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Global Infections—Avian Influenza and Other Significant Emerging Pathogens: An Overview

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The single greatest threat to man's continued existence on earth is the virus.
Joshua Lederberg, Nobel Laureate

Infections remain a leading cause of death worldwide.[1-7] Although the United States has been able to significantly control many of the infectious diseases that continue to afflict much of the rest of the world, these pathogens remain a threat to us nevertheless.[2,3] Control of emerging infectious diseases can be a daunting task given the large number of disease-causing organisms and the opportunity for adaptation, evolution of antimicrobial resistance, and host factors.[1-7] Also, newer pathogens are emerging, such as metapneumovirus.[8] Other new viruses, often from East Asia, nosocomial infections continue to be a persistent cause of preventable death in U.S. hospitals, and mutations of existing pathogens into highly virulent strains is likely to continue.[1,5] In addition to the natural evolution of pathogens, global modernization and development are increasingly placing people into new regions and environments and thus new exposures. Bioterrorism represents another risk of exposure to emerging diseases through the intentional use of biological agents—military grade and adapted naturally found pathogens.[1,4] As such, there are numerous emerging infectious threats that are suitable for an entire edition of *Disease-a-Month* to address. Global travel, immigration into the U.S. from countries with endemic illnesses not commonly found in North America, and societal factors (domestic and international) that include poverty, homelessness, institutionalization, overcrowding, and lack of access to health care set the stage to create conditions that facilitate the emergence and spread of previously unknown, little recognized, or emerging illnesses that are endemic to or novel strains in foreign lands that can become very quickly clinical realities to the United States.[1-7]

Although the scope of this edition focuses on avian influenza, it is important to recognize that preparedness efforts as a response to a potential pandemic can also enhance awareness, diagnostic, and treatment

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capabilities toward other significant infectious diseases worldwide and underscore the importance of continued vigilance for and training about these pathogens.[1,4,5,7] The following are pathogens that have the potential to cause outbreaks and remain significant public health problems.

Tuberculosis (*Mycobacterium tuberculosis*; TB) is the second most common cause of death in the world, resulting in 3-4 million deaths annually and 8 million new cases a year. It is also the most common opportunistic infection associated with HIV.[9] This is not just a global threat, but a domestic one, with drug- and multidrug-resistant TB continuing as a significant public health concern. Of concern, extremely drug-resistant TB (XDR-TB) is emerging. TB is often problematic to treat in the most common form; a strain that is resistant to most of the first- and second-line treatments could be devastating if allowed to go unchecked.

Infection such as measles is a virus long viewed as both a childhood disease and one that has been controlled in the U.S. This notwithstanding, measles is still the cause of severe illness worldwide. Moreover, there continue to be outbreaks in the U.S. among unimmunized or inadequately immunized individuals. In 2006, a computer programmer from India infected with measles arrived in Boston, Massachusetts.[10] In response to his infecting several individuals, 23,000 doses of measles vaccine were ordered and/or distributed in anticipation of the potential for a significant public health crisis. Only 56% of infants in India are vaccinated against this potentially lethal pathogen, whereas 93% of U.S. children are. Measles is one of the top 5 causes of death worldwide for children. Clearly, global travel can bring infections from far-off lands into our waiting rooms and communities with relative ease!

Malaria remains a significant global health problem and is vector borne. How many of us or our colleagues have seen or treated a case, yet it is one of the leading causes of death for children and adults worldwide. Plague remains a significant public health problem in selected nations worldwide, with sporadic cases occurring in the U.S., sometimes being diagnosed long distances away from where the infection occurred. Recall the couple visiting New York City who fell ill, only to be diagnosed with *Yersinia pestis* (plague), which they were exposed to from rodent excreta at the Southwest home.

