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Insight, part of a Special Feature on Risk mapping for avian influenza: a social-ecological problem

Public Health and Epidemiological Considerations For Avian Influenza Risk Mapping and Risk Assessment

Joseph P. Dudley [1,2]

ABSTRACT. Avian influenza viruses are now widely recognized as important threats to agricultural biosecurity and public health, and as the potential source for pandemic human influenza viruses. Human infections with avian influenza viruses have been reported from Asia (H5N1, H5N2, H9N2), Africa (H5N1, H10N7), Europe (H7N7, H7N3, H7N2), and North America (H7N3, H7N2, H11N9). Direct and indirect public health risks from avian influenzas are not restricted to the highly pathogenic H5N1 "bird flu" virus, and include low pathogenic as well as high pathogenic strains of other avian influenza virus subtypes, e. g., H1N1, H7N2, H7N3, H7N7, and H9N2. Research has shown that the 1918 Spanish Flu pandemic was caused by an H1N1 influenza virus of avian origins, and during the past decade, fatal human disease and human-to-human transmission has been confirmed among persons infected with H5N1 and H7N7 avian influenza viruses. Our ability to accurately assess and map the potential economic and public health risks associated with avian influenza outbreaks is currently constrained by uncertainties regarding key aspects of the ecology and epidemiology of avian influenza viruses in birds and humans, and the mechanisms by which highly pathogenic avian influenza viruses are transmitted between and among wild birds, domestic poultry, mammals, and humans. Key factors needing further investigation from a risk management perspective include identification of the driving forces behind the emergence and persistence of highly pathogenic avian influenza viruses within poultry populations, and a comprehensive understanding of the mechanisms regulating transmission of highly pathogenic avian influenza viruses between industrial poultry farms and backyard poultry flocks. More information is needed regarding the extent to which migratory bird populations to contribute to the transnational and transcontinental spread of highly pathogenic avian influenza viruses, and the potential for wild bird populations to serve as reservoirs for highly pathogenic avian influenza viruses. There are still uncertainties regarding the epidemiological and ecological mechanisms that regulate "spill-over" and "spill-back" transmission of highly pathogenic avian influenza viruses between poultry and wild bird populations, and the interspecies transmission of avian influenza from infected birds to humans and other species of mammals. Further investigations are needed to evaluate the effectiveness of poultry vaccination programs for the control and eradication of avian influenza in poultry populations at the national and regional level, and the effect of long term poultry vaccination programs on human public health risks from avian influenza viruses. There is a need to determine risk factors associated with the extent of direct human involvement in the spread and proliferation of avian influenza viruses through commercial supply chain and transportation networks, and specific risk factors associated with domestic and international trade in live poultry, captive wild birds, poultry food products, (meat, eggs), poultry by-products (feathers, poultry meal), poultry manure, and poultry litter. Addressing these issues will greatly enhance our ability to implement economically and ecologically sustainable programs for the control of avian influenza outbreaks in wild and domesticated birds, increase our capability for promoting the protection of wild bird populations from disease and disruption, and help improve food security and public health in countries worldwide.

Key Words: *avian influenza; biosecurity; epidemiology; geographic distribution; health; risk assessment; risk mapping.*

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INTRODUCTION

Risk mapping is the process of identifying areas at different levels of risk ....

the representation of the results of risk assessment on specific maps,

showing the levels of expected losses which can be anticipated in specific areas ...

Interregional Response To Natural and Man-Made Catastrophies Project 2007

Risk assessment:

The evaluation of the likelihood of entry, establishment, or spread of a pest or disease ... . the associated potential biological and economic consequences, and ... ... potential for adverse effects on human or animal health.

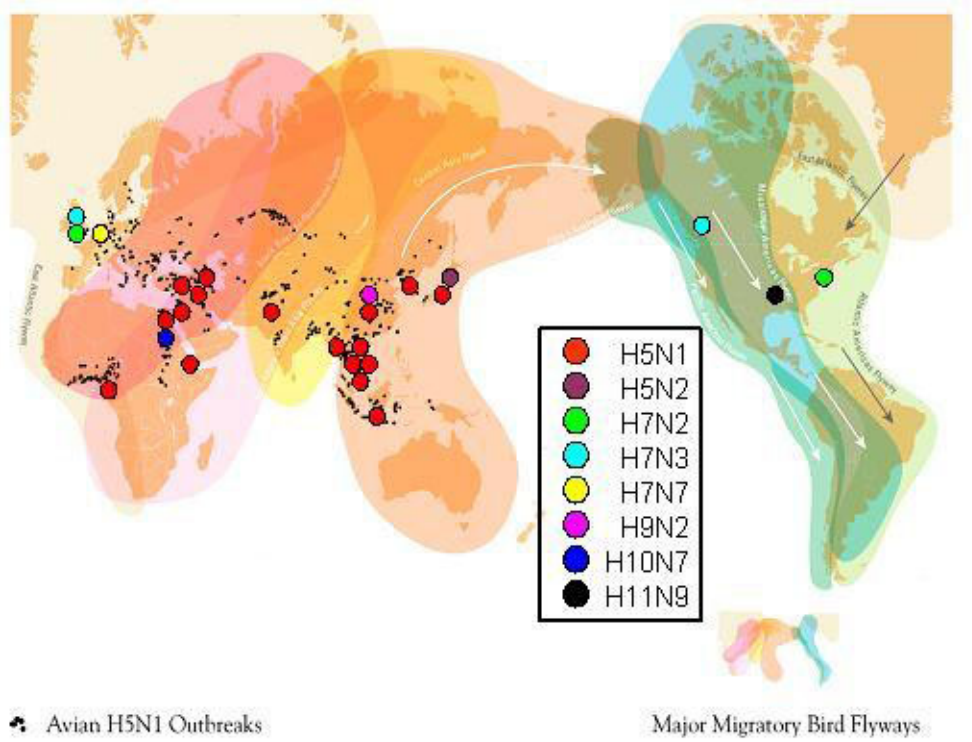
World Trade Organization 1995

The global publicity surrounding the impacts of the H5N1 highly pathogenic avian influenza virus has fostered wide public recognition of the potentially serious economic and public health impacts of avian influenza outbreaks (Alexander 2006), and research over the past decade has identified avian influenza viruses as a source for pandemic human influenza viruses that could have severe economic and public health impacts on countries worldwide (WHO 2005*a*). All known avian influenza viruses are Type A influenza viruses, and Type A viruses are the most pathogenic of the known classes of influenza viruses. Public awareness of the potential economic and public health risks associated with avian influenza outbreaks has increased dramatically during the past decade, in conjunction with radical increases in the frequency, magnitude, duration, and economic impacts of highly pathogenic avian influenza (HPAI) outbreaks in commercial poultry populations worldwide (Alexander 2006). Human health risks from avian influenzas are not restricted to the highly pathogenic H5N1 "bird flu" virus, however, and there have been documented human infections with high pathogenic and low pathogenic strains of other avian influenza virus subtypes.

