illustrated in the figure by the increase in the number of infectious virions (green) following each passage of the virus from bird to bird until a mutant virus emerges that replicates to high levels and can kill the infected bird. Poultry harboring low pathogenic virus can make a full recovery, but those with highly pathogenic mutant forms of the virus almost always succumb to the virus and die. A highly pathogenic strain of H5N1 avian influenza virus replicates more efficiently and can be transmitted among poultry and from poultry to pigs and other mammals, including humans, through direct or indirect contact and via transport of infected poultry to other farms and markets. Susceptible migratory birds can become infected with the highly pathogenic mutant forms of the virus. Recently, migratory birds have started to show signs of disease from infection with the highly pathogenic H5N1 strain and may be able to transmit the more virulent virus to other birds, both wild and domestic, along their flight path, leading to rapid spread of the virulent virus.

assumes a presentation as a newly emerging disease, very different from what the global society has previously experienced (antigenic shift). Seasonal influenza kills about 250,000 to 500,000 people worldwide each year, mostly older individuals; in the United States, an average of 36,000 influenza-related deaths occur each year. In addition to the ever-present and largely predictable threat of seasonal influenza, the world also faces the threat of a much more unpredictable pandemic influenza, caused by the emergence of a new strain of influenza virus to which humans have never been exposed. Over the past two years, the risk of an influenza pandemic has grown, as an exceptionally virulent form of the H5N1 avian influenza virus has circulated widely among domestic poultry and wild migratory birds in Asia, Eastern Europe, the Middle East, and Africa. As of February 9, 2006, the

virus also has infected more than 166 people since late 2003, of whom half have died (WHO) (see Figure 1).

Pandemics occur when a new influenza virus variant emerges to which the human population has no immunity. Influenza A viruses are most dangerous to humans because of their wide host range, their rapid mutation rate, and their capacity to cause serious disease (Wright and Webster, 2001). Influenza A subtypes are defined by the expression of two key surface proteins: hemagglutinin (H) and neuraminidase (N). Sixteen hemagglutinins are known to exist, each of which can be "paired" with one of nine neuraminidase proteins. These influenza A subtypes are all maintained in aquatic birds, which serve as a continual source of new viruses. A key factor in the possible emergence of an avian influenza virus as a human pandemic strain is the evolution and adaptation of

the virus to the human species. By understanding the etiology of previous influenza pandemics, scientists are trying to elucidate the steps that currently circulating H5N1 avian influenza viruses would need to take to become capable of efficient transmission from human to human.

In 1918, the H1N1 avian influenza virus subtype emerged, and the ensuing pandemic called the Spanish Flu killed an estimated 40–50 million people worldwide. In subsequent years, humans built up a degree of immunological memory to H1N1 influenza as it circulated in the general population, causing less severe yearly influenza epidemics. Then, in 1957, another strain to which humans had no prior experience—the H2N2 influenza virus—appeared and triggered a pandemic that resulted in the deaths of an estimated 1–2 million people globally. In 1968, the H3N2 subtype emerged,

yet another strain to which humans had no prior exposure; this pandemic resulted in the deaths of approximately 700,000 individuals. Since 1968, variants of H3N2 have circulated to cause seasonal epidemics; in 1977, human H1N1 viruses reappeared, and these also continue to circulate (Wright and Webster, 2001).

The 1918 virus was an avian virus that adapted to humans through a series of point mutations (Taubenberger et al., 2005). In contrast, the 1957 and 1968 pandemic influenza viruses were the products of reassortment, that is, they derived three genes from an avian influenza virus and their remaining five genes from the previously circulating human influenza viruses (Wright and Webster, 2001).

The H5N1 virus was first recognized in chickens in Scotland in 1959. At an unknown point in time, the H5N1 avian influenza virus began to appear in poultry flocks in Southeast Asia, causing only mild symptoms of disease in birds before the mid 1990s. In late 1996, it became evident that the virus had mutated to a highly pathogenic form that could kill chickens within 48 hr, with a nearly 100 percent mortality rate. In 1997, the first human cases of highly lethal H5N1 influenza occurred in Hong Kong; 18 people were infected, and 6 died. Public health authorities in Hong Kong ordered a massive culling of poultry, which apparently prevented further spread of the virus at that time. However, in early 2003, the virus reappeared in a Hong Kong family who had recently visited mainland China. In late 2003, H5N1 surfaced again, first in Vietnam and then Thailand (http://www.who.int/csr/disease/avian_influenza).

