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Avian Influenza Virus H5N1: A Review of Its History and Information Regarding Its Potential to Cause the Next Pandemic

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Avian influenza virus H5N1, which has been limited to poultry, now has spread to migrating birds and has emerged in mammals and among the human population. It presents a distinct threat of a pandemic for which the World Health Organization and other organizations are making preparations. This article reviews information about the virus itself and its spread among poultry, migrating birds, mammals, and humans.
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According to a report of the World Health Organization (WHO) issued in December 2004, the threat of an influenza pandemic occurring in the near future has been exacerbated with the recent appearance and widespread distribution of the avian influenza virus H5N1. The report warned that the next pandemic would result in the deaths of at least 2 to 7 million people, with tens of millions requiring medical attention, in the best-case scenario.[1]

An influenza pandemic is defined as a global outbreak of disease that occurs when a new strain of influenza A virus emerges in the human population, causes serious illness, and then spreads easily from person to person worldwide. Pandemic viruses result from antigenic shift, abrupt and major changes caused by new combinations of the hemagglutinin (HA) and/or neuraminidase (NA) proteins on the surface of the virus.[2] The reassortment that occurs when two different viruses (eg, avian H5N1 and human H3N2) infect the same cell and exchange some of their gene segments is facilitated by the organization of the influenza virus into eight gene segments.[3]

The twentieth century witnessed three pandemics, all of which spread throughout the world within a year of being detected. The first one, called "Spanish flu" (H1N1) occurred between 1918 and 1919 and caused the highest number of known deaths, more than 500,000 in the United States and possibly as many as 50 million worldwide. Most of the deaths occurred within a few days of the person being infected, and nearly half of those who died were young, healthy adults. The H1N1 was reintroduced into the human population in the 1970s. The second pandemic, called "Asian flu" (H2N2) occurred 40 years later (1957-1958) and caused approximately 70,000 deaths in the United States. It was identified first in China in February 1957 and reached the United States by June of that year. The third and most recent pandemic occurred a decade later, in 1968 to1969. Known as the "Hong Kong flu" (H3N2), it was detected first in Hong Kong in early 1968 and later that year reached the United States, where it took 34,000 lives. The origin of the first pandemic virus remains unknown; the latter two pandemics were caused by viruses containing combinations of genes from both a human influenza virus and an avian influenza virus.[2] WHO has identified a number of lessons learned from the three pandemics (Table 1).[3]

H5N1 (Fig 1), which has been limited to poultry, now has spread to migrating birds and has emerged among the human population, causing 54 deaths among 108 cases as of June 28, 2005, and presenting a distinct threat of a pandemic for which WHO and other organizations are making preparations. These preparations include defining the phases of development of a pandemic (Table 2).[2] This article reviews information about the virus itself and its spread among poultry, migrating birds, mammals, and humans.

Avian Influenza Virus A

Avian influenza, an infectious disease of birds that is caused by influenza virus type A strains, was identified first in Italy in

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Table 1 Lessons Learned from the Three Pandemics of the 20th Century

- Pandemics are as unpredictable as the viruses that cause them and demonstrate great variations in mortality, severity of illness, and patterns of spread.
- A rapid surge in the number of cases and their exponential increase over a brief period of time, often in a matter of weeks, is a consistent characteristic.
- The ability of the virus to cause severe disease in young adults is a major determinant of a pandemic's overall impact.
- The epidemiological potential of a virus tends to occur in waves, with age groups and geographic areas initially not affected being likely to prove vulnerable during the next wave.
- Subsequent waves tend to be more severe than previous ones, although for different reasons.
- Virological surveillance conducted by the WHO laboratory network performs a vital function in rapidly confirming the onset of pandemics and in turn alerting health services, isolating and characterizing the virus, and making it available to vaccine manufacturers.
- Most pandemics have originated in parts of Asia, where dense populations of humans live in close proximity to ducks and pigs.
- Temporary banning of public gatherings and closure of schools may be effective measures to help delay the international spread of a pandemic.
- Delaying the spread can flatten the epidemiological peak so that cases are distributed over a longer period of time, with fewer cases at a given time, thereby increasing the likelihood that medical and other services can be maintained.
- The impact of vaccines on a pandemic remains to be demonstrated.
- Countries with domestic manufacturing capacity will be the first to receive vaccines.
- The tendency of later waves to be more severe may extend the time before large supplies of vaccines are needed.
- Countries with good programs for yearly vaccination will have experience in the logistics of vaccine administration, which might reduce excess rates of mortality.
- Regardless of measures taken, sudden and large increases in the rates of morbidity and a corresponding high demand for medical care should be anticipated.