Although wild-type low pathogenic avian influenza (LPAI) virus strains generally cause few if any clinical disease symptoms in affected birds, mortality rates from highly pathogenic avian influenza (HPAI) virus strains in poultry flocks may be as high as 90–100% (Alexander 2006). Prior to the onset of the current H5N1 avian influenza epizootic in 1997, only a few isolated instances of avian influenza virus infections in humans had been reported, all involving H7N7 avian influenza viruses, and none of which were believed responsible for causing serious human disease (Campbell et al. 1970, Taylor and Turner 1977, Kurtz et al. 1996, Subbarao and Katz 2000). During the past decade, however, human infections with avian influenza viruses have been reported from Asia (H5N1, H5N2, H9N2), Africa (H5N1, H10N7), Europe (H7N7, H7N3, H7N2), and North America (H7N2, H7N3, H11N9), and more than 200 people are known to have died from fatal disease caused by H5N1 and H7N7 avian influenza viruses (Gill et al. 2006, Luke and Subbaro 2006, CDC 2007, WHO 2008*b*: Fig. 1). Although human infections with most avian influenza viruses typically involve mild symptoms and non-contagious infections, fatal human disease and human-to-human transmissions have been confirmed from persons infected with avian influenza viruses of the H5N1 and H7N7 subtypes (Chan 2002, Koopmans et al. 2004, du Ry van Beest Holle et al. 2005, Ungchusak et al. 2005, Kandun et al. 2006, Yang et al. 2007, WHO 2008*c*.)

The emergence of a potentially lethal zoonotic H5N1 avian influenza virus in China during 1997, and the subsequent transcontinental spread and proliferation of strains of this virus in poultry and human populations, have imposed significant public health and economic burdens on many countries in Asia, Europe, Africa, Indonesia, and the Middle East. Bans on the importation of poultry products from countries affected by avian influenza outbreaks since 1997 have resulted in economic losses that may be as high as U.S. $50 billion, and reports collected by the author indicate that at least one billion domesticated fowl, e.g., chickens, ducks, geese, turkeys, ostriches, quail, pheasants, peafowl, have been killed or culled in conjunction with outbreaks of highly pathogenic avian influenza (HPAI) outbreaks in poultry worldwide since 1997. The current H5N1 HPAI avian influenza panzootic has now become the most extensive animal disease epidemic ever recorded, an event complicated by the fact that this epizootic involves a pathogen that can cause fatal disease in birds, mammals, and

Fig. 1. Global distribution of reported human infections with avian influenza viruses, laboratory-related cases excluded, as of March 2008. Avian H5N1 outbreak records are as of March 2008 and include poultry, and free-living or captive wild birds. Migratory bird flyway configurations after Olsen et al.(2006), based on migration data from Wetlands International for sandpipers, plovers, snipes, and allied taxa of the Order Charidriiformes. Arrows show potential transit routes for H5N1-infected migratory birds from Asia and Europe into the Americas.



humans. The current H5N1 avian influenza panzootic is unique and unprecedented as either an animal disease or zoonotic disease outbreak in terms of its virulence, duration, and geographic scope (WHO 2005*a*).

First reported as a highly pathogenic poultry virus strain from Guangzhou Province in southeastern China during 1996, the H5N1 avian influenza emerged as a potentially lethal zoonotic pathogen in 1997 following the acquisition of internal genes from H9N2 virus found in domestic quail (Guan et al. 2000, Cheung et al. 2007). This newly reassorted H5N1 virus caused widespread outbreaks among chicken populations in Hong Kong during 1997 and resulted in 18 known human infections, 6 of which were fatal (Mounts et al. 1999, To et al. 2001, Tam 2002). Although the 1997 Hong Kong H5N1 virus strain was successfully extirpated through the institution of a draconian culling and market disinfection regime, the precursor of the Hong Kong H5N1 virus continued to circulate and evolve within poultry populations on mainland China (Guan et al. 2000, 2002, Webster et al. 2006*a*). Genetic analyses show H5N1 virus strains spread from an epicenter in southern China to Thailand, Vietnam, and Indonesia during 2002 and 2003 (Wang et al. 2008). Since 2003, natural or experimentally induced H5N1 infections have been reported from more than 100 species of birds and at least 9 species of wild and domestic mammals, including domestic swine and domestic cats (USGS 2007). Evidence of

recurrent outbreaks of H5N1 HPAI virus in Asia, Africa, and Europe indicates that the virus has become endemic and possibly ineradicable within poultry populations in many of the countries affected by widespread H5N1 outbreaks during the past several years, e.g., China, Vietnam, Indonesia, Egypt, Nigeria, Bangladesh (FAO 2007).

The first reported human fatalities subsequent to the 1997 H5N1 avian influenza epizootic in Hong Kong were recorded in China during February 2003 (Edwards et al. 2004, Peiris et al. 2004), followed by additional cases in Vietnam during October 2003 and China during November 2003 (Zhu et al. 2006, WHO 2008*a*). During the 6-mo period from November 2005 to April 2006, the number of countries in which wild birds or poultry infected by the H5N1 HPAI virus had been confirmed increased from 16 countries to 55 countries, whereas the number of countries with confirmed fatal human cases increased from only 5 countries in Asia to a total of 9 countries in Asia, Africa, and the Middle East (China, Vietnam Thailand, Cambodia, Indonesia, Turkey, Egypt, Iraq, Azerbaijan). By December 2007, H5N1 outbreaks in wild birds or poultry had been reported from at least 61 countries in Asia, Africa, Europe, and the Middle East (FAO 2007). As of March 2008, fatal human H5N1 bird flu infections have been confirmed from 12 countries in Asia, Africa, Europe, and the Middle East (WHO 2008*b*). Although the average case fatality rates for H5N1 among officially confirmed human cases worldwide since 1997 is approximately 60%, it is important to recognize that Indonesia, the country with the highest numbers of confirmed human cases of any country, had a case rate mortality of >80% as of March 2008 (WHO 2008*b*).

