Avian Influenza in Turkey – Will It Influence Health in All Europe?

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Avian influenza is an infection caused by avian influenza (bird flu) viruses, which occur naturally among birds. Wild birds worldwide carry the viruses in their intestines, but usually do not get sick. However, avian influenza is very contagious among birds and can cause illness and death in some domesticated birds, including chickens, ducks, and turkeys. The virus can transmit from birds to humans, causing lethal infections, but as yet the virus does not easily transmit from human to human. However, there is a substantial risk of either re-assortment of virus (combination of avian and human influenza), or adaptation of the influenza virus to humans. The present situation in Turkey emphasizes the importance of good surveillance and updated pandemic plans in all countries.

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The recent avian influenza epidemic in Asia has been an effective reminder to the public health community of the world's vulnerability to emerging epidemics. The importance of early interventions to prevent a pandemic cannot be underestimated. The alarm bells that went off in December 2003 (1) are still ringing, keeping the threat of a large pandemic real.

All influenza A epidemics in humans originate from birds, and the advent of a new epidemic virus strain is mostly the result of viral re-assortment, ie "antigenic shift" (2,3). This is a process in which genetic material from a pure avian influenza A virus and an influenza virus adapted to humans mix in the same host – a pig or a human.

Avian influenza

Influenza viruses that infect birds are called avian influenza viruses. Only influenza A viruses infect birds, and all known subtypes of influenza A viruses can infect birds (4). However, there are substantial genetic differences between the subtypes that typically infect both humans and birds. Within subtypes of avian influenza A viruses, there are also different strains. Avian influenza A H5 and H7 viruses can be distinguished as "low pathogenic" and "high pathogenic" forms, respectively, on the basis of genetic features of the virus and the severity of the illness they cause in poultry; influenza H9 virus has been identified only in a "low pathogenicity" form (5). Each of these three avian influenza A viruses (H5, H7, and H9) can theoretically be partnered with any one of nine neuraminidase surface proteins; thus, there are potentially nine different forms of each subtype, eg, H5N1, H5N2, H5N3, or H5N9 (5). Although avian influenza A viruses usually do not infect humans, more than 100 confirmed cases of human infection with avian influenza viruses have been reported since 1997 (5).

Most cases of avian influenza infection in humans are thought to have resulted from direct contact with infected poultry or contaminated surfaces. Since 1997, human infections with avian influenza A viruses have not resulted in sustained human-to-human transmission. However, because influenza A viruses have the potential to change and gain the ability to spread easily among people, monitoring for human infection and person-to-person transmission is important (4).

Do migratory birds spread highly pathogenic avian influenza viruses?

The role of migratory birds in the spread of highly pathogenic avian influenza is not fully understood. Wild waterfowl is considered a natural reservoir of all influenza A viruses (6-8). The waterfowls have probably carried influenza viruses, with no apparent harm, for centuries. They are known to carry H5 and H7 virus subtypes, but usually their low pathogenic form. Considerable circumstantial evidence suggests that migratory birds can introduce low pathogenic H5 and H7 viruses, which then mutate to the highly pathogenic form, to poultry flocks (6-8).

What is special about the current outbreaks in poultry?

The current outbreaks of highly pathogenic avian influenza, which began in Southeast Asia in mid-2003, are the largest and most severe on record. Never before in the history of this disease have so many countries been simultaneously affected, resulting in the loss of so many birds (7). The causative agent, H5N1 virus, has been proved to be especially tenacious. Despite the death or destruction of an estimated 150 million birds, the virus is now considered endemic in many parts of Indonesia and Viet Nam and in some parts of Cambodia, China, Thailand, and possibly also the Lao People's Democratic Republic. Control of the disease in poultry is expected to take several years (9,10). From mid-December 2003 through early February 2004, poultry outbreaks caused by the H5N1 virus were reported in eight Asian nations (listed in order of reporting): the Republic of Korea, Viet Nam, Japan, Thailand, Cambodia, Lao People's Democratic Republic, Indonesia, and China (Table 1). Most of these countries had never before experienced an outbreak of highly pathogenic avian influenza (8,12). In early August 2004, Malaysia reported the first outbreak of H5N1 in poultry, becoming the ninth Asian country affected. Russia reported its first H5N1 outbreak in poultry in late July 2005, followed by reports of disease in adjacent parts of Kazakhstan in early August (13). Deaths of wild birds from highly pathogenic H5N1 were reported in both countries. Almost simultaneously, Mongolia reported the detection of H5N1 in dead migratory birds (13). In October

2005, H5N1 was confirmed in poultry in Turkey and Romania. Outbreaks in wild and domestic birds are under investigation in other countries, too (13-16).