Adapted from WHO.[3]

1878. In 1955, studies revealed that the disease is caused by influenza A viruses, all subtypes of which have been detected in more than 90 species of apparently healthy wild birds. Wild waterfowl, gulls, and shorebirds are the natural reservoir of all influenza A viruses. They likely have carried the viruses, without developing symptoms, for thousands of years in an environment that is optimal for adaptation of the virus to the host. These particular birds are highly mobile, and wild waterfowl particularly are known to carry viruses over great distances and to excrete large quantities in their feces while remaining perfectly healthy.[3]

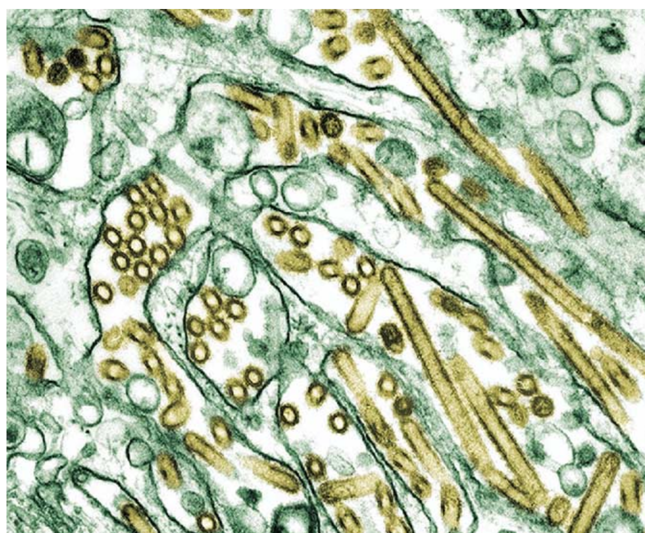

Figure 1 Transmission electron micrograph of avian influenza A H5N1 viruses (seen in gold) grown in MDCK cells (seen in green). (Courtesy of the Public Health Image Library, #1841.) (Color version of figure is available online.)

All other bird species are thought to be susceptible to being infected with avian influenza, although some more so than others, with less favorable consequences. Infected birds demonstrate a wide spectrum of symptoms, ranging from mild illness to a highly contagious and rapidly fatal disease that results in severe epidemics, the latter being known as "highly pathogenic avian influenza" and characterized by sudden onset, severe illness, and rapid death. The mortality rate can approach 100 percent within 48 hours.[2]

A total of 15 subtypes of influenza virus are known to infect birds, with the result that an extensive reservoir of influenza viruses is potentially circulating in bird populations. After circulating for short periods of time in a poultry population, viruses of low pathogenicity can mutate into highly pathogenic viruses. An example was the H5N2 virus that circulated in the United States in 1983 to 1984, beginning with a low mortality rate but within 6 months becoming highly pathogenic, with a mortality rate approaching 90 percent. Another example was the epidemic in Italy of the H7N1 virus, which began with low pathogenicity but mutated within 9 months of a highly pathogenic form, with more than 13 million birds dying or being put to death.[3,4]

Historically, avian influenza viruses have been extremely rare findings in humans. When they did occur, they caused only mild illness, usually viral conjunctivitis, followed by a full recovery. H5N1 has proved to be an exception, having caused six deaths in the first 18 cases reported by Hong Kong Special Administration Region (SAR), China, in 1997.[3]

Table 2 Stages of Development of a Pandemic as Defined by WHO

Interpandemic Period*	
Phase 1	No new influenza virus subtypes have been identified in humans. An influenza virus subtype that has caused human disease may be present in animals, but the risk of human infection occurring is considered to be low.
Phase 2	No new influenza virus subtypes have been detected in humans, but a circulating animal influenza virus subtype poses a substantial risk of causing human disease.
Pandemic Alert Period†	
Phase 3	Human infection with a new subtype has occurred, but no human-to-human transmission or vary rare human-to-human spread has occurred.
Phase 4	Small cluster(s) of human-to-human transmission has occurred but is highly localized, suggesting that the virus is not well adapted to humans.
Phase 5	Larger cluster(s) of human-to-human transmission has occurred, but spread remains localized, suggesting that the virus is becoming increasingly better adapted to humans but may not yet be full transmissible (substantial risk of a pandemic)
Pandemic Period	
Phase 6	Pandemic: increased and sustained transmission in the general population

Reprinted from CDC.[2]

*The distinction between Phases 1 and 2 is based on the risk of human infection or disease resulting from circulating strains in animals; the risk is based on various factors, including pathogenicity in animals and humans, occurrence in domesticated animals and livestock or only in wildlife, whether the virus is enzootic or epizootic, the geographic spread, and/or other scientific parameters.

†The distinctions among Phases 4, 5, and 6 are based on an assessment of the risk of a pandemic occurring, according to current scientific knowledge that may include factors such as rate of transmission, geographical location and spread, severity of illness, presence of genes from human strains (if derived from an animal strain), and/or other scientific parameters.

Because of certain characteristics, influenza A viruses are of great public concern. First, they all are genetically labile and well-adapted to elude host defenses. Because they lack mechanisms for the "proofreading" and repair of errors that occur during replication, the genetic composition of the viruses changes as they replicate in humans and animals such that the initial strain is replaced with a new antigenic variant (ie, antigentic "drift"). Hence, the global situation and the annual adjustments in the composition of vaccines must be monitored constantly. Second, influenza A viruses also undergo antigenic "shift," whereby they reassort genetic materials and merge together, resulting in a novel subtype different from both parent viruses. Because populations will have no immunity to the new subtype and no vaccine will be available to confer protection, viruses that have undergone such shift historically have resulted in highly lethal pandemics.[4] Several other factors of influenza A viruses also contribute to their ability to cause pandemics (Table 3).