The epidemiological characteristics of the H5N1 virus in humans have changed significantly since the time of the 1997 Hong Kong epizootic, with higher observed rates of morbidity and mortality occurring among children and adolescents recorded in laboratory confirmed cases reported since 2003 (Tran et al. 2004, Chotpitayasunondh et al. 2005, Areechokchai et al. 2006, WHO Regional Pacific Office 2007). Should the H5N1 bird flu virus acquire the capability for efficient sustained human-to-human transmission, the H5N1 bird flu strain could generate a human influenza pandemic that could have serious impacts on the public heath, food security, and economic vitality of countries all across the globe (Webby and Webster 2003, Guan et al. 2004, Bartlett and Hayden 2005). Research has shown that the 1918 Spanish Flu pandemic virus, which may have killed as many as 50-100 million people worldwide between 1918–1919, was an H1N1 influenza virus of purely avian origins (Stevens et al. 2004, Taubenberger et al. 2005).

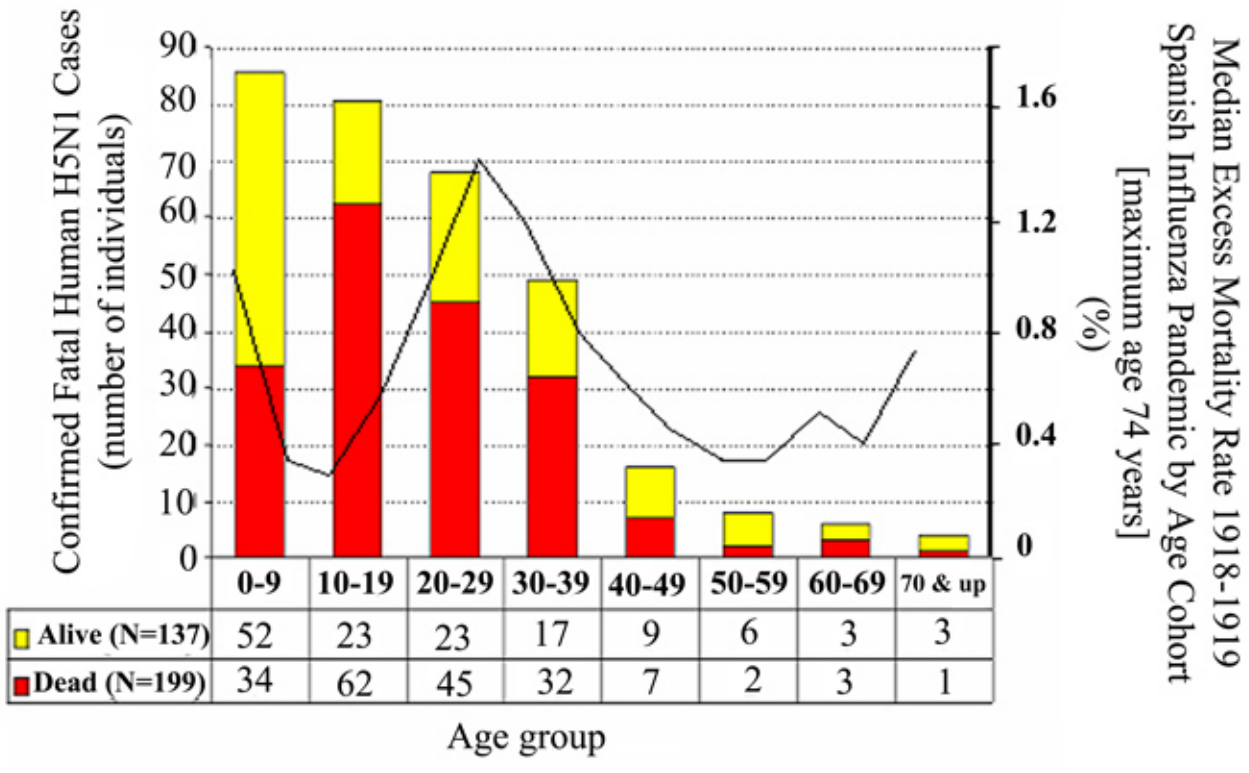
Given the current high level of virulence of the H5N1 virus in humans, human mortality worldwide from a pandemic strain of the H5N1 virus could reach levels as high as 180–360 million people (Osterholm 2005). Although there appear to be marked parallels in the clinical presentations of fatal cases of the H5N1 bird flu and 1918 Spanish Flu, the age-specific mortality profiles for these two viruses is markedly different, i.e., peak mortality from the 1918 Spanish Flu was concentrated among infants, the elderly, and individuals in the 25–35-yr age range (Taubenberger and Morens 2006), whereas peak mortality among confirmed human cases of the H5N1 bird flu occurs among individuals in the 10–19-yr age cohort (Fig. 2). This observed difference in age-specific mortality rates is significant in view of the potential differences in the terms of the generally higher relative and absolute numbers of individuals within younger age cohorts of developing countries in Asia and Africa, where the highest rates of human mortality from avian influenza infections have been recorded.

This paper identifies and discusses phenomena and issues that are important to a comprehensive understanding of the potential direct and indirect effects of avian influenza viruses on human health and human society, with the goal of facilitating the development of more accurate risk assessments of the potential impacts of avian influenza outbreaks on ecosystems, agriculture, and human society.

HUMAN DISEASE RISKS

Clinical symptoms of avian influenza infections in humans range from asymptomatic infection or mild conjunctivitis to fatal systemic disease and multiorgan failure, including severe or fatal respiratory, gastrointestinal, or neurological syndromes (de Jong and Hien 2006*a*, Sandrock and Kelly 2007, Abdel-Gafar et al. 2008). Avian influenza infections in humans are believed to occur through virus contact and inoculation of the eyes, respiratory tract, and possibly the gastrointestinal tract: gastrointestinal infection by the H5N1 avian influenza viruses has been demonstrated in other species of mammals and is a normal route of

Fig. 2. Comparison of age-specific mortality from H5N1 "Bird Flu" and H1N1 "Spanish Influenza" viruses. Bar graph shows proportions of confirmed fatal and non-fatal human H5N1 cases by 10-yr age cohort as of September 2007 (data from WHO Regional Pacific Office, WHO Epidemic and Pandemic Alert and Response Network). Line graph (after Murray et al. 2006) shows estimated age specific excess mortality rates from the 1918-1919 H1N1 Spanish Influenza pandemic.



infection in birds (Rimmelzwaan et al. 2006, Songserm et al. 2006, Wong and Yuen 2006, Gu et al. 2007). Although most human infections by avian influenza viruses are attributable to exposure to infected poultry, human infections resulting from exposure to avian influenza viruses from wild birds have been documented from Eurasia (H5N1: Azerbaijan), North America (H11N9: United States), and Africa (H10N7: Egypt) (PAHO 2004, Gill et al. 2006, Gilsdorf et al. 2006).