Why are pandemics such dreaded events?

Influenza pandemics are remarkable events that can rapidly infect virtually all countries. Once international spread begins, pandemics are considered unstoppable as they are caused by a virus spreading very rapidly by coughing or sneezing. The fact that infected people can shed virus before symptoms appear, adds to the risk of international spread via asymptomatic air travelers (17). The severity of disease and the number of deaths caused by a pandemic virus vary greatly, and cannot be known prior to the emergence of the virus. During past pandemics, attack rates reached 25%-35% of the total population. Under the best circumstances, assuming that the new virus causes mild disease, the world could still experience an estimated 2-7.4 million deaths (projected from data obtained during the 1957 pandemic). Projections for a more virulent virus are much higher. The 1918 pandemic, which was exceptional, killed at least 40 million people (18). In the USA, the mortality rate during that pandemic was around 2.5% (18).

Pandemics can cause large surges in the numbers of people requiring or seeking medical or hospital treatment, temporarily overwhelming health services. High rates of worker absenteeism can also interrupt other essential services, such as law enforcement, transportation, and communications. Because populations will be fully susceptible to an H5N1-like virus, rates of illness could peak fairly rapidly within a given community. They may, however, be amplified in today's closely interrelated and interdependent systems of trade and commerce. Based on past experience, a second wave of global spread should be anticipated within a year.

As all countries are likely to experience emergency conditions during a pandemic, opportunities for inter-country assistance, such as those seen during natural disasters or localized disease outbreaks, may be curtailed once the international spread has begun and governments focus on protecting domestic populations (19).

Situation in Turkey

The Ministry of Health in Turkey has confirmed its first two cases of human infection caused by an avian influenza H5 virus subtype on December 31, 2005. Both cases were fatal. They occurred in two family members in the rural district of Dogubayazit, in the eastern province of Agri, which borders Iran and Armenia. A 14-year-old boy was hospitalized on January 1, 2006 and died on the same day. His 15-year-old sister was hospitalized on January 1, 2006, and died on January 5, 2006. Two cases were hospitalized because of high fever (>39°C) and cough. Although many symptoms of bird flu are the same as in other respiratory infections, in addition there is a sudden onset of three-day fever, with muscle pain and a degree of prostration that is out of proportion in comparison with the severity of other symptoms. These two cases mark the first

Table 1. Cumulative number of confirmed human cases of avian influenza A/(H5N1) reported to the World Health Organization*

	No. od cases													
	Cambodia		China		Indonesia		Thailand		Turkey		Viet Nam		Total	
Year of onset	case	death	case	death	case	death	case	death	case	death	case	death	case	death
2003	0	0	0	0	0	0	0	0	0	0	3	3	3	3
2004	0	0	0	0	0	0	17	12	0	0	29	20	46	32
2005	4	4	7	3	16	11	5	2	0	0	61	19	93	39
2006	0	0	3	3	1	1	0	0	21	4	0	0	25	8
Total	4	4	10	6	17	12	22	14	21	4	93	42	167	82

*World Health Organization reports only laboratory-confirmed cases (ref. 11).

confirmed reports of human infection with avian influenza outside East Asia.

Preliminary information suggests that the two patients acquired their infection after close contact with chickens. Although no poultry outbreak has been officially reported in Dogubayazit district, a confirmed outbreak of H5N1 avian influenza in chickens and ducks was reported on December 27, 2005, in the neighboring province of Igdir.