To date, the outbreaks of the highly pathogenic forms have been limited to those of subtypes H5 and H7. Some variants of these two subtypes are capable of causing highly lethal disease, but an intermediate step is required. Highly pathogenic viruses have no natural reservoir and, instead, emerge by mutation when a virus carried in its mild form by a wild bird is introduced into poultry. At that point, the previously stable virus begins to evolve rapidly and can mutate into a highly lethal version of the same initially mild strain. This propensity for rapid mutation from a mild to a lethal strain is what raises concern when H5 or H7 infection is detected in poultry. If the virus is detected early, it can be eliminated before it has the opportunity to mutate to the highly pathogenic form.[3,4]

Avian H5N1

H5N1 is of particular concern because it mutates rapidly and has a propensity to acquire genes from viruses infecting other animal species. Its ability to cause severe disease and death in humans has been documented. The increasing incidence of H5N1 in birds and the accompanying increase in opportunities for direct infection of humans pose the likelihood that humans concurrently infected with human and avian influenza strains could become "mixing vessels" for the emergence of a novel subtype with sufficient human genes to be transmitted easily from person to person.[4]

Between January and April 2005, some important epidemiological features of human H5N1 were noted in northern

Table 3 Characteristics of Influenza A Viruses That Pose Particular Threat for Causing Pandemics

- They mutate much more rapidly than do type B viruses, giving them great flexibility.
- In addition to humans, they infect pigs, horses, sea mammals, and birds.
- They have numerous subtypes, all of which are maintained in aquatic birds, which provide a perpetual source of viruses and a huge pool of genetic diversity.
- They regularly cause seasonal epidemic in humans, with heavy tolls in morbidity and mortality.
- They are described by scientists as being "sloppy, capricious, and promiscuous."
- They undergo antigenetic drift, which serves as a survival tactic for the virus.
- They undergo antigentic shift, which serves well as a long-term survival tactic.

Adapted from WHO.[3]

Table 4 Epidemiological Changes in Human H5N1 in Vietnam in 2005

- An increase in the number of case clusters in the north compared with the south
- A prolonged interval between the first and last cases in clusters, which may reflect a mixture of modes of transmission
- Detection of subclinical infections
- An expanded age range of cases and older average age of cases, with the exception of southern Vietnam
- Decline in case fatality rate, except in southern Vietnam

Adapted from WHO.[5]

Vietnam that appeared to differ in some respects from those seen in southern Vietnam and earlier in 2004 in other parts of Asia (Table 4). Although human-to-human transmission has not been documented, the pattern of disease appears to be changing in a manner consistent with this possibility. The changes in epidemiological patterns indicate that H5N1 viruses may be more infectious for humans, and sequencing analyses indicate that they are becoming more antigenically diverse and may be forming distinguishable groupings, based on phylogenetic analyses.[5]

Recent Outbreaks of H5N1: Poultry

First Phase

In late 2003 and early 2004, outbreaks of avian influenza H5N1 occurred in eight countries in Asia: Cambodia, China, Indonesia, Japan, Lao, South Korea, Thailand, and Vietnam. On January 8, Vietnam officials confirmed that large numbers of poultry at two farms in a southern province had died from H5N1. Three days later, Japan reported a large outbreak of highly pathogenic avian influenza, caused by the H5N1 strain, at a single poultry farm in Kyoto prefect. During the next three weeks, Vietnam reported more than 400 outbreaks throughout the country, affecting at least 3 million poultry.[3] These outbreaks had unique characteristics (Table 5).[6] Because at least two human deaths in Hanoi at the same time were confirmed as being caused by H5N1, these outbreaks in poultry were now recognized to be a health threat to populations in affected countries and, possibly, worldwide. The wide and rapid spread geographically and the consequences for agriculture, which spanned a spectrum from large commercial farms to rural subsistence agriculture, were unprecedented. In three months, more than 120 million birds died or were destroyed, representing a figure greater than the total of all previous large outbreaks of highly pathogenic avian influenza recorded worldwide in the previous four decades.[3] In China, where 60 percent of chickens are raised on small farms, outbreaks occurred in more than half of the 31 provinces and municipalities. Compulsory vaccination was introduced to supplement standard control measures.[3]

Table 5 Unique Characteristics of Outbreak in Six Asian Countries

- Geographic scope
- International spread
- Economic consequences for the agricultural sector
- First instance of highly pathogenic avian influenza in more than half of countries affected

Adapted from WHO.[6]

Table 6 Characteristics of H5N1 That Pose the Potential for Causing a Pandemic

- It has become progressively more pathogenic in poultry and in the mammalian mouse model.
- It is now hardier than previously, and it survives several days longer in the environment.
- It appears to be expanding its mammalian host range.
- It has been found in its highly pathogenic form in dead migratory birds, and the role of migratory waterfowl in the evolution and maintenance of highly pathogenic H5N1 may be changing.
- It has been found in its highly pathogenic form in domestic ducks, which can excrete large quantities of lethal virus without the warning signs of visible illness.
- It is occurring in concentrated poultry outbreaks in rural areas, where most households maintain free-ranging flocks and ducks and chickens mingle freely.