Although documented human infections with most avian influenza viruses have involved only conjunctivitis or only mild respiratory disease symptoms, fatal disease has been reported from persons infected with H5N1 and H7N7 viruses (Fouchier et al. 2004, Beigel et al. 2005). Human infections with the H5N1 virus are typically associated with pneumonia and other severe acute respiratory tract symptoms (Cheung et al. 2002, de Jong et al. 2006, Sandrock and Kelly 2007). Nonetheless, the clinical spectrum of H5N1 infections in humans is quite broad, and H5N1 virus has been recovered from many different body tissues, i.e., lung, brain, large intestine, small intestine, cerebrospinal fluid, kidney, spleen, liver, pharynx, blood, placenta, and the in-utero transmission of H5N1 from mother to fetus has also been reported (de Jong and Hien 2006, Gu et al. 2007, Ng and To 2007, Shu et al. 2008). Fatal

atypical human H5N1 infections involving only gastrointestinal and neurological symptoms have been documented from patients in Vietnam and Thailand (Apisarnthanarak et al. 2004, de Jong et al. 2005), and asymptomatic human infections with H5N1 have been reported from China, Vietnam, Japan, and Korea.

Avian influenza infections have been reported from North America (H7N2) and China (H5N1) from individuals with no evident direct exposure to diseased birds or poultry (Yu et al. 2007). No specific risk factors for human infection with the H5N1 virus other than exposure to sick and dead poultry or birds have been identified with absolute certainty (Dinh et al. 2006, Nicoll 2006), and it remains unclear why acute illness from H5N1 infections is so infrequently reported among poultry industry workers in countries where H5N1 outbreaks have been reported on commercial poultry farms (Bridges et al. 2002, Croisier et al. 2007). Plucking and butchering of diseased poultry or wild birds, handling of fighting cocks, exposure to live poultry, consumption of uncooked duck's blood, and intimate contact with infected humans in household or hospital settings have been implicated as risk factors for human infection with the H5N1 virus (Bridges et al. 2000, 2002, Beigel et al. 2005, CDC 2006, Dinh et al. 2006, Gilsdorf et al. 2006). Environmental exposure to poultry viruses through swimming or bathing in contaminated water, and exposure to poultry manure fertilizer, have been identified as possible risk factors for human infection with the H5N1 avian influenza virus (de Jong et al. 2005, Abdel-Ghafar et al. 2008, Giriputro 2008).

Serological surveys conducted during an epidemiological investigation of the 1997 H5N1 outbreak in Hong Kong detected possible asymptomatic infections in 10 people (de Jong and Hien 2006). Confirmed asymptomatic H5N1 cases were identified in three people in Vietnam who were close relatives of confirmed H5N1 cases, and two animal attendants who had contact with infected tigers in Thailand (WHO 2005*b*). Serological studies have detected mild or asymptomatic H5N1 infections in five people involved in culling operations in Japan during 2004 (Hayden and Croisier 2005), and among 10 poultry workers in Korea exposed to the H5N1 virus during outbreaks in 2003–2004 and 2006. The serologically confirmed human cases reported from H5N1 outbreaks in Japan and Korea are unusual in at least two respects: first, because all the recorded infections were from poultry workers or people involved in culls, and second, because all reported cases in these countries involved asymptomatic or only very mild clinical disease symptoms. Serological surveys have confirmed at least 13 human infections with an H5N2 virus in conjunction with outbreaks of a low pathogenic H5N2 on commercial poultry farms in Japan during 2005 (Ogata et al. 2008).

Although most human infections with H7N7 viruses have involved conjunctivitis or mild respiratory symptoms, a fatal H7N7 case involving severe acute respiratory distress syndrome was reported from a veterinarian involved in culling operations during a widespread outbreak of an H7N7 virus in the Netherlands during 2003 (Fouchier et al. 2004). Conjunctivitis was reported as the principal symptom for human H7N3 infections in the United Kingdom in 2006, and conjunctivitis and mild respiratory illness were reported for human H7N3 cases recorded in Canada during 2004 (Tweed et al. 2004). Human infections from an H9N2 virus have been recorded in Hong Kong and mainland China on several occasions since 1999, and involved patients who presented with nonfatal respiratory or influenza-like disease symptoms (Lin et al. 2000). Conjunctivitis and respiratory symptoms were reportedly exhibited by suspected human H7N2 cases during a May 2007 outbreak in the United Kingdom (National Public Health Service for Wales 2007). Three of four confirmed human H7N2 cases from this outbreak reportedly exhibited respiratory disease symptoms, whereas one confirmed case was reportedly hospitalized for treatment of gastrointestinal and neurological symptoms.

Human-to-human transmission

Human-to-human transmission has been documented for H5N1 and H7N7 avian influenza viruses (Bridges et al. 2000, du Ry van Beest Holle et al. 2005, Unguchusak et al. 2005), and human-to-human transmission of an H7N2 avian influenza virus may have occurred during a May 2007 outbreak in the United Kingdom (DEFRA 2007*a*, *b*). Human-to-human transmission of an H5N1 HPAI virus was first documented during the 1997 outbreak in Hong Kong, and subsequent instances of probable human-to-human transmission of H5N1 viruses have been reported from Thailand, Vietnam, Indonesia, and Pakistan (Bridges et al. 2000, Chan

2002, Parry 2004, Beigel et al. 2005, Ungchusak et al. 2005, Kandun et al. 2006, Wong and Yuen 2006, Yang et al. 2007, Finkelstein et al. 2007, WHO 2008*c*). Human-to-human transmission of highly pathogenic H7N7 virus was documented in conjunction with a widespread series of outbreaks of a highly pathogenic H7N7 virus among poultry farms in the Netherlands during March–May 2003, in which there was at least one human fatality from this virus among the 89 cases diagnosed at the time of the outbreak (Koopmans et al. 2004, du Ry van Beest Holle et al. 2005). Subsequent serological investigations documented at least 33 instances of human-to-human transmission among the families of infected poultry workers, and estimated that at least 1000 individuals and possibly as many as 2000 people in the Netherlands were infected by the H7N7 virus over the course of the 2003 outbreak (Bosman et al. 2005, van Boven et al. 2007). Epidemiological investigations were undertaken to determine whether human-to-human transmission of an H7N2 avian influenza virus occurred during an outbreak in the United Kingdom during May 2007 involving at least four confirmed human cases, three of whom were hospitalized for treatment prior to their diagnosis as human avian influenza cases (National Public Health Service for Wales 2007, DEFRA 2007*b*.)