The highly pathogenic H5N1 strains of influenza currently circulating—predominantly in poultry—are primarily animal pathogens and already constitute a true pandemic among chickens. Whether the virus develops into a strain capable of spreading from human to human in an efficient and sustained manner, thereby triggering a human pandemic, will depend

on how the virus evolves and adapts to new hosts. Since its re-emergence in Southeast Asia in 2003, the virus has appeared in poultry in at least 18 countries and in multiple species of migratory birds. The virus also has been found in other animals, including pigs, tigers, and leopards. The virus has infected at least 93 people and killed 42 people in Vietnam. As of February 9, 2006, there have been at least 22 human cases and 14 deaths in Thailand, 4 cases (all fatal) in Cambodia, 25 cases and 18 deaths in Indonesia, 12 cases and 8 deaths in China, 12 cases and 4 deaths in Turkey, and 1 fatal case in Iraq, with the toll continuing to rise every week (see Figure 1).

H5N1 influenza viruses had originally circulated in wild birds without causing disease and without mutating into highly virulent forms. Ominously, however, the currently circulating H5N1 viruses appear to have the ability to mutate in domestic poultry to highly pathogenic forms. As the virus has infected chickens and other domestic poultry, it has become increasingly virulent and has achieved the capability of jumping species to humans and to other animals with lethal consequences. Most alarmingly, the virus now seems to be transmitted from poultry back to migratory birds and, for the first time, is causing disease in the migrating bird population. This unprecedented pattern of transmission is an important reason why public health officials are watching the H5N1 virus carefully because it is a strain with the potential to cause the next influenza pandemic (see Figure 2) (http://www.fao.org/ag/againfo/subjects/en/health/diseases-cards/special_avian.html).

Researchers recently reconstructed the entire coding sequence of the H1N1 virus that triggered the 1918 influenza pandemic (Taubenberger et al., 2005). They found that this virus, presumably avian in origin, did not reassort with putative human viruses circulating at that time. Rather, the virus accumulated a series of mutations that enabled it to more efficiently infect and replicate in human cells, explaining its rapid prop-

agation among humans. By comparing sequences of the 1918 virus with known avian and human influenza viruses, it was possible to identify a set of 10 amino acid residues among the three viral polymerase proteins that are associated with the ability of the virus to infect and replicate efficiently in human cells. Thus far, the H5N1 virus has accumulated five of the ten changes in the encoded polymerase protein sequences that were found in the 1918 virus and are commonly found in human influenza viruses. This suggests that the H5N1 virus may be accumulating changes associated with an increased likelihood of human-to-human transmission (Taubenberger et al., 2005).

A Multifaceted Response

The 1918 pandemic caught public health officials completely by surprise—it was not even known then that the illness was caused by a virus. Today, however, as we face the prospect of another global influenza pandemic, we have a unique opportunity that did not exist in 1918. We have the tools to monitor genetic sequences of influenza viruses as they evolve in both humans and birds. We also have the capacity to develop and manufacture countermeasures against new strains of influenza. As we prepare for the possibility of the next pandemic influenza it will be important to optimize the use of available public health measures and scientific tools and technologies.

An effective response to H5N1 avian influenza virus or any emerging and re-emerging infection requires a comprehensive, multifaceted approach. Surveillance, public health measures, and biomedical research—including the ability to isolate infectious agents, decipher pathogenic mechanisms, and develop appropriate diagnostics, therapies, and vaccines—are all critical components of a multipronged response to emerging and re-emerging infectious diseases, including both seasonal and pandemic influenza.

As noted, H5N1 avian influenza viruses are rapidly evolving pathogens with the potential to trigger a

possible pandemic. It will be critical to maintain diligent surveillance of the virus in both animal and human populations in order to monitor its evolution and capacity to sustain efficient human-to-human spread. Isolation and characterization of the virus in real time are critical as we develop vaccines and antiviral drugs that are effective among the circulating viruses with potential to cause widespread disease.