Adapted from WHO.[3]

Second Phase

Although the number of human cases slowed after February 2004 and the outbreak appeared to be contained, within 4 months, reports of new lethal outbreaks among poultry began coming from several Asia countries, including Malaysia, which previously had been spared.[7] Although these outbreaks were much smaller, affecting fewer than 1 million poultry during the summer and autumn, they also proved to be more tenacious. This phase also included human cases, many of which were fatal (see below).[3] This phase also provided additional information concerning the H5N1 virus that indicates it has multiple opportunities for a pandemic virus to emerge (Table 6), and experts readily agree that H5N1 has demonstrated considerable potential for such to occur.[3]

Third Phase

On March 27, 2005, state media in the Democratic People's Republic of Korea reported the country's first outbreak of avian influenza in poultry. The outbreaks occurred in commercial poultry farms, and mass culling was undertaken by the authorities in an effort to prevent further spread of the virus.[8]

On June 20, 2005, another outbreak was reported on a farm in a poultry-raising household in Changji City, Xinijiang Province, China. More than 1490 birds were culled to contain the outbreak.[3] Seven hundred chickens on a farm in An Khanh commune in Vietnam had been culled on June 11 after 6000 of them died within 4 days. The birds subsequently were found to be positive for H5 virus.[9]

H5N1 was detected as early as July 1, 2005, in poultry at a duck farm in the village of Calumpit, in Bulcan province north of Manila, The Philippines.[10] Despite some apparent secrecy on the part of government officials as to the location of the duck farm, reporters learned that the infection was detected in Barangay Puno, Calumpit, and that migratory birds were thought to be the source of the avian virus that infected the ducks in Calumpit.[11] This event was the first case of avian influenza in the Philippines, where poultry exports to Japan were halted immediately.[12]

Less than two weeks later, the Japanese government reported that 8500 chickens at a poultry farm in Bando, Ibaraki prefecture, would be destroyed after scientists found genes of the avian flu virus. The farm, located within a restricted area where other farms had been hit by a diluted strain of the avian virus, is only 0.7 miles west of the first farm hit by the flu, where the strain had been confirmed on June 26. Chickens at five other farms had antibodies indicating they had been infected with the virus, and the same diluted strain of the bird virus was confirmed on July 1 at one of the farms.[13]

Spread of H5N1: Domestic Ducks and Wild Geese

Domestic Ducks

Recently, symptomatic domestic ducks have been shown experimentally to excrete H5N1 in its highly pathogenic form. This finding poses a great concern because it indicates that ducks may play an important silent role in maintaining transmission. The ducks' ability to excrete large quantities of lethal virus without showing warning signs of visible disease renders giving rural residents advice on how to avoid exposure very difficult. This finding also may explain why several recent cases of human disease could not be traced to contact with diseased poultry. Exacerbating the problem is the practice among most households in rural areas to maintain free-ranging flocks in which ducks and chickens mingle freely in areas in which children also may play; frequently, poultry and ducks may be allowed in the domestic areas as well. In addition to the health problems posed is the economic one because most of the households depend on the ducks and chickens for both food and income.[3]

Migratory Geese and Other Birds

Until recently, outbreaks among birds have occurred only among captive birds, free-flying crows, and other raptors. In 2004, H5N1 was isolated in two outbreaks in Cambodia. A large variety of captive birds were affected in the outbreak at Tamao Zoo, Kandal province, as were free-flying crows. The disease first appeared in gray-headed fish eagles, serpent eagles, hawk eagles, spotted wood owls, brown fish owls, spot-bellied eagle owls, and buffy fish owls. The raptors had been fed chicken meat or carcasses obtained from the Kandal Market in central Phnom Penh, which may have been the source of the disease. Also thought to be a likely source was a live poultry market located approximately 30 to 40 miles from the enclosure of the serpent eagle. Subsequently, herons, egrets, and cranes were affected, suggesting respiratory transmission or transmission mediated through free or wild birds that frequent the aviary areas. In a further outbreak, Psittacines were affected, but only two recent introductions died in an aviary group of 30. A total of 86 birds died, and 261 remained clinically unaffected.[14]

China reported on May 1, 2005, an outbreak of H5N1 among wild birds, with 1000 deaths of migratory birds; on June 8, 2005, an outbreak among birds in Xinjiang autonomous region was reported, with the death of 460 geese and the destruction of another 13,500 geese. No human cases were reported.[15] By July 7, 6000 migratory birds were reported to have died of the H5N1 influenza.[16]

The outbreak among different varieties of wild geese created particular concern because it is the first instance of viral transmission occurring between wild birds (previously, the flu was seen to move only to wild birds from domestic fowl), other than one report in January 2004 of a case of H5N1 in a peregrine falcon (*Falco peregrinus*).[17] Also, the migratory birds' ability to fly great distances (one thousand miles a day at maximum according to Yi Guan of the University of Hong Kong, China) has the potential for extremely widespread transmission. One of the species, the bar-headed geese (*Anser indicus*), is known to move south to Burma and north over the Himalayas to India.[18,19]

Illustrating another potential source for worldwide transmission of H5N1 was the recent case of two smuggled mountain hawks detected in Belgium on a flight from Thailand (Fig 2). On October 18, 2004, the two crested hawk eagles (*Spizaetus nipalensis*) were seized at the Brussels International Airport. The birds had been transported in hand luggage that had been left open enough to allow air to enter. The traveler, a Thai resident, had taken connecting flights from Bangkok to Brussels, with a stopover in Vienna; the luggage was placed in overhead compartments on both flights. Although neither bird showed any symptoms of disease, they both were humanely killed in accordance with the European Union's restriction on imports of birds and products from several Asian countries. Both birds tested positive for H5N1 in its pathogenic form.[3,20] Precautionary measures were taken immediately. The 25 persons who had been in direct or indirect contact with the infected eagles in the Brussels airport were identified, examined, and given oseltamivir prophylaxis. The traveler and a close contact were hospitalized and put into an isolation unit for 4 days, monitored, and given oseltamivir prophylaxis. None of the exposed persons developed symptoms, except for the veterinarian who euthanized the birds; he developed bilateral conjunctivitis two days after examining the birds, and his family was given prophylaxis as well. No details were available about how the birds were infected. They may have been infected by eating infected chicken carcasses very shortly before being transported, which might explain why they exhibited no symptoms. More likely is that avian wildlife may have a higher resistance to the disease before they exhibit clinical signs and then die suddenly.[20]