Antiviral resistance

Antiviral resistance is an increasingly important issue because human avian influenza vaccines are not yet widely available, and treatment of human infections is currently limited to supportive therapy and treatment with antivirals (Hayden et al. 2005, Hayden 2006). Many of the H5N1 virus strains circulating in southeast Asia are genetically resistant to adamantane antivirals, (e.g., amantidine, rimantadine), and H5N1 strains that are genetically resistant to oseltamivir have been documented in Vietnam and Egypt (Le et al. 2005, WHO 2007). Cheung et al. (2006) found that although >95% of H5N1 viruses isolated in Vietnam and Thailand contained mutations that confer resistance to adamantine antivirals, much lower frequencies of resistant H5N1 strains are seen among samples from Indonesia (6.3% of isolates) and China (8.9%). The H5N1 viruses circulating in Indonesia during 2005 have been shown to be 15–30 times less sensitive to oseltamivir than 2003 H5N1 virus strains from Vietnam, and H5N1 viruses from the 2005 outbreak in Turkey have been shown to be approximately 60 times less sensitive to oseltamivir than 2004 H5N1 strains from Vietnam. Research has shown that H5N1 strains recovered from Cambodia in 2005 exhibited a 6–7-fold decrease in oseltamivir sensitivity compared to 2004 H5N1 samples from the same area (McKimm-Breschkin et al. 2007). The current prevalence of adamantane resistant H5N1 HPAI viruses in Hebei province of northern China, where five of six H5N1 viruses collected during 2005 were found to be amantadine-resistant strains, has been linked to the widespread use of amantadine antivirals by poultry farmers in the region (He et al. 2007).

H5N1 HIGHLY PATHOGENIC AVIAN INFLUENZA: A CASE STUDY

The highly pathogenic H5N1 viruses circulating among poultry and wild bird populations in Asia, Europe, and Africa are significantly more virulent in both poultry and humans than the 1997 Hong Kong H5N1 virus strain. Death rates confirmed for recent human cases of the H5N1 avian influenza virus in Asia, Africa, and the Middle East since 2004, (60–80% case rate mortality) are more than twice as high as that reported for the 1997 Hong Kong H5N1 bird flu virus, (30%), and comparable to those recorded from human outbreaks of the Ebola hemorrhagic fever virus in central Africa. At least some H5N1 viruses are beginning to show indications of possible human adaptation through the acquisition and transmission of amino acid sequences characteristic of human influenza viruses (cf., Finkelstein et al. 2007, Twu et al. 2007), and there is a possibility that the H5N1 HPAI bird flu virus could become a pandemic human influenza virus through random genetic recombination or reassortment with a more human-adapted influenza virus. Both pigs and cats have been identified as potential "mixing vessels" or incubatoria for the reassortment of avian influenza viruses with swine or human viruses (Kida et al. 1994, Rimmelzwaan et al. 2006). This factor is particularly significant with regard to the H5N1 HPAI virus, because domestic pigs infected with H5N1 have been detected in China and Indonesia (Li et al. 2004, Cyranowski 2005), and H5N1-infected domestic cats have been reported from Indonesia, Europe, Asia, and the Middle East (Kuiken et al. 2004, Yingst et al. 2006).

The H5N1 virus has increased progressively in virulence, environmental stability, and infectiousness

to birds and mammals since 1997, when the first known human deaths from this virus were confirmed in Hong Kong (Chen et al. 2006). Empirical and experimental studies have demonstrated that most H5N1 HPAI strains tested under laboratory trials exhibit significantly higher levels of virulence and infectivity in birds, mammals, and humans than strains of earlier provenances (Chen et al. 2004, Li et al. 2004, Maines et al. 2005, Chen et al. 2006, Webster et al. 2006*a*, Webster et al. 2007: Table 1). The epidemiological characteristics of the H5N1 virus in humans has also changed significantly since the time of the 1997 outbreak, with higher observed rates of morbidity and mortality occurring among children and adolescents recorded in laboratory confirmed cases reported since 2003 (Tran et al. 2004, Chotpitayasunondh et al. 2005, Areechokchai et al. 2006, WHO Pacific Regional Office 2007). Given that domestic ducks are typically asymptomatic carriers of HPAI viruses (Hulse-Post et al. 2005), one of the most significant observed changes in the epidemiology of the H5N1 avian influenza virus from the evolutionary and ecological standpoints was the first appearance of fatal H5N1 outbreaks among domestic ducks and wild waterfowl during 2002, when flock mortality rates of 30% were observed during outbreaks among duck flocks in China and Vietnam (Chen et al. 2004, Sturm-Raimirez et al. 2004). Other observed changes of key evolutionary significance include a decrease in the stability of the H5N1 virus in water and a shift in the dominant modality of H5N1 virus shedding in infected poultry from gastrointestinal/fecal to respiratory/aerosol modes (Webster et al. 2006*a*, 2007, Brown et al. 2007). Although the continued widespread circulation and proliferation of H5N1 HPAI viruses in Asia, Africa, Europe, and the Middle East increases the potential opportunities for reassortment or stochastic recombination of an H5N1 strain into a pandemic human virus, the absolute level of risk for the emergence of a pandemic human influenza virus containing virulence factors derived from a H5N1 HPAI strain remains uncertain (Perdue and Swayne 2005).