According to the latest information received from the joint team of experts, as of January 8, 2006, a total of 13 avian influenza (H5) cases have been confirmed by virus isolation in 8 provinces (Igdir, Erzurum, Sanli Urfa, Erzincan, Agri, Bitlis, Yozgat, and Ankara), mostly in backyard flocks. Within the Ankara region, avian influenza (H5) virus was isolated in one wild duck. The very bad weather condition in Eastern Turkey makes any technical intervention very difficult and also favors a longer survival of the animal virus in the environment. Neighboring countries may also be susceptible to avian influenza outbreaks and should therefore increase their levels of surveillance.

January 5, 2006

National authorities have informed World Health Organization (WHO) that Dogubayazit district has been placed under quarantine; no people or animals are allowed to move in or out of the district. Culling operations are currently under way. Since January 2004, a total of 142 human cases of H5N1 infection have been reported in Viet Nam, Thailand, Cambodia, Indonesia, and China (10). The cases in Turkey bring the number of affected countries to six, from which 144 cases have now been reported.

Turkey reported its first outbreak of H5N1 avian influenza in poultry in mid-October 2005. That outbreak, which occurred in the northwestern part of the country, was attributed to contact between domestic poultry and migratory waterfowl. The outbreak in Igdir and other suspected outbreaks in this part of the country are thought to have occurred following introduction of the virus by migratory birds. The region, which has several large lakes, is known to lie along migratory routes (Figure 1).

January 7, 2006

The Ministry of Health in Turkey has confirmed an additional two cases of human infec-

Figure 1. Migratory routes of birds and possible paths of H5N1 avian influenza virus spread.

tion with the H5N1 avian influenza virus. Both cases were children, aged 5 and 8 years, and both were hospitalized. This brought the total number of laboratory-confirmed cases in Turkey to four. Two of these cases were fatal.

January 9, 2006

Laboratory tests conducted in Turkey have confirmed detection of the H5 subtype of avian influenza virus in samples from an additional 10 patients. Five of these cases were announced by the Ministry of Health on January 8 and additional five on January 9, 2006. Most patients were children and all have been hospitalized for treatment and evaluation. Of the five patients announced on January 8, three were from Ankara Province – two brothers, aged 5 and 2 years, and a 65-year-old man. All three patients were hospitalized in Ankara. The additional two cases, a 9-year-old girl and her 3-year-old brother, were from the Dogubayazit district in Agri Province, and were hospitalized in the city of Van. The five cases announced on January 9, 2006 were from Kastamonu, Corum, and Samsun provinces, bordering the Black Sea in the north-central part of the country, and from Van Province in the East Anatolia. This brings the total number of cases in Turkey, confirmed by laboratory tests, to 14 as of January 9, 2006. Of these patients, two have died. WHO will add these numbers to its cumulative total following further verification by an external H5 reference laboratory. The quality of laboratory testing at Turkey's National Influenza Centre in Ankara is high. Results from the tests conducted there the previous week were fully confirmed by a WHO collaborating laboratory in the United Kingdom (UK). WHO considers it likely that test results on the newly announced cases will be confirmed by the UK laboratory, where samples are being sent for further analysis.

H5N1 is the only strain within the H5 subtype known to infect humans. In the event of a confirmed H5N1 outbreak in birds, it is expected that human cases of avian influenza will be caused by the same virus strain. The initial WHO team, accompanied by the Turkish Minister of Health, arrived in Van Province on January 8, 2006. The team investigated the epidemiological situation, assessing risk factors and control measures, and discussed with local authorities the possible need for additional equipment and supplies. The team also assessed patients in the Van hospital where some 38 people are currently being treated and evaluated for possible H5N1 infection. The initial investigation has found no evidence that the virus has increased its transmissibility or is spreading from person to person. Most persons under investigation are children, often from the same family, and almost all have a documented link to dead or diseased poultry. Outbreaks in poultry are now known to be occurring in several parts of the country. In recent days, the Ministry of Agriculture has confirmed H5N1 outbreaks in birds in 10 of the country's 81 provinces. Extensive culling is under way and several other possible outbreaks are under investigation.

With the agreement of the Ministry of Health of Turkey, two epidemiologists and two experts in laboratory diagnosis will join the initial WHO team. Given the present high level of awareness of the disease and its presence in poultry in several parts of the country, the number of people concerned about possible exposure is expected to increase. This additional support should expedite understanding of the epidemiological situation and increase the capacity to rapidly confirm or rule out persons under investigation for possible infection.