Unexpected pathogens in the 1990s, such as West Nile Virus (WNV), have become almost household words by 2007. In fact, WNV has become almost synonymous with mosquito-borne illness, yet worldwide Dengue is the most common mosquito-borne infection and is quickly becoming a global public health concern, given that 2.5 billion people live in areas where dengue viruses can be transmitted! The geographical spread of

both the mosquito vector and dengue viruses has led to a global resurgence of both dengue fever and dengue hemorrhagic viruses.[7] How many clinicians have seen a case or could readily recognize dengue or other hemorrhagic fever viruses in a patient?

It is important to note that servicemen and servicewomen returning from the Middle East and other foreign lands may harbor endemic illnesses that U.S. physicians may be unaware of or unaccustomed to treating. In anticipation of veterans returning from the Persian Gulf and other places across the globe, it is important to familiarize ourselves with pathogens that are likely to infect them.

During the 20th century there were several major influenza outbreaks and three pandemics occurring in 1918, 1957, and 1968. The most important was the Spanish Flu global epidemic of 1918 that resulted in 50 million deaths, although some estimates suggest an even higher loss of life.[6,11] This does not reflect the full toll that such outbreaks inflict upon a society, which includes economic, emotional with the loss of loved ones, and of course illness that does not result in death. Experts express concern that it is only a matter of time until the next pandemic occurs; it's not "if" but "when" an influenza virus mutates into a highly virulent, contagious strain.

In 1997 the world was introduced to a likely candidate to create such a pandemic: highly pathogenic avian influenza HPA H5N1.[6] H5N1 is a particularly worrisome strain of influenza virus not only because it mutates rapidly and has a tendency to acquire genes from other strains of influenza viruses that may concomitantly be infecting other animal species, but because it has demonstrated several of the characteristics necessary for a pathogen to cause a pandemic: ability to cause severe disease and death in humans against a backdrop of a population with little to no inherent immunity for which no widely available vaccine exists and capable of person-to-person transmission. Evidence from subsequent outbreaks of H5N1 in Vietnam suggest changes in the virus consistent with this possibility. Of the latter two, the FDA recently approved an H5N1 vaccine, and H5N1 remains at the present inefficient at person-to-person transmission, albeit it is likely to acquire that ability given the adaptability of this virus. During that year, several persons became infected with an avian influenza strain that resulted in significant illness in chickens and resulted in the almost total destruction of Hong Kong poultry flocks in an attempt to contain the disease. It was a successful strategy, for the moment.

In 2002 an antigenically distinct strain of avian influenza emerged in the same location in China, and by 2005, was infecting humans subsequently

as well as spreading to numerous species of birds and resulting in the deaths of hundreds of millions of birds and almost 200 people. A new Euro-African lineage of H5N1 has resulted in several fatal human infections in Egypt by 2007.[11,12] Genetically the virus is becoming more antigenically diverse and forming distinguishable groupings. Genome analysis has shown that H5N1 now has 3 distinct lineages (clades) with sublineages and reassortment occurring. This is worrisome as it demonstrates the virus persisting and evolving.[12]

In 2003 another pathogen became recognized as a global threat by the World Health Organization (WHO) with the potential to become a global pandemic—a novel coronavirus, Severe Acute Respiratory Syndrome (SARS), or SARS CoV.[13] The first known cases of SARS occurred in Guangdong province, China in November 2002. SARS CoV is believed to be an animal virus that crossed the species barrier to humans, perhaps as a result of ecological changes or human behaviors that placed people in greater proximity to coronavirus that lead to viral adaptation and subsequent human to human transmission. By July 2003, SARS CoV spread internationally and resulted in over 8000 cases in 26 countries with 774 deaths reported.[13] Although WHO considers the world to be in an inter-epidemic period, it remains difficult to predict when or if another SARS will emerge, let alone cause another outbreak, especially given that the natural reservoir of SARS CoV has not been identified or contained.

In terms of birds infected and killed across several continents, avian influenza has already caused a global pandemic. Will the next human pandemic be the result of avian influenza? We hope this issue of *Disease-a-Month* will assist the reader in understanding the highly pathogenic avian influenza H5N1 and enhance your preparedness efforts.

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