The extent of the involvement of wild bird species in the transmission and proliferation of highly pathogenic avian influenza viruses, including but not limited to the H5N1 HPAI virus, is still uncertain (Cattoli and Capua 2007, Munster et al. 2007, Olsen et al. 2007, Pfeiffer 2007, Zepeda 2007). Wild birds imported for the exotic pet trade were responsible for an H5N1 outbreak in a quarantine facility in the United Kingdom during 2005 (Dudley 2006), and two eagles infected with H5N1 were confiscated by customs officials from the carry-on bag of a Thai national at an international airport in Belgium (van Borm et al. 2005). Experimental studies have shown that some species of wild ducks can survive infections with H5N1 virus strains that are highly pathogenic to poultry, and could potentially serve as long-distance vectors of highly pathogenic avian influenza viruses under some circumstances (Keawcharoen et al. 2008). Although transmission by wild birds appears to have been a factor in the spread of the H5N1 virus at the transnational and regional levels, it has yet to be demonstrated conclusively that infected asymptomatic migratory birds have served as vectors for highly pathogenic avian influenza outbreaks in poultry through the dispersal of viruses along seasonal long-distance migration routes (Kilpatrick et al. 2006). The first reported outbreaks of the H5N1 HPAI virus among poultry flocks in at least five countries in Europe and Africa, i.e., United Kingdom, Germany, Czech Republic, Israel, Nigeria, occurred within indoor poultry facilities, in the absence of any contemporaneous evidence of the virus within local wild bird or free-range poultry populations (FAO 2006). Intensive wild bird surveillance programs conducted in Europe during 2007 failed to detect any cases of H5N1 among any wild birds in most areas where domestic flocks were affected (Newman et al. 2007), which indicates that other routes of infection through poultry supply or distribution chains were responsible for outbreaks in domestic poultry populations in Europe during 2007 (Needham et al. 2007). An intensive wild bird surveillance program conducted under the auspices of the United Nations Food and Agriculture Organization (FAO) in Africa during 2006 subsequent to the appearance of widespread H5N1 outbreaks among poultry in Egypt and Nigeria found no evidence of H5N1 virus or any other highly pathogenic avian influenza virus among more than 4500 birds tested (Gaidet et al. 2007*a*), or in any of the birds tested during a parallel surveillance program in Eastern Europe and the Middle East (Gaidet et al. 2007*b*).

Detailed investigations are needed to critically evaluate the role of poultry supply chain mechanisms for the regional and transcontinental dissemination of the H5N1 HPAI virus among commercial poultry flocks (Weber and Stilianakis 2007). The phylogenetic relationships between H5N1 viruses from southern China and Southeast

Table 1. Key observed changes in epidemiological characteristics of the H5N1 HPAI virus.

Year	Reported changes in virulence, infectivity, or environmental resilience of H5N1 HPAI virus
1996	pathogenic H5N1 outbreak recorded from domestic geese in southern China (Webster et al. 2006)
1997	duck H5N1 reassorts with quail H9N2, becomes highly pathogenic strain (Guan et al. 2000); acquires capability for causing fatal disease in humans, and human-to-human transmission (Tam 2002)
1999	NS genes of post 1998-strains enhance virus replication in mammalian cells (Twu et al. 2007); increased lethality in mammals demonstrated by laboratory trials in mice (Guan et al. 2002)
2000	infectivity for domestic ducks increased, although domestic ducks remain asymptomatic carriers (Li et al. 2004)
2001	increase in infection duration and length of virus shedding period in domestic ducks (Hulse-Post et al. 2005); increased virulence in mammals (Lipatov et al. 2003); infections among swine discovered in Fujian, China (Shu et al. 2006)
2002	acquires capability to cause fatal disease in wild and domestic ducks (Sturm-Ramirez et al. 2004); further increased infectivity to mammals (Chen et al. 2004); fatal infections of tigers and cats recorded in China (Xia et al. 2003).
2003	decreased environmental stability in water (Brown et al. 2007); fatal infections of tigers and leopards in Thailand (Keawcharoen at al. 2004)
2004	further increased lethality in mammals and humans (Maines et al. 2005); case rate mortalities of 70-80% recorded for confirmed human H5N1 cases in Vietnam and Thailand (Tran et al. 2004, Areechokchai at al. 2006)
2005	oseltamivir resistant strain emerges in Vietnam (de Jong et al. 2005); amantadine/rimantadine resistant H5N1 strain recorded in northern China (He at al. 2007); H5N1 infections of village swine documented in Indonesia (Cyranoski 2005)
2006	vaccine-resistant "*Fujian strain*" attains dominance in China (Smith et al. 2006); first human H5N1 cases reported from Europe, Central Asia, Africa, and the Middle East (Turkey, Iraq, Azerbaijan, Egypt, Djibouti: WHO 2008)
2007	oseltamivir-resistant strain emerges in Egypt (WHO 2007); H5N1 infections detected among vaccinated poultry in Egypt (WHO 2008*a*)

Asia suggest that poultry trade may have been responsible for the dissemination of a progenitor H5N1 virus from Yunnan Province in southern China to Vietnam and Thailand during 2002–2003 (Wang et al. 2008). International trade in live poultry (hatching eggs, day-old chicks, fighting cocks), uncooked poultry products, and captive wild birds have been identified as potential vectors for the international spread of the H5N1 HPAI virus; other possible mechanisms for the international and transcontinental spread of H5N1 include animal feeds containing unsterilized poultry by-products or poultry litter, used poultry equipment, and faulty vaccines, i.e., "killed virus" vaccines contaminated

with live virus. Genetic data indicating that some H5N1 strains circulating in China are derived from artificially created vaccine strains suggests that H5N1 vaccine strain viruses have escaped in China, and perhaps elsewhere, as the result of poor laboratory biosecurity practices or poor quality control procedures in poultry vaccine production facilities (Duan et al. 2007). The risk of virus escapes from vaccine production facilities is a real one, as demonstrated by a recent outbreak of foot-and-mouth disease in the United Kingdom that was traced to the escape of a vaccine strain virus from a vaccine research and production facility (DEFRA 2007*d*).

The H5N1 virus involved in an outbreak in the United Kingdom during November 2007 was found to be genetically distinct from the H5N1 virus found in the outbreaks in United Kingdom during February 2007, and most closely related to the strain recovered from outbreaks in Germany and the Czech Republic during June-July 2007 (DEFRA 2007*c*). H5N1 HPAI viruses from outbreaks in Germany and the Czech Republic during June-July 2007 have been linked genetically (99.5% similarity) to virus recovered from poultry outbreaks in Kuwait in March 2007 (Newman et al. 2007). A single feed supplier was linked to seven of nine sites in Israel affected by an outbreak of H5N1 during March 2006 (Balicer et al. 2007), whereas the spread of H5N1 among commercial poultry farms in Sudan has been linked to trucks used for the collection and transport of poultry manure (G. Macgregor-Skinner, *personal communication*). A study of the 2003 H7N7 HPAI outbreak in the Netherlands attributed the higher observed risk of transmission among commercial chicken layer flocks to fomites on reused cardboard egg transport trays (Thomas et al. 2005), and this same mechanism could be a risk factor for the transcontinental spread and proliferation of the H5N1 HPAI virus through the international trade in hatching eggs and day-old chicks.

