



Avian influenza ("bird flu") - Fact sheet

February 2006

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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 recommendations from the World Organisation for Animal Health (OIE) 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 H5N1 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 been documented 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.

The virus can improve its transmissibility among humans via two principal mechanisms. The first is a "reassortment" event, in which genetic material is exchanged between human and avian viruses during co-infection of a human or pig. Reassortment could result in a fully transmissible pandemic virus, announced by a sudden surge of cases with explosive spread.

The second mechanism is a more gradual process of adaptive mutation, whereby the capability of the virus to bind to human cells increases during subsequent infections of humans. Adaptive mutation, expressed initially as small clusters of human cases with some evidence of human-to-human transmission, would probably give the world some time to take defensive action, if detected sufficiently early.

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 an influenza 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 since mid-2003, 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 two to three days. Current data for H5N1 infection indicate an incubation period ranging from two to eight 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 seven 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 five 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 six days, with a range of four to 13 days. In severe cases in Turkey, clinicians have observed respiratory failure three to five days after symptom onset. Another common feature is multiorgan dysfunction. Common laboratory abnormalities, include leukopenia (mainly lymphopenia), mild-to-moderate thrombocytopenia, elevated aminotransferases, and 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 five days. Oseltamivir is not indicated for the treatment of children younger than one 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 seven to ten 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, followed by the first reported case in Iraq on 30 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 of 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 Yıl 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).*



Avian influenza frequently asked questions

revised 5 December 2005

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What is avian influenza?

Avian influenza, or “bird flu”, is a contagious disease of animals caused by viruses that normally infect only birds and, less commonly, pigs. Avian influenza viruses are highly species-specific, but have, on rare occasions, crossed the species barrier to infect humans.

In domestic poultry, infection with avian influenza viruses causes two main forms of disease, distinguished by low and high extremes of virulence. The so-called “low pathogenic” form commonly causes only mild symptoms (ruffled feathers, a drop in egg production) and may easily go undetected. The highly pathogenic form is far more dramatic. It spreads very rapidly through poultry flocks, causes disease affecting multiple internal organs, and has a mortality that can approach 100%, often within 48 hours.

Which viruses cause highly pathogenic disease?

Influenza A viruses¹ have 16 H subtypes and 9 N subtypes². Only viruses of the H5 and H7 subtypes are known to cause the highly pathogenic form of the disease. However, not all viruses of the H5 and H7 subtypes are highly pathogenic and not all will cause severe disease in poultry.

On present understanding, H5 and H7 viruses are introduced to poultry flocks in their low pathogenic form. When allowed to circulate in poultry populations, the viruses can mutate, usually within a few months, into the highly pathogenic form. This is why the presence of an H5 or H7 virus in poultry is always cause for concern, even when the initial signs of infection are mild.

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 are considered the natural reservoir of all influenza A viruses. They have probably carried influenza viruses, with no apparent harm, for centuries. They are known to carry viruses of the H5 and H7 subtypes, but usually in the low pathogenic form. Considerable circumstantial evidence suggests that migratory birds can introduce low pathogenic H5 and H7 viruses to poultry flocks, which then mutate to the highly pathogenic form.

In the past, highly pathogenic viruses have been isolated from migratory birds on very rare occasions involving a few birds, usually found dead within the flight range of a poultry outbreak. This finding long suggested that wild waterfowl are not agents for the onward transmission of these viruses.

Recent events make it likely that some migratory birds are now directly spreading the H5N1 virus in its highly pathogenic form. Further spread to new areas is expected.

What is special about the current outbreaks in poultry?

The current outbreaks of highly pathogenic avian influenza, which began in South-East 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.

The causative agent, the H5N1 virus, has 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.

The H5N1 virus is also of particular concern for human health, as explained below.

Which countries have been affected by outbreaks in poultry?

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. Most of these countries had never before experienced an outbreak of highly pathogenic avian influenza in their histories.

In early August 2004, Malaysia reported its first outbreak of H5N1 in poultry, becoming the ninth Asian nation 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. 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. In October 2005, H5N1 was confirmed in poultry in Turkey and Romania. Outbreaks in wild and domestic birds are under investigation elsewhere.

