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## Human Bird Flu Cases Present Puzzling Patterns

**New U.N. fact sheet details observations, as human cases mount**



A young bird flu patient is monitored in a Chinese hospital, January 13, 2006. (©AP/WWP)

The document also describes physicians' observations about the "unusually aggressive clinical course" of the disease in humans.

The World Health Organization (WHO) has issued a new fact sheet on avian influenza, the first since the disease moved out of Asia into Europe.

The document summarizes the course of bird flu in its two-year spread across Eurasia. In regard to the human cases that have appeared in six nations, the fact sheet points out some puzzling unknown factors. Human cases of disease have not appeared in commercial poultry enterprises or culling operations, as might be expected. Instead, the majority of cases have stricken previously healthy children and young adults exposed to small flocks kept in domestic settings.

The fact sheet follows:

World Health Organization  
 [Geneva, Switzerland]  
 Avian influenza ("bird flu") - Fact Sheet  
 January 2006

### THE DISEASE IN BIRDS

Avian influenza is an infectious disease of birds caused by type A strains of the influenza virus. The disease occurs worldwide. While all birds are thought to be susceptible to infection with avian influenza viruses, many wild bird species carry these viruses with no apparent signs of harm.

Other bird species, including domestic poultry, develop disease when infected with avian influenza viruses. In poultry, the viruses cause two distinctly different forms of disease – one common and mild, the other rare and highly lethal. In the mild form, signs of illness may be expressed only as ruffled feathers, reduced egg production, or mild effects on the respiratory system. Outbreaks can be so mild they escape detection unless regular testing for viruses is in place.

In contrast, the second and far less common highly pathogenic form is difficult to miss. First identified in Italy in 1878, highly pathogenic avian influenza is characterized by sudden onset of severe disease, rapid contagion, and a mortality rate that can approach 100% within 48 hours. In this form of the disease, the virus not only affects the respiratory tract, as in the mild form, but also invades multiple organs and tissues. The resulting massive internal haemorrhaging has earned it the lay name of "chicken Ebola".

All 16 HA (haemagglutinin) and 9 NA (neuraminidase) subtypes of influenza viruses are known to infect wild waterfowl, thus providing an extensive reservoir of influenza viruses perpetually circulating in bird populations. In wild birds, routine testing will nearly always find some influenza viruses. The vast majority of these viruses cause no harm.

To date, all outbreaks of the highly pathogenic form of avian influenza have been caused by viruses of the H5 and H7 subtypes. Highly pathogenic viruses possess a tell-tale genetic "trade mark" or signature – a distinctive set of basic amino acids in the cleavage site of the HA – that distinguishes them from all other avian influenza viruses and is associated with their exceptional virulence.

Not all virus strains of the H5 and H7 subtypes are highly pathogenic, but most are thought to have the potential to become so. Recent research has shown that H5 and H7 viruses of low pathogenicity can, after circulation for sometimes short periods in a poultry population, mutate into highly pathogenic viruses. Considerable circumstantial evidence has long suggested that wild waterfowl introduce avian influenza viruses, in their low pathogenic form, to poultry flocks, but do not carry or directly spread highly pathogenic viruses. This role may, however, have changed very recently: at least some species of migratory waterfowl are now thought to be carrying the H5N1 virus in its highly pathogenic form and introducing it to new geographical areas located along their flight routes.

Apart from being highly contagious among poultry, avian influenza viruses are readily transmitted from farm to farm by the movement of live birds, people (especially when shoes and other clothing are contaminated), and contaminated vehicles, equipment, feed, and cages. Highly pathogenic viruses can survive for long periods in the environment, especially when temperatures are low. For example, the highly pathogenic H5N1 virus can survive in bird faeces for at least 35 days at low temperature (4° C). At a much higher temperature (37° C), H5N1 viruses have been shown to survive, in faecal samples, for six days.