Domestic cats are the mammal species that has been most frequently observed to have become infected with the Asian H5N1 bird flu. Infections or deaths of domestic cats from H5N1 have been reported from Thailand, Indonesia, Iraq, China, Germany, and Austria (Rimmelzwaan et al. 2006, Yingst et al. 2006, Patrick Blair, *personal communication*). Studies have demonstrated that domestic cats and tigers can become infected with H5N1 through eating infected raw poultry or dead birds, and that these infected felines can then transmit H5N1 directly to others of their species (Xia et al. 2003, Keawcharoen et al. 2004, Kuiken et al. 2004, Rimmelzwaan et al. 2006). Die-offs of domestic or feral cats that coincide with mass mortality events in wild birds or poultry may serve as a potential indicator of H5N1 outbreaks (Yingst et al. 2006). The magnitude of the risk of H5N1 transmission from infected cats to humans is not known at the present time (Rimmelzwaan et al. 2006), but domestic cats that have intimate contact with humans may hunt wild birds and kill or scavenge sick or dead poultry, and could potentially serve as a direct or indirect vector for transmission of avian influenza between birds and humans.

POULTRY VACCINATION EFFICACY AND RISKS

Important factors often overlooked in avian influenza risk analyses are that vaccination, and concurrent infection by low-pathogenic avian influenza viruses, do not prevent poultry from becoming infected with the H5N1 highly pathogenic influenza virus but can prevent poultry infected from exhibiting disease symptoms or mortality (Webster et al 2006*b*). Although rates of mortality among poultry flocks infected with the H5N1 virus are typically extremely high (70–100%), H5N1 infections not accompanied by clinical disease can occur in vaccinated poultry, and experimental studies have shown that vaccinated or non-vaccinated birds can be infected from contact with infected vaccinated ducks and chickens. Vaccination of poultry against avian influenza viruses can prevent the appearance of disease symptoms and mortality in vaccinated flocks, but may not prevent vaccinated birds from becoming infected with an avian influenza virus, or from transmitting avian influenza viruses to other vaccinated or unvaccinated birds (Capua and Marangon 2004, Cardona et al. 2006, Savill et al. 2006, van der Groot et al. 2007), a problem that may be exacerbated by the use of defective poultry vaccines or improper vaccination procedures (Savill et al. 2006). Smith et al. (2006) attributed the emergence and dominance of the H5N1 Clade 2.3 lineage "Fujian-like strain" in mainland China to the vaccine-resistance properties of this particular strain. Incompletely inactivated virus from poultry vaccines have been implicated as the probable cause of outbreaks of an H5N2 LPAI virus on poultry farms in Japan and Taiwan (Ozawa et al. 2006,

Okamatsu et al. 2007), and as probable progenitors for some H5N1 strains in China (Duan et al. 2007).

Empirical and experimental evidence also shows that wild birds and poultry which have been previously infected by other avian influenza viruses may not exhibit clinical disease symptoms or mortality when subsequently infected by an H5N1 HPAI virus. Laboratory studies have demonstrated that chickens previously infected with an H9N2 virus were protected from disease signs and death when challenged with highly pathogenic H5N1, but that the chickens still shed H5N1 virus in their feces and could still be capable of infecting other birds (O'Neill et al. 2001, Seo and Webster 2001), and potentially humans. Adult mute swans with avian influenza virus antibodies from prior naturally acquired infections, experimentally infected with H5N1 HPAI virus, developed asymptomatic infections and shed virus, whereas swans with no avian influenza antibodies exhibited clinical disease symptoms and died (Kalthoff et al. 2008). Similarly, an experimental study using wild-caught Canada geese showed that prior infection with a North American H5N2 LPAI virus protected juvenile Canada geese against disease when challenged with a lethal H5N1 HPAI virus strain (Pasick et al. 2007). The potential role of co-circulating low pathogenic avian influenza viruses in allowing the cryptic circulation of highly pathogenic H5N1 between and among poultry and wild bird populations is an important unresolved risk factor that warrants further investigation.

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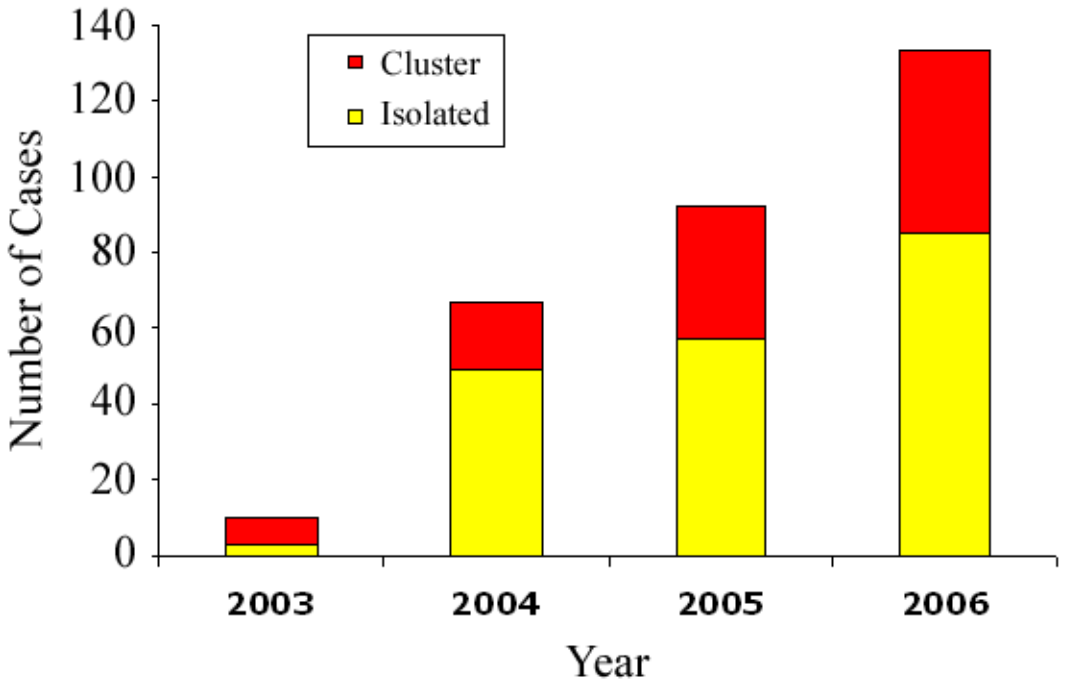
Further research is needed to understand the immediate and long-term health risks of avian influenzas for human populations, and to identify those members of exposed populations who are at greatest risk of infection and serious disease from avian influenza viruses (Ferguson et al. 2004, Croisier et al. 2007). The numbers of confirmed human H5N1 cases in China and Indonesia with no evident history of exposure to diseased poultry or birds appears to be increasing. Although most reported human H5N1 cases to date have involved severe respiratory infections and pneumonia-like symptoms, fatal infections from the H5N1 HPAI virus have been confirmed from patients who exhibited no respiratory disease symptoms. Asymptomatic or very mild infections in humans have been reported for several avian influenza subtypes. Although a few ad hoc investigations of possible nosocomial or human-to-human transmission of H5N1 in hospital settings have been performed (e.g., Liem et al. 2005, Schultsz et al. 2005), further studies are needed to evaluate potential risks of nosocomial and human-to-human transmission of H5N1 virus to hospital or laboratory personnel through exposure to H5N1 virus in blood and feces of infected persons (Hayden and Croisier 2006, Buchy et al. 2007).