Antiviral medications such as oseltamivir and zanamivir have been shown to reduce the severity and duration of seasonal influenza. However, their efficacy in treating a potential influenza pandemic is uncertain. Therefore, a vaccine against circulating strains of the H5N1 virus will be critical in preventing widespread transmission of the virus should it develop the ability to spread readily among humans. In this regard, techniques to rapidly isolate and sequence circulating influenza viruses have been developed. Using a technique known as reverse genetics, researchers in academia and industry have developed prototype vaccines against the H5N1 virus and are currently testing their safety and immunogenicity in human volunteers. In a recent clinical trial, 451 healthy adult volunteers were vaccinated with two intramuscular doses of an inactivated H5N1 vaccine produced by Sanofi-Pasteur. Preliminary data indicate that the vaccine was well-tolerated and induced an antibody response predictive of protection, albeit at high doses (unpublished data). A trial of the same vaccine among >260 elderly volunteers is underway, with a third trial in pediatric volunteers planned for the spring of 2006.

Scientists also are investigating ways to increase the immunogenicity of H5N1 vaccines, including the use of adjuvants, employing intradermal rather than intramuscular administration, and developing live-attenuated vaccines. In this regard, a library of live-attenuated vaccines against all 16 major avian influenza subtypes is being developed through a Cooperative Research and Development

Agreement (CRADA) between MedImmune, Inc. and researchers at the National Institute of Allergy and Infectious Diseases. Once generated, production of these pre-existing stock vaccines could be scaled up and used to "pre-prime" individuals in an emergency situation while more specific vaccine formulations are being developed. Recent collaborative studies by researchers in the United States and China, involving genetic analysis of samples from 13,000 migratory birds and 50,000 domestic poultry, reveal that H5N1 viruses have been circulating among both wild and domestic birds in China for the past 10 years. These viruses have evolved into distinct genetic clusters associated with particular geographic regions. The studies suggest that the virus originated in China and has spread to neighboring and distant regions over the past decade (Chen et al., 2006).

The World Health Organization, along with the World Organization for Animal Health (OIE) and the Food and Agriculture Association of the United Nations (FAO, 2006), are coordinating efforts to monitor transmission of the H5N1 virus throughout the world and to prepare for the possibility of an influenza pandemic. Activities include increased surveillance of viral evolution and transmission among wild birds, domestic poultry, and humans, confirmation of etiologic agents in symptomatic patients and contacts, vaccine development and distribution, and stockpiling of antiviral treatments. WHO oversees a network of laboratories that monitor evolution of the H5N1 virus and prepare prototype vaccine strains for vaccine manufacturers. Currently ten countries have domestic vaccine manufacturers and several of these companies are developing pandemic vaccines. Although several countries have reported that efforts to vaccinate poultry are planned or underway, no companies are currently prepared to produce pandemic vaccines commercially for use in humans.

A major challenge to an effective response to influenza and the threat of a pandemic is the need to repair

our fragile vaccine production enterprise. In the 1970s, more than two dozen pharmaceutical companies were licensed to sell vaccines in the United States. Today, only four are licensed to manufacture influenza vaccine for distribution within the United States. It is important to develop partnerships among government, academia, and industry to increase the capability of developing new vaccine manufacturing technologies, such as cell-based culture techniques that will allow for greater flexibility and surge capacity in the production of vaccines. Indeed, it is essential for the U.S. Federal government to partner with pharmaceutical companies to develop and sustain the manufacturing capacity for vaccines and therapies that can be made available in an expeditious manner in the eventuality of a pandemic. Equally important is the institution of policies that will provide incentives to vaccine manufacturers to enter and remain in business.

Influenza and the threat of an influenza pandemic present a unique challenge to public health and the biomedical research enterprise worldwide. Although available technology offers sophisticated tools with which to monitor the evolution and characteristics of the virus, it will also be essential to use our knowledge and resources wisely. Increased cooperation among governments and public health agencies will be critical. The sharing of epidemiological data and deployment of countermeasures in the geographic areas where they are most likely to result in disease containment are equally important. Ongoing efforts in basic biomedical research also are critical to the comprehensive pandemic preparedness effort, including studies to understand viral pathogenesis; the ongoing search for new antivirals; new platforms and targets for vaccines, such as recombinant DNA and vector approaches; as well as improved vaccine manufacturing methods.

We do not know whether H5N1 will be the virus that triggers the next influenza pandemic. However, as we increase our efforts to improve our

capacity to respond to this virus, we also will increase the likelihood that we can efficiently and effectively respond to any future pandemic influenza as well as to any emerging or re-emerging pathogen that threatens mankind.

ACKNOWLEDGMENTS

The author thanks Nancy Touchette, Gregory K. Folkers, Hillery Harvey, Kanta Subbarao, and Brian Murphy for helpful discussions and for reviewing the manuscript.

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