In another report issued by the BBC News on April 5, 2005, Hans Wagner of the Food and Agriculture Organization stated that North Korea had a different strain of bird flu,

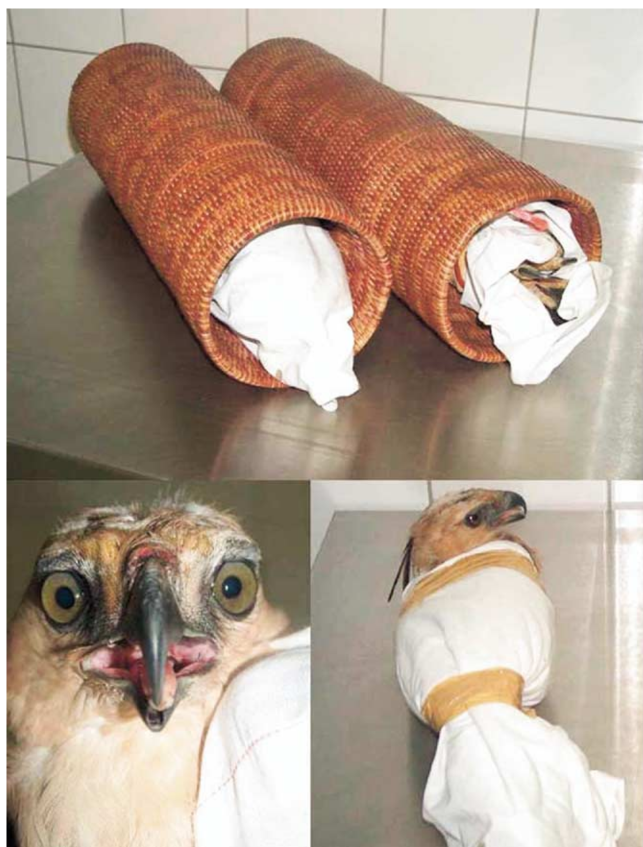

Figure 2 Crested hawk-eagles confiscated at Brussels International Airport in the hand luggage of a Thai passenger. The birds were wrapped in a cotton cloth, with the heads free, and each of them inserted in a wicker tube ≈60 cm in length, with one end open. (Pictures courtesy of Paul Meuleneire, custom investigations officer, antidrug group. Used courtesy of the Centers for Disease Control and Prevention, Emerging Infectious Diseases, Van Borm S, Thomas I, Hanquet G and coworkers. Highly pathogenic H5N1 virus in smuggled Thai eagles, Belgium. Emerg Infect Dis 11:5, May 2005 [serial on the Internet]. http://www.cdc.gov/ncidod/eid/vol11no05/05-0211.htm. (Color version of figure is available online.)

H7, which had resulted in the destruction of 219,000 birds.[21] That strain is less deadly to humans.

H5N1 Occurrence in Mammals

In the 1970s, experiments with domestic cats revealed that they could be infected with the Hong Kong influenza virus A2.[22] Similarly, tests were performed after the outbreak of H5N1 in 2003 to 2004 on cats by experimentally inoculating them with H5N1 virus intratracheally and by feeding them virus-infected chickens. The cats excreted virus, developed severe diffuse alveolar damage, and transmitted virus to sentinel cats, revealing their susceptibility to the virus and their possible role in the epidemiology of the virus.[23]

After avian influenza A virus was reported in seals, suggesting that viruses are transmitted from birds to mammals in nature, experimental studies performed in the 1980s showed that avian influenza A viruses could be replicated in the respiratory tract of three mammals—pigs, ferrets, and cats—in high titers (10^5 to 10^7). Peak titers occurred at two to four days postinoculation, consistent with the pattern of human and other mammalian viruses in these animals. The conclusion reached by those researchers was that influenza A viruses circulating at that time represented a source of viruses capable of infecting mammals, thereby contributing to the influenza A antigenic pool from which new pandemic strains might originate.[24]

In December 2003, two tigers (*Panthera tigris*) and two leopards (*Panthera pardus*) in a zoo in Suphanburi, Thailand, showed clinical signs of influenza and died unexpectedly. Many of the chickens in the area were dying with respiratory and neurologic symptoms. Subsequently, retrospective studies revealed that the symptoms were those of H5N1 virus infection. The animals had been fed fresh chicken carcasses from a local slaughterhouse. Postmortem examinations were performed on the four zoo felids, all of which were found by reverse transcriptase-polymerase chain reaction (PCR-RT) analysis, with primer pairs specific for HA and NA, to be positive for H5N1with both primers. The identity of the PCR products was confirmed by nucleotide sequencing. This report, the first of influenza virus infection causing disease or death in nondomestic felids, extended the host range of the virus and suggested that H5N1 is more pathogenic for felids than are other influenza viruses.[25]

A large and deadly outbreak of H5N1 in tigers began on October 11, 2004, in Thailand. A total of 147 tigers in a population of 418 developed high fevers, usually progressing to severe pneumonia. Infection was linked to the feeding of chicken carcasses, and preliminary investigation found no evidence of tiger-to-tiger transmission. Before this event, tigers were not considered to be susceptible to disease from any influenza A virus.[3]