For highly pathogenic disease, the most important control measures are rapid culling of all infected or exposed birds, proper disposal of carcasses, the quarantining and rigorous disinfection of farms, and the implementation of strict sanitary, or "biosecurity", measures. Restrictions on the movement of live poultry, both within and between countries, are another important control measure. The logistics of recommended control measures are most straightforward when applied to large commercial farms, where birds are housed indoors, usually under strictly controlled sanitary conditions, in large numbers. Control is far more difficult under poultry production systems in which most birds are raised in small backyard flocks scattered throughout rural or periurban areas.

When culling – the first line of defence for containing outbreaks – fails or proves impracticable, vaccination of poultry in a high-risk area can be used as a supplementary emergency measure, provided quality-assured vaccines are used and OIE recommendations are strictly followed. The use of poor quality vaccines or vaccines that poorly match the circulating virus strain may accelerate mutation of the virus. Poor quality animal vaccines may also pose a risk for human health, as they may allow infected birds to shed virus while still appearing to be disease-free.

Apart from being difficult to control, outbreaks in backyard flocks are associated with a heightened risk of human exposure and infection. These birds usually roam freely as they scavenge for food and often mingle with wild birds or share water sources with them. Such situations create abundant opportunities for human exposure to the virus, especially when birds enter households or are brought into households during adverse weather, or when they share areas where children play or sleep. Poverty exacerbates the problem: in situations where a prime source of food and income cannot be wasted, households frequently consume poultry when deaths or signs of illness appear in flocks. This practice carries a high risk of exposure to the virus during slaughtering, defeathering, butchering, and preparation of poultry meat for cooking, but has proved difficult to change. Moreover, as deaths of birds in backyard flocks are common, especially under adverse weather conditions, owners may not interpret deaths or signs of illness in a flock as a signal of avian influenza and a reason to alert the authorities. This tendency may help explain why outbreaks in some rural areas have smouldered undetected for months. The frequent absence of compensation to farmers for destroyed birds further works against the spontaneous reporting of outbreaks and may encourage owners to hide their birds during culling operations.

#### THE ROLE OF MIGRATORY BIRDS

During 2005, an additional and significant source of international spread of the virus in birds became apparent for the first time, but remains poorly understood. Scientists are increasingly convinced that at least some migratory waterfowl are now carrying the H5N1 virus in its highly pathogenic form, sometimes over long distances, and introducing the virus to poultry flocks in areas that lie along their migratory routes. Should this new role of migratory birds be scientifically confirmed, it will mark a change in a long-standing stable relationship between the H5N1 virus and its natural wild-bird reservoir.

Evidence supporting this altered role began to emerge in mid-2005 and has since been strengthened. The die-off of more than 6000 migratory birds, infected with the highly pathogenic H5N1 virus, that began at the Qinghai Lake nature reserve in central China in late April 2005, was highly unusual and

probably unprecedented. Prior to that event, wild bird deaths from highly pathogenic avian influenza viruses were rare, usually occurring as isolated cases found within the flight distance of a poultry outbreak. Scientific studies comparing viruses from different outbreaks in birds have found that viruses from the most recently affected countries, all of which lie along migratory routes, are almost identical to viruses recovered from dead migratory birds at Qinghai Lake. Viruses from Turkey's first two human cases, which were fatal, were also virtually identical to viruses from Qinghai Lake.

#### COUNTRIES AFFECTED BY OUTBREAKS IN BIRDS

The outbreaks of highly pathogenic avian influenza that began in south-east Asia in mid-2003 and have now spread to a few parts of Europe, are the largest and most severe on record. To date, nine Asian countries have reported outbreaks (listed in order of reporting): the Republic of Korea, Viet Nam, Japan, Thailand, Cambodia, the Lao People's Democratic Republic, Indonesia, China, and Malaysia. Of these, Japan, the Republic of Korea, and Malaysia have controlled their outbreaks and are now considered free of the disease. Elsewhere in Asia, the virus has become endemic in several of the initially affected countries.