Japan, the Republic of Korea, and Malaysia have announced control of their poultry outbreaks and are now considered free of the disease. In the other affected areas, outbreaks are continuing with varying degrees of severity.

What are the implications for human health?

The widespread persistence of H5N1 in poultry populations poses two main risks for human health.

The first is the risk of direct infection when the virus passes from poultry to humans, resulting in very severe disease. Of the few avian influenza viruses that have crossed the species barrier to infect humans, H5N1 has caused the largest number of cases of severe disease and death in humans. Unlike normal seasonal influenza, where infection causes only mild respiratory symptoms in most people, the disease caused by H5N1 follows an unusually aggressive clinical course, with rapid deterioration and high fatality. Primary viral pneumonia and multi-organ failure are common. In the present outbreak, more than half of those infected with the virus have died. Most cases have occurred in previously healthy children and young adults.

A second risk, of even greater concern, is that the virus – if given enough opportunities – will change into a form that is highly infectious for humans and spreads easily from person to person. Such a change could mark the start of a global outbreak (a pandemic).

Where have human cases occurred?

In the current outbreak, laboratory-confirmed human cases have been reported in four countries: Cambodia, Indonesia, Thailand, and Viet Nam.

Hong Kong has experienced two outbreaks in the past. In 1997, in the first recorded instance of human infection with H5N1, the virus infected 18 people and killed 6 of them. In early 2003, the virus caused two infections, with one death, in a Hong Kong family with a recent travel history to southern China.

How do people become infected?

Direct contact with infected poultry, or surfaces and objects contaminated by their faeces, is presently considered the main route of human infection. To date, most human cases have occurred in rural or periurban areas where many households keep small poultry flocks, which often roam freely, sometimes entering homes or sharing outdoor areas where children play. As infected birds shed large quantities of virus in their faeces, opportunities for exposure to infected droppings or to environments contaminated by the virus are abundant under such conditions. Moreover, because many households in Asia depend on poultry for income and food, many families sell or slaughter and consume birds when signs of illness appear in a flock, and this practice has proved difficult to change. Exposure is considered most likely during slaughter, defeathering, butchering, and preparation of poultry for cooking.

Is it safe to eat poultry and poultry products?

Yes, though certain precautions should be followed in countries currently experiencing outbreaks. In areas free of the disease, poultry and poultry products can be prepared and consumed as usual (following good hygienic practices and proper cooking), with no fear of acquiring infection with the H5N1 virus.

In areas experiencing outbreaks, poultry and poultry products can also be safely consumed provided these items are properly cooked and properly handled during food preparation. The H5N1 virus is sensitive to heat. Normal temperatures used for cooking (70°C in all parts of the food) will kill the virus. Consumers need to be sure that all parts of the poultry are fully cooked (no “pink” parts) and that eggs, too, are properly cooked (no “runny” yolks).

Consumers should also be aware of the risk of cross-contamination. Juices from raw poultry and poultry products should never be allowed, during food preparation, to touch or mix with items eaten raw. When handling raw poultry or raw poultry products, persons involved in food preparation should wash their hands thoroughly and clean and disinfect surfaces in contact with the poultry products. Soap and hot water are sufficient for this purpose.

In areas experiencing outbreaks in poultry, raw eggs should not be used in foods that will not be further heat-treated as, for example by cooking or baking.

Avian influenza is not transmitted through cooked food. To date, no evidence indicates that anyone has become infected following the consumption of properly cooked poultry or poultry products, even when these foods were contaminated with the H5N1 virus.

Does the virus spread easily from birds to humans?

No. Though more than 100 human cases have occurred in the current outbreak, this is a small number compared with the huge number of birds affected and the numerous associated opportunities for human exposure, especially in areas where backyard flocks are common. It is not presently understood why some people, and not others, become infected following similar exposures.

What about the pandemic risk?

A pandemic can start when three conditions have been met: a new influenza virus subtype emerges; it infects humans, causing serious illness; and it spreads easily and sustainably among humans. The H5N1 virus amply meets the first two conditions: it is a new virus for humans (H5N1 viruses have never circulated widely among people), and it has infected more than 100 humans, killing over half of them. No one will have immunity should an H5N1-like pandemic virus emerge.