More efforts also need to be made to establish and evaluate the potential background rates of asymptomatic and mild cases of human avian influenza in communities where human H5N1 clusters have been documented. One of the only available published studies to directly address this issue (Vong et al. 2006), was restricted to a situation in Cambodia involving a single confirmed human case rather than a human disease cluster. Given the relatively high percentage of confirmed human cases that have been associated with human disease clusters (approximately 30%: Fig. 3), in-depth studies comparable to those conducted following the 2003 H7N7 outbreak in the Netherlands are necessary for a definitive evaluation of this issue. Indeed, it seems probable that the available data may significantly underestimate the number of human H5N1 clusters, because anecdotal evidence from media reports suggests that many "index" or isolated confirmed H5N1 cases were associated with prior fatal disease incidents among family members, neighbors, or close associates (N. J. Cox, *personal communication*).

The significance of atypical (non-respiratory, non-ocular) disease symptoms documented in association with avian influenza virus infections in humans is a potentially important epidemiological factor that is frequently overlooked in analyses of human disease and public health risks from avian influenza viruses, because the current case definition for human H5N1 cases categorically excludes the official confirmation and reporting of any human H5N1 cases not associated with lower respiratory tract disease, even when H5N1 infection may have been confirmed through laboratory testing (WHO 2006). Nonetheless, fatal human H5N1 infections have been documented from patients in Thailand and Vietnam who exhibited no respiratory symptoms (Apisarnthanarak et al. 2004, de Jong et al. 2005), and media reports indicate that one of four reported confirmed H7N2 avian influenza cases

Fig. 3. Proportion of reported confirmed human H5N1 cases associated with human disease clusters.



from the United Kingdom during an outbreak in May 2007 was hospitalized for treatment of neurological and gastrointestinal symptoms, and not respiratory disease. The existence of confirmed fatal human H5N1 cases involving only encephalitis and gastroenteritis syndromes in Thailand and Vietnam is particularly important from the risk management and disease surveillance perspectives because of the high prevalence of other diseases typically associated with fatal gastroenteritis or encephalitis syndromes in these countries, e.g., Japanese encephalitis, amoebic dysentery, cholera, dengue, and the possibility that atypical H5N1 presentations in patients may be mistakenly attributed to one of these more common severe and fatal diseases (Apisarnthanarak et al. 2004, de Jong et al. 2005, Areechokchai et al. 2006).

CONCLUSIONS

Our ability to make accurate predictions regarding the location and socioeconomic costs of future avian influenza outbreaks is predicated upon access to reliable and comprehensive information regarding the epidemiology and spatiotemporal distribution of avian influenza outbreaks in birds and humans. The reliability of risk assessments for avian influenza viruses are currently constrained by important gaps in our knowledge regarding the epidemiology of avian influenza outbreaks in birds and humans, and uncertainties regarding the precise spatiotemporal relationships between avian influenza outbreaks in poultry and wild birds in many countries in which outbreaks have been confirmed in wild birds and poultry. Our knowledge of the spatiotemporal distribution of avian influenza outbreaks is further constrained by limitations on our ability to implement effective field surveillance and monitoring programs for avian influenza in

birds, humans, and animals, and by limitations on the timeliness and transparency of avian influenza outbreak reporting from countries where outbreaks are occurring. Expanded field surveillance programs for avian influenza are needed to evaluate the role of wild bird populations as vectors and reservoirs for highly pathogenic avian influenza viruses, and for investigations to identify and evaluate the mechanisms through which avian influenza viruses may be disseminated through international trade networks and poultry industry supply chains.

The observed patterns of avian influenza virus infections in humans clearly demonstrate that avian influenza surveillance programs in poultry and wild birds are important risk assessment and risk management tools for international public health and economic development programs. The continuing evolution and proliferation of highly pathogenic H5N1 avian influenza virus strains across an area spanning nearly half the globe increases the likelihood of a reassortment with a human influenza virus or another avian influenza virus into a genetic configuration that would enhance the virulence and infectivity of this virus for humans and other mammals, and expand the potential efficiency of transmission between poultry, wild birds, humans, and other animals. Given the range and frequency of non-respiratory symptoms reported from confirmed human H5N1 cases in Vietnam and Thailand, case definitions for human avian influenza should be expanded to include gastrointestinal and neurological symptoms, along with ocular (conjunctivitis) and respiratory presentations, as potential indicators of human disease from avian influenza.

Although highly pathogenic H5N1 strains constitute the most important avian influenza threat in terms of economic impacts and health risks to poultry, humans, and wildlife, we must not allow the current focus on H5N1 strains to blind us to the potential public health risks presented by both low-pathogenic and high pathogenic strains of other avian influenza virus subtypes. Although most known instances of serious human disease from avian influenza infections have been associated with avian influenza virus strains that are highly pathogenic in poultry, low-pathogenic avian influenza strains of H5N2, H7N3, H7N2, H7N7, and H9N2 viruses have demonstrated the ability to infect humans, and could potentially acquire the ability to cause serious systemic disease in humans through stochastic mutation, recombination, or reassortment.

Responses to this article can be read online at:
http://www.ecologyandsociety.org/vol13/iss2/art21/responses/

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