In late July 2005, the virus spread geographically beyond its original focus in Asia to affect poultry and wild birds in the Russian Federation and adjacent parts of Kazakhstan. Almost simultaneously, Mongolia reported detection of the highly pathogenic virus in wild birds. In October 2005, the virus was reported in Turkey, Romania, and Croatia. In early December 2005, Ukraine reported its first outbreak in domestic birds. Most of these newer outbreaks were detected and reported quickly. Further spread of the virus along the migratory routes of wild waterfowl is, however, anticipated. Moreover, bird migration is a recurring event. Countries that lie along the flight pathways of birds migrating from central Asia may face a persistent risk of introduction or re-introduction of the virus to domestic poultry flocks.

Prior to the present situation, outbreaks of highly pathogenic avian influenza in poultry were considered rare. Excluding the current outbreaks caused by the H5N1 virus, only 24 outbreaks of highly pathogenic avian influenza have been recorded worldwide since 1959. Of these, 14 occurred in the past decade. The majority have shown limited geographical spread, a few remained confined to a single farm or flock, and only one spread internationally. All of the larger outbreaks were costly for the agricultural sector and difficult to control.

#### THE DISEASE IN HUMANS

History and epidemiology. Influenza viruses are normally highly species-specific, meaning that viruses that infect an individual species (humans, certain species of birds, pigs, horses, and seals) stay "true" to that species, and only rarely spill over to cause infection in other species. Since 1959, instances of human infection with an avian influenza virus have occurred on only 10 occasions. Of the hundreds of strains of avian influenza A viruses, only four are known to have caused human infections: H5N1, H7N3, H7N7, and H9N2. In general, human infection with these viruses has resulted in mild symptoms and very little severe illness, with one notable exception: the highly pathogenic H5N1 virus.

Of all influenza viruses that circulate in birds, the H5N1 virus is of greatest present concern for human health for two main reasons. First, the H5N1 virus has caused by far the greatest number of human cases of very severe disease and the greatest number of deaths. It has crossed the species barrier to infect humans on at least three occasions in recent years: in Hong Kong in 1997 (18 cases with six deaths), in Hong Kong in 2003 (two cases with one death) and in the current outbreaks that began in December 2003 and were first recognized in January 2004.

A second implication for human health, of far greater concern, is the risk that the H5N1 virus – if given enough opportunities – will develop the characteristics it needs to start another influenza pandemic. The virus has met all prerequisites for the start of a pandemic save one: an ability to spread efficiently and sustainably among humans. While H5N1 is presently the virus of greatest concern, the possibility that other avian influenza viruses, known to infect humans, might cause a pandemic cannot be ruled out.

During the first documented outbreak of human infections with H5N1, which occurred in Hong Kong in 1997, the 18 human cases coincided with an outbreak of highly pathogenic avian influenza, caused by a virtually identical virus, in poultry farms and live markets. Extensive studies of the human cases determined that direct contact with diseased poultry was the source of infection. Studies carried out in family members and social contacts of patients, health workers engaged in their care, and poultry cullers found very limited, if any, evidence of spread of the virus from one person to another. Human infections ceased following the rapid destruction – within three days – of Hong Kong's entire poultry population, estimated at around 1.5 million birds. Some experts believe that that drastic action may

have averted a pandemic.

All evidence to date indicates that close contact with dead or sick birds is the principal source of human infection with the H5N1 virus. Especially risky behaviours identified include the slaughtering, defeathering, butchering and preparation for consumption of infected birds. In a few cases, exposure to chicken faeces when children played in an area frequented by free-ranging poultry is thought to have been the source of infection. Swimming in water bodies where the carcasses of dead infected birds have been discarded or which may have been contaminated by faeces from infected ducks or other birds might be another source of exposure. In some cases, investigations have been unable to identify a plausible exposure source, suggesting that some as yet unknown environmental factor, involving contamination with the virus, may be implicated in a small number of cases. Some explanations that have been put forward include a possible role of peri-domestic birds, such as pigeons, or the use of untreated bird faeces as fertilizer.