These incidents raise other concerns: (1) H5N1 virus infection may threaten the survival of endangered felids, especially considering that the virus may be transmitted horizontally between domestic cats; (2) if the higher pathogenicity of H5N1 virus for felids also means longer periods of excretion of more virus, the role played by felids in avian influenza epidemiology will need to be reevaluated; and (3) more species of mammals may be at risk of acquiring infection with H5N1.[25]

H5N1 Occurrence in Humans

The world's first cases of human infection with the H5N1 strain were documented in 1997 in Hong Kong SAR. For the first time, evidence showed that the H5N1 strain can infect humans directly without prior adaptation in a mammalian host. A striking feature of this outbreak was the presence of primary viral pneumonia in severe cases. Usually, pneumonia that occurs in patients with influenza is a secondary bacterial infection. In these cases, however, pneumonia was caused directly by the virus, it did not respond to antibiotics, and it frequently was rapidly fatal.[3] The outbreak, which involved 18 cases, six of which were fatal, coincided with outbreaks of infection of H5N1 in domestic poultry on farms and in live markets. Within three days, the entire poultry

Table 7 Cases of Avian Influenza Infections in Humans Since 1997

Year	Location	Strain	Case
1997	Hong Kong	H5N1	Infection in both poultry and humans. Represented first time an avian influenza virus was found to transmit directly from bird to humans. A total of 18 people were hospitalized; 6 died. Authorities destroyed 1.5 million chickens to remove the source of the virus. Spread was primarily from birds to humans, but rare person-to-person infection was noted.
1999	China and Hong Kong	H9N2	Illness confirmed in 2 children, both of whom recovered; no additional cases were confirmed. Transmission likely was from birds to humans but human-to-human transmission could not be ruled out. Several additional human cases were reported from mainland China in 1998 to 1999.
2002	Virginia, USA	H7N2	Outbreak among poultry in the Shenandoah Valley, with 1 person found to have seriologic evidence of infection.
2003	China and Hong Kong	H5N1	Two cases occurred among members of a Hong Kong family who had traveled to China; 1 recovered, and 1 died. Source of infection was not determined. Another family member died of a respiratory illness in China, but no testing was performed.
2003	Netherlands	H7N7	Outbreaks in poultry on several farms, followed by infections among pigs and humans. A total of 89 people were confirmed to have infection; most were poultry workers. One death occurred, a veterinarian who visited one of the affected farms. Most cases resulted from direct contact with infected poultry; 3 cases possibly were person-to-person transmission.
2003	Hong Kong	H9N2	One case occurred in a child, who was hospitalized and recovered.
2003	New York, USA	H7N2	One patient hospitalized and recovered from what was first thought to be H1N1 but later proved to be H7N2.
2004	Thailand and Vietnam	H5N1	Outbreaks of highly pathogenic influenza A in Asia first reported by the WHO. From December 30, 2003 to March 17, 2004, 12 confirmed human cases in Thailand and 23 in Vietnam, resulting in a total of 23 deaths.
2004	Canada	H7N3	Human infections among poultry workers associated with outbreak among poultry; illnesses consisted of eye infections.
2004-2005	Thailand and Vietnam	H5N1	Beginning late June 2004, new lethal outbreaks among poultry were reported in several countries in Asia, followed by renewed sporadic reporting of human cases beginning in August and continuing into 2005, including 1 possible human-to-human case.
2004-2005	Vietnam and Cambodia	H5N1	Between December 16, 2004, and June 28, 2005, 60 cases with 18 deaths were reported in Vietnam and 4 cases, all fatal, in Cambodia.

Adapted from CDC.[27]

population of Hong Kong SAR was culled, probably averting a pandemic on that occasion.[4,26] Since that date, sporadic cases of avian influenza caused by various strains have been reported (Table 7).[27]

Interspecies transmission occurred again in Hong Kong SAR in February 2003. Two human cases, one of which was fatal, were reported in a family that recently had traveled to southern China. Another child in the family had died during the visit, but the cause of death remains unknown.[3,4,26]

A wave of human cases began to occur during the last days of December 2003. On January 5, 2004, Vietnamese health authorities reported an unusual cluster of severe respiratory disease in 11 previously healthy children hospitalized in Hanoi; seven had died, and two were in critical condition. Two weeks later, on January 23, Thailand announced its first human cases of H5N1, two young boys. These cases were announced on the same day that a large outbreak at a poultry farm, affecting nearly 70,000 birds, was announced. A small but steady number of human cases, most of them fatal, were reported during the remainder of the month.[3] Between December 30, 2003, and March 17, 2004, 12 confirmed human cases of H5N1 were reported in Thailand and 23 in Vietnam, with a total of 23 deaths. These figures, twice those of the 1997 outbreak, were historically unprecedented, and the virus was far more deadly. The cases were linked directly to outbreaks of the highly pathogenic H5N1 in poultry initially reported in the Republic of Korea in December of the previous year and later confirmed in seven other Asian countries.[3,26]