The European Commission has been informed through the WHO that available results from National and University Laboratories in Ankara suggest that four people, including a boy and a girl who died respectively on January 7 and 8, 2006, have been infected with avian influenza virus. There may be additional suspected cases. An outbreak of this disease was confirmed in chickens in eastern Turkey, in the vicinity of the

border with Armenia and Iran, a few days ago. A community veterinary expert, who is also a member of the World Organization for Animal Health/Food and Agriculture Organization of the United Nations (OIE/FAO) network of expertise for Avian Influenza (OFFLU), an epidemiologist from the European Centre for Disease Prevention and Control (ECDC) together with WHO experts, arrived Turkey on January 9, 2006 to review the situation in cooperation with the Turkish authorities. In the meantime, samples from the sick chickens, which might have transmitted the disease to humans, are expected to arrive at the Community Reference Laboratory for Avian Influenza in Weybridge. This will clarify whether the animal outbreak was due to the deadly H5N1 strain of avian influenza. The Turkish authorities are also sending samples from the human cases to a WHO reference laboratory in Colindale (UK), to confirm if the virus in question is the same as that in the chickens. The European Commission together with the ECDC and the WHO is closely monitoring the situation especially from an epidemiological point of view. Obviously, the complete ban on any import from Turkey of live birds and poultry products adopted in early October 2005 remains in place.

Experts at WHO and elsewhere believe that the world is now closer to another influenza pandemic than at any time since 1968, when the last of the previous century's three pandemics occurred. WHO uses a series of six phases of pandemic alert as a system for informing the world of the seriousness of the threat and of the need to launch progressively more intense preparedness activities (Table 2). The designation of phases, including decisions on when to move from one phase to another, is made by the Director-General of WHO (15). Each phase of alert coincides with a series of recommended activities to be undertaken by WHO, the international community, governments, and industry. Changes from one phase to another are triggered by several factors, which include the epidemiological behavior of the disease and the characteristics of circulating viruses. The world is presently in phase 3: a new influenza virus subtype is causing disease in humans, but is not yet spreading efficiently and is not yet sustainable among humans.

January 12, 2006

Laboratory tests conducted in Turkey have confirmed detection of the H5 subtype of avian influenza virus in samples from two new patients. The patients are residents of Sanliurfa Province, near the southern border with Syria, and Siirt Province, which is neighboring to Van in the eastern part of the country. Human cases have now been reported from nine of the country's 81 provinces. Both patients are young children, aged 4 and 6 years, and both have a documented history of direct contact with diseased birds. In Sanliurfa Province, outbreaks in backyard poultry are now thought to date back to late November 2005. Altogether, agricultural officials have confirmed poultry outbreaks in 11 provinces and are investigating possible outbreaks in an additional 14 provinces across the country.

Laboratory tests completed today in Turkey have detected the H5 virus subtype in postmortem specimens taken from a 12-year-old girl, from Agri Province, who died on January 7, 2006. The child was the sibling of two other pa-

Table 2. Phases of alert in the World Health Organization global influenza preparedness plan (15)

Level of alert	İnfection risk and transmission	Phase
1	Low risk of human cases	inter-pandemic phase (new virus in animals, no human cases)
2	Higher risk of human cases	
3	No or very limited human-to-human transmission	pandemic alert (new virus in humans)
4	Evidence of increased human-to-human transmission	
5	Evidence of significant human-to-human transmission	
6	Efficient and sustained human-to-human transmission	pandemic

tients who died earlier. Their infection with the H5N1 virus was subsequently confirmed by a WHO collaborating laboratory in the UK. The Ministry of Health is now reporting 18 laboratory-confirmed cases, of which three, all from the same family, have been fatal.

Arrangements have been made to send specimens from several patients to the UK collaborating laboratory for further analysis. Due to official holidays in Turkey, specimens are not expected to arrive in the UK before January 16, 2006. The head of the collaborating laboratory is now in Ankara to support diagnostic work at the country's national influenza center. Ways are being sought to expedite the testing of patient samples. High awareness of the disease in the Turkish population, combined with almost daily reports of poultry outbreaks in new areas, has resulted in a large number of people concerned about exposure and seeking reassurance.