At present, H5N1 avian influenza remains largely a disease of birds. The species barrier is significant: the virus does not easily cross from birds to infect humans. Despite the infection of tens of millions of poultry over large geographical areas for more than two years, fewer than 200 human cases have been laboratory confirmed. For unknown reasons, most cases have occurred in rural and periurban households where small flocks of poultry are kept. Again for unknown reasons, very few cases have been detected in presumed high-risk groups, such as commercial poultry workers, workers at live poultry markets, cullers, veterinarians, and health staff caring for patients without adequate protective equipment. Also lacking is an explanation for the puzzling concentration of cases in previously healthy children and young adults. Research is urgently needed to better define the exposure circumstances, behaviours, and possible genetic or immunological factors that might enhance the likelihood of human infection.

Assessment of possible cases. Investigations of all the most recently confirmed human cases, in China, Indonesia, and Turkey, have identified direct contact with infected birds as the most likely source of exposure. When assessing possible cases, the level of clinical suspicion should be heightened for persons showing influenza-like illness, especially with fever and symptoms in the lower respiratory tract, who have a history of close contact with birds in an area where confirmed outbreaks of highly pathogenic H5N1 avian influenza are occurring. Exposure to an environment that may have been contaminated by faeces from infected birds is a second, though less common, source of human infection. To date, not all human cases have arisen from exposure to dead or visibly ill domestic birds. Research published in 2005 has shown that domestic ducks can excrete large quantities of highly pathogenic virus without showing signs of illness. A history of poultry consumption in an affected country is not a risk factor, provided the food was thoroughly cooked and the person was not involved in food preparation. As no efficient human-to-human transmission of the virus is known to be occurring anywhere, simply travelling to a country with ongoing outbreaks in poultry or sporadic human cases does not place a traveller at enhanced risk of infection, provided the person did not visit live or "wet" poultry markets, farms, or other environments where exposure to diseased birds may have occurred.

Clinical features (1) In many patients, the disease caused by the H5N1 virus follows an unusually aggressive clinical course, with rapid deterioration and high fatality. Like most emerging disease, H5N1 influenza in humans is poorly understood. Clinical data from cases in 1997 and the current outbreak are beginning to provide a picture of the clinical features of disease, but much remains to be learned. Moreover, the current picture could change given the propensity of this virus to mutate rapidly and unpredictably.

The incubation period for H5N1 avian influenza may be longer than that for normal seasonal influenza, which is around 2 to 3 days. Current data for H5N1 infection indicate an incubation period ranging from 2 to 8 days and possibly as long as 17 days. However, the possibility of multiple exposure to the virus makes it difficult to define the incubation period precisely. WHO currently recommends that an incubation period of 7 days be used for field investigations and the monitoring of patient contacts.

Initial symptoms include a high fever, usually with a temperature higher than 38°C, and influenza-like symptoms. Diarrhoea, vomiting, abdominal pain, chest pain, and bleeding from the nose and gums have also been reported as early symptoms in some patients.

Watery diarrhoea without blood appears to be more common in H5N1 avian influenza than in normal seasonal influenza. The spectrum of clinical symptoms may, however, be broader, and not all confirmed patients have presented with respiratory symptoms. In two patients from southern Viet Nam, the clinical diagnosis was acute encephalitis; neither patient had respiratory symptoms at presentation. In another case, from Thailand, the patient presented with fever and diarrhoea, but no respiratory symptoms. All three patients had a recent history of direct exposure to infected poultry.

One feature seen in many patients is the development of manifestations in the lower respiratory tract early in the illness. Many patients have symptoms in the lower respiratory tract when they first seek treatment. On present evidence, difficulty in breathing develops around 5 days following the first symptoms. Respiratory distress, a hoarse voice, and a crackling sound when inhaling are commonly seen. Sputum production is variable and sometimes bloody. Most recently, blood-tinted respiratory secretions have been observed in Turkey. Almost all patients develop pneumonia. During the Hong Kong outbreak, all severely ill patients had primary viral pneumonia, which did not respond to antibiotics. Limited data on patients in the current outbreak indicate the presence of a primary viral pneumonia in H5N1, usually without microbiological evidence of bacterial supra-infection at presentation. Turkish clinicians have also reported pneumonia as a consistent feature in severe cases; as elsewhere, these patients did not respond to treatment with antibiotics.