Sporadic human cases were reported during August to October 2004 in Vietnam and Thailand. A total of nine cases, of which eight were fatal, were reported between August 1 and October 9 in Thailand (n = 5) and Vietnam (n = 4) and included one isolated instance of probable human-to-human transmission in Thailand in September.[3,7] A massive door-to-door search was undertaken, but no further evidence of continuing transmission was detected. Most of the cases occurred in rural areas. These cases brought the 2004 totals in the two countries to 44, of which 32 were fatal. These cases had two unusual patterns: they occurred more frequently in previously health children and young adults, and they had a higher mortality rate than any previously recorded.[3]

On February 2, 2005, WHO reported the first case of Cambodian human infection with H5N1 in a 25-year-old woman from Kampot Province in Cambodia. After developing respiratory symptoms in the latter part of January, she sought medical care in neighboring Vietnam, where she died in the Kien Giang Provincial Hospital on January 30.[28] By May 4, three other people had died of confirmed H5N1 virus.[16] As of June 15, 2005, a total of 103 human cases (54 deaths) had been reported since January 2004. The most recent figures on that date included 55 human cases since December 2004 reported primarily from the southern and northern parts of Viet Nam, and four fatal cases reported in Cambodia. By June 28, 2005 a total of 108 cases (87 in Vietnam, 17 in Thailand, and 4 in Cambodia) and 54 deaths (38 in Vietnam, 12 in Thailand, and 4 in Cambodia) had been reported.[7,29]

After a team of international experts was dispatched to Viet Nam at the request of the Vietnamese Ministry of Health, WHO issued a report on July 1, 2005, stating that no evidence was found by a WHO team that H5N1 infections are spreading readily among humans, despite three waves of epidemics in poultry. Hence, the level of pandemic alert initiated in January 2004, after WHO received confirmation from Viet Nam and Thailand of human cases of severe disease caused by H5N1, remained unchanged, based on preliminary findings.[30]

Implications

Although no sustained human-to-human transmission of the H5N1 virus has occurred so far and no evidence of genetic reassortment between human and avian influenza virus genes has been found, the epizootic outbreak in Asia poses an important public health risk. If the H5N1 viruses develop the ability for efficient and sustained transmission between humans, an influenza pandemic likely would result, with high rates of illness and death. Of particular concern are that (1) little preexisting natural immunity to H5N1 infection exists in the human population and (2) genetic sequencing shows that H5N1 has resistance to the two antiviral medications most commonly used for treating influenza, amantadine and rimantadine. Although efforts are under way to produce a vaccine, mass production and availability of such a vaccine are not likely to occur in the near future. Other factors raising concern are findings that indicate currently circulating strains of H5 viruses are becoming more capable of causing disease for mammals than were earlier strains, that these strains are becoming more widespread in birds in the region, and that ducks infected with H5N1 are now shedding more virus for longer periods of time without showing any symptoms of the disease. Also, H5 infection has been documented in pigs in China (initially thought to be the obligatory mixing vessel for reassortment of viruses because they possess receptors for both avian and human influenza viruses on the cells of their respiratory tract) and in felines (experimental infection in house cats), suggesting that cats could host or transmit infections. Reassortment of avian influenza genomes is most likely to occur when these viruses demonstrate a capacity to infect multiple species, as is the case now in Asia.[3,7]

The other mechanism by which a pandemic virus can emerge is adaptive mutation, in which stepwise changes occur as the virus mutates during infection of humans or other mammals and thereby gradually improves its transmissibility to humans. Such mutation likely would be expressed in a series of independent chains of very limited human-to-human transmission. If this were to occur, the present high lethality probably would not be retained, as an avian influenza virus usually loses pathogenicity when it acquires the improved transmissibility required to cause a pandemic. However, because no virus of the H5 subtype has circulated among humans, at least not within the lifetime of today's world population, vulnerability to an H5N1-like pandemic virus would be universal.[3]

Current Status

Although at one point reports began to circulate stating that WHO had downgraded its assessment of the threat of a pandemic, such was not the case. On June 30, 2005, WHO issued a communication clearly stating that these reports "are unfounded" and that "testing of clinical specimens by international experts working in Vietnam provided further suggestive evidence of more widespread infection with the virus, raising the possibility of community-acquired infection." Because firm evidence of improved ability for transmission had not been established, WHO retained the level of pandemic alert, noting that a cautious approach combined with heightened vigilance was being taken because of the huge consequences of raising the level of the alert.[31] That level of alert was still in effect when this article went to press.

Future Biosecurity

Biosecurity is a term used for the holistic concept of preventing disease entry (or escape) that to be successful must be practiced by all farmers, cooperatives, abattoirs, and the like. Any breach in the sanitary barrier of biosecurity measures would increase the risk for spread of the disease or for infection to enter the production unit, market, or any commercial layer operation. Precautions delineated by the UN Food and Agriculture Organization (FAO) in June of 2004 were designed to offset the common breaks that occur in biosecurity (Table 8): bringing contaminated materials such as clothing or soiled hands into quarters where susceptible animals are housed; using contaminated equipment or instruments, usually by re-use of equipment or purchase of used equipment; or, the most common breach, bringing animals that are incubating disease or are diseased into contact with susceptible animals.[32]

Now that the virus is endemic in poultry and expanding its avian and mammalian host range, averting a pandemic by eliminating further opportunities for human exposure no longer appears feasible. If adaptive mutation allows the virus to improve its capacity to be transmitted among humans, clusters of cases likely will occur, which, if detected in time,