The rapid assessment of patients with a possible exposure history is providing a unique opportunity to learn more about the disease in humans. It is also generating data that can be used to assess the efficacy of antiviral drugs, as most people with an exposure history or respiratory symptoms are receiving oseltamivir either for prophylaxis or very early after the onset of symptoms.

Members of the international teams, in Van Province and Ankara, are working with local experts to plan relevant studies. These studies should deepen the understanding of the epidemiology of the disease, including the possibility that any human-to-human transmission may have occurred, the vulnerability to infection for health care workers and other occupationally-exposed groups, and the possibility that milder forms of the disease might be occurring in the general population.

January 16, 2006 – Final Report

Laboratory tests conducted in Turkey's national influenza center in Ankara have confirmed two additional cases of human infection with the H5N1 avian influenza virus. The first newly confirmed case is a 5-year-old boy from the district of Dogubayazit in Agri Province. He remains hospitalized in a stable condition. His 14-year-old sister died on January 15, 2006 of a respiratory disease with clinical features similar to those seen in H5N1 infection. Test results received on January 16, 2006 have confirmed the infection. As with all other cases seen in Turkey to date, both children developed illness following direct exposure to diseased poultry. Ducks began dying in the family's household flock on January 1, 2006. On that day, the girl, assisted by her brother, slaughtered a duck. Both children developed symptoms of fever >39°C on January 4, 2006 and both were hospitalized on January 11, 2006. No other family members have developed signs of illness. These newly confirmed cases bring the total in Turkey to 21, four of which were fatal. Of the 21 cases, 18 have been children aged between 4 and 18 years.

Discussion

All available evidence indicates that no sustained human-to-human transmission has occurred. As in Asia, contact with infected birds is the principal source of infection. The risk of infection for travelers to Turkey is negligible provided direct contact with dead or diseased domestic and wild birds is avoided.

The WHO Collaborating Centre for Reference and Research on influenza at the Medical Research Center National Institute for Medical Research in Mill Hill, London, has completed genetic and antigenic analyses of viruses recovered from the first two fatal human cases in the Turkish outbreak.

Information provided to WHO indicates that these viruses are very similar to current avian H5N1 viruses isolated from birds in Turkey. They are also closely related to viruses isolated from the large outbreak in migratory birds that occurred at the Qinghai Lake nature reserve in

China, beginning in late April of 2005. These analyses indicate that the Turkish viruses are sensitive to both classes of antiviral drugs, including oseltamivir and amantadine. WHO and collaborating experts will review the data on amantadine sensitivity. Oseltamivir remains the drug of first choice recommended by WHO.

Virus from one of the patients shows mutations at the receptor-binding site. One of the mutations has been seen previously in viruses isolated from a small outbreak in Hong Kong in 2003 (two cases, one of which was fatal) and from the 2005 outbreak in Viet Nam. Research has indicated that the Hong Kong 2003 viruses bind preferentially to human cell receptors more so than to avian cell receptors. Researchers at the Mill Hill Laboratory anticipate that the Turkish virus will also have the same characteristics (10).

The present WHO level of pandemic alert remains at phase 3: human infections with a new virus subtype are occurring, but the vast majority of these infections are acquired directly from animals.

With more than 100 million birds either dead from infection or culled, the present outbreak of avian influenza in Asia and Anatolia is unprecedented in size. The virus is capable of transmitting to human, causing lethal infections, but as yet the virus does not easily transmit from human to human. However, there is a substantial risk of either re-assortment of virus (combination of avian and human influenza), or adaptation of the influenza virus to humans. If this happens we may be on the verge of a new influenza pandemic with grave consequences both for human health and the world economy. The present situation emphasizes the importance of good surveillance and updated pandemic plans in all countries. To minimize the risk of double infection and viral adaptations into forms that may cause human-to-human transmission, persons with an occupational exposure to highly pathogenic avian influenza (HPAI) should be vaccinated against influenza A. International collaboration on surveillance of epidemics among birds and humans is needed. Low- and middle-income countries are likely to need international support to meet surveillance requirements according to WHO guidelines.

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