In patients infected with the H5N1 virus, clinical deterioration is rapid. In Thailand, the time between onset of illness to the development of acute respiratory distress was around 6 days, with a range of 4 to 13 days. In severe cases in Turkey, clinicians have observed respiratory failure 3 to 5 days after symptom onset. Another common feature is multiorgan dysfunction, notably involving the kidney and heart. Common laboratory abnormalities include lymphopenia, leukopenia, elevated aminotransferases, and mild-to-moderate thrombocytopenia with some instances of disseminated intravascular coagulation.

Limited evidence suggests that some antiviral drugs, notably oseltamivir (commercially known as Tamiflu), can reduce the duration of viral replication and improve prospects of survival, provided they are administered within 48 hours following symptom onset. However, prior to the outbreak in Turkey, most patients have been detected and treated late in the course of illness. For this reason, clinical data on the effectiveness of oseltamivir are limited. Moreover, oseltamivir and other antiviral drugs were developed for the treatment and prophylaxis of seasonal influenza, which is a less severe disease associated with less prolonged viral replication. Recommendations on the optimum dose and duration of treatment for H5N1 avian influenza, also in children, need to undergo urgent review, and this is being undertaken by WHO.

In suspected cases, oseltamivir should be prescribed as soon as possible (ideally, within 48 hours following symptom onset) to maximize its therapeutic benefits. However, given the significant mortality currently associated with H5N1 infection and evidence of prolonged viral replication in this disease, administration of the drug should also be considered in patients presenting later in the course of illness.

Currently recommended doses of oseltamivir for the treatment of influenza are contained in the product information at the manufacturer's web site. The recommended dose of oseltamivir for the treatment of influenza, in adults and adolescents 13 years of age and older, is 150 mg per day, given as 75 mg twice a day for 5 days. Oseltamivir is not indicated for the treatment of children younger than 1 year of age.

As the duration of viral replication may be prolonged in cases of H5N1 infection, clinicians should consider increasing the duration of treatment to 7 to 10 days in patients who are not showing a clinical response. In cases of severe infection with the H5N1 virus, clinicians may need to consider increasing the recommended daily dose or the duration of treatment, keeping in mind that doses above 300 mg per day are associated with increased side effects. For all treated patients, consideration should be given to taking serial clinical samples for later assay to monitor changes in viral load, to assess drug susceptibility, and to assess drug levels. These samples should be taken only in the presence of appropriate measures for infection control.

In severely ill H5N1 patients or in H5N1 patients with severe gastrointestinal symptoms, drug absorption may be impaired. This possibility should be considered when managing these patients.

#### COUNTRIES WITH HUMAN CASES IN THE CURRENT OUTBREAK

To date, human cases have been reported in six countries, most of which are in Asia: Cambodia, China, Indonesia, Thailand, Turkey, and Viet Nam. The first patients in the current outbreak, which were reported from Viet Nam, developed symptoms in December 2003 but were not confirmed as H5N1 infection until 11 January 2004. Thailand reported its first cases on 23 January 2004. The first case in Cambodia was reported on 2 February 2005. The next country to report cases was Indonesia, which confirmed its first infection on 21 July. China's first two cases were reported on 16 November 2005. Confirmation of the first cases in Turkey came on 5 January 2006. All human cases have coincided with outbreaks of highly pathogenic H5N1 avian influenza in poultry. To date, Viet Nam has been the most severely affected country, with more than 90 cases.

Altogether, more than half of the laboratory-confirmed cases have been fatal. H5N1 avian influenza in

humans is still a rare disease, but a severe one that must be closely watched and studied, particularly because of the potential this virus to evolve in ways that could start a pandemic.

(1) This section has been reviewed by a virtual network of clinicians experienced in the treatment of H5N1 infections and other severe respiratory diseases. The network was convened for the first time on 16 January 2006. Physicians from Yüzüncü Yil University, Faculty of Medicine, Van, Turkey participated in the exchange of information and experiences. Other institutions represented include the University of Hong Kong (China); the Hospital for Tropical Diseases, Ho Chi Minh City (Viet Nam); and the University of Virginia, Charlottesville, Virginia (USA).

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