All prerequisites for the start of a pandemic have therefore been met save one: the establishment of efficient and sustained human-to-

human transmission of the virus. The risk that the H5N1 virus will acquire this ability will persist as long as opportunities for human infections occur. These opportunities, in turn, will persist as long as the virus continues to circulate in birds, and this situation could endure for some years to come.

What changes are needed for H5N1 to become a pandemic virus?

The virus can improve its transmissibility among humans via two principal mechanisms. The first is a “reassortment” event, in which genetic material is exchanged between human and avian viruses during co-infection of a human or pig. Reassortment could result in a fully transmissible pandemic virus, announced by a sudden surge of cases with explosive spread.

The second mechanism is a more gradual process of adaptive mutation, whereby the capability of the virus to bind to human cells increases during subsequent infections of humans. Adaptive mutation, expressed initially as small clusters of human cases with some evidence of human-to-human transmission, would probably give the world some time to take defensive action.

What is the significance of limited human-to-human transmission?

Though rare, instances of limited human-to-human transmission of H5N1 and other avian influenza viruses have occurred in association with outbreaks in poultry and should not be a cause for alarm. In no instance has the virus spread beyond a first generation of close contacts or caused illness in the general community. Data from these incidents suggest that transmission requires very close contact with an ill person. Such incidents must be thoroughly investigated but – provided the investigation indicates that transmission from person to person is very limited – such incidents will not change the WHO overall assessment of the pandemic risk. There have been a number of instances of avian influenza infection occurring among close family members. It is often impossible to determine if human-to-human transmission has occurred since the family members are exposed to the same animal and environmental sources as well as to one another.

How serious is the current pandemic risk?

The risk of pandemic influenza is serious. With the H5N1 virus now firmly entrenched in large parts of Asia, the risk that more human cases will occur will persist. Each additional human case gives the virus an opportunity to improve its transmissibility in humans, and thus develop into a pandemic strain. The recent spread of the virus to poultry and wild birds in new areas further broadens opportunities for human cases to occur. While neither the timing nor the severity of the next pandemic can be predicted, the probability that a pandemic will occur has increased.

Are there any other causes for concern?

Yes. Several.

- Domestic ducks can now excrete large quantities of highly pathogenic virus without showing signs of illness, and are now acting as a “silent” reservoir of the virus, perpetuating transmission to other birds. This adds yet another layer of complexity to control efforts and removes the warning signal for humans to avoid risky behaviours.
- When compared with H5N1 viruses from 1997 and early 2004, H5N1 viruses now circulating are more lethal to experimentally infected mice and to ferrets (a mammalian model) and survive longer in the environment.
- H5N1 appears to have expanded its host range, infecting and killing mammalian species previously considered resistant to infection with avian influenza viruses.
- The behaviour of the virus in its natural reservoir, wild waterfowl, may be changing. The spring 2005 die-off of upwards of 6,000 migratory birds at a nature reserve in central China, caused by highly pathogenic H5N1, was highly unusual and probably unprecedented. In the past, only two large die-offs in migratory birds, caused by highly pathogenic viruses, are known to have occurred: in South Africa in 1961 (H5N3) and in Hong Kong in the winter of 2002–2003 (H5N1).

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, caused as they are by a virus that spreads 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 travellers.

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 million to 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. In the USA, the mortality rate during that pandemic was around 2.5%.

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. This means that local social and economic disruptions may be temporary. 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, as seen during natural disasters or localized disease outbreaks, may be curtailed once international spread has begun and governments focus on protecting domestic populations.

What are the most important warning signals that a pandemic is about to start?

The most important warning signal comes when clusters of patients with clinical symptoms of influenza, closely related in time and place, are detected, as this suggests human-to-human transmission is taking place. For similar reasons, the detection of cases in health workers caring for H5N1 patients would suggest human-to-human transmission. Detection of such events should be followed by immediate field investigation of every possible case to confirm the diagnosis, identify the source, and determine whether human-to-human transmission is occurring.

Studies of viruses, conducted by specialized WHO reference laboratories, can corroborate field investigations by spotting genetic and other changes in the virus indicative of an improved ability to infect humans. This is why WHO repeatedly asks affected countries to share viruses with the international research community