Table 8 Means to Preclude Breaches in Biosecurity

Exposing susceptible animals to contaminated materials
• Prevent access of strangers to areas where animals are housed
• Provide protective clothing, including boots, to anyone visiting the flock
• Provide baths with disinfectant for boots
• Provide showers for all persons entering areas where poultry are kept
• Ensure that all clothing used on the farm does not leave the farm
• Ensure that outside workers do not own poultry of their own
• Ensure that all animal health officials visiting affected premises are conscientious that they could be responsible for spread of infection and disease
• Be aware of the origin of feed and water and check their quality periodically
Introducing contaminated equipment to flocks
• Clean and disinfect any equipment and instrumentation to be used
• Disinfect any equipment used in a cooperative group (eg, egg trays)
Exposing susceptible animals to incubating or diseased animals
• Ensure that all animals introduced to the farm or flock are healthy; obtain health certification if possible
• Establish a quarantine area for housing new animals, keeping them away from flocks already on the farm
• Keep housing areas as far from each other as possible
• Use separate workers to handle the different animals if possible
• If separate workers cannot be used, handle and feed the new animals last
• Establish mechanisms such as enclosures or nets to protect poultry production farms from wildlife
• Establish barriers to protect poultry from cats, dogs, rats, and other vermin

Adapted from FAO.[32]

might provide an opportunity to avert a pandemic by rapid intervention with a vaccine, if available at the time, and antiviral drugs, if sufficient quantities exist.[3]

After a Hong Kong delegation attended a WHO meeting in Hanoi from May 10 to 23, 2005, Hong Kong implemented several activities in an attempt to prevent and control the spread of H5N1: (1) preparing a pandemic preparedness plan, (2) conducting human and poultry surveillance programs, (3) stockpiling antiviral drugs for treatment and prophylaxis, (4) maintaining close liaison with WHO to stay aware of the development of pandemic influenza vaccine, and (5) raising public awareness of issues related to an influenza pandemic.[13]

Shortly before the meeting, on May 6 to 7, 2005, an intercountry consultation met in Manila, Philippines, and issued an epidemic alert response that included recommendations for precautionary measures. Among the recommendations were that all countries move ahead as quickly as possible and develop or finalize practical operational pandemic preparedness plans, that WHO continue to explore and develop international approaches that can be used to reduce the threat or impact of pandemic influenza, that further exercises be undertaken by individual countries, and that WHO explore all possible mechanisms for making human H5N1 vaccine available to affected countries in Asia before the start of a pandemic.[5]

Other measures that have been taken include a three-day international conference that was held in Kuala Lumpur, the results of which were published on July 6, 2005. The conference was attended by experts from Asia as well as by senior representatives of the FAO, the World Organization for Animal Health (OIE), and WHO. It determined to set a priority on small-scale and backyard farms, the scene of most human cases, and set forth a multipoint plan to reduce the risk of H5N1 avian influenza spreading from poultry to humans (Table 9).[33]

A global strategy for the control of highly pathogenic avian influenza was issued by the FAO in May 2005. The 64-page file may be obtained at http://www.fao.org/ag/againfo/resources/documents/empres/AI_globalstrategy.pdf.

The US Congress recently responded to a call by WHO for more money and attention to be devoted to an effective preventive action plan that included an appeal for $100 million. A bipartisan group of senators obtained $25 million for prevention efforts, and the Senate Foreign Relations Committee unanimously approved legislation directing the President to form a senior-level task force to put in place an international strategy to deal with the avian flu. Two members of the Committee, Barack Obama (D, Illinois) and Richard Lugar (R, Indiana, Chairman) urged the Bush administration to form the task force immediately and made recommendations accordingly.[34]

According to other sources, experts told the House Energy and Commerce Committee that the United States is "woefully unprepeared to respond to the next flu pandemic." Marcia Crosse, Director of Health Care Issues for the Government Accountability Office was quoted as saying that our "vaccine is fragile and our current antiviral stockpile is insufficient. We also have an insufficient health work force and limited

Table 9 Recommendations of International Conference, July 6, 2005

• Educate farmers and their families concerning the danger of high-risk behaviors and how to change their farming practices
• Ensure the segregation of different species, including chickens, ducks, and pigs, and eliminate intermingling between these animals and humans
• Provide adequate compensation and/or rewards for farmers to encourage them to report suspected avian influenza outbreaks in their flocks and to apply control measures
• Pursue the vaccination of poultry flocks as part of a multi-element response to the avian influenza threat in high-risk areas

Adapted from OIE.[33]

hospital capacity." The same report noted that stockpile purchases of 2.3 million doses of the antiviral drug Tamiflu (Hoffman La-Roche, Inc.), made by the Department of Health and Human Services, are only enough to treat less than 1 percent of the population, which would require 60 million to 150 million doses. This minimal figure is in contrast to countries such as the United Kingdom, France, Finland, Norway, Switzerland, and New Zealand, which are ordering sufficient Tamiflu to cover between 20 and 40 percent of their populations. Because of the difficulty of rapidly producing effective vaccines, drugs will be the first line of defense, but Dominick A. Iacuzio, medical director at Hoffman La-Roche, Inc. said he could not ensure an adequate supply of the drug at the outbreak of a pandemic and that unless the United States makes a commitment to secure the drug, the global demand for Tamiflu will force the company to export the drug to countries with committed orders. Representative Michael Ferguson (R, New Jersey) was noted to sum up the situation with these words: "We are staring at the barrel of a loaded gun ready to fire. This is nature's weapon of mass destruction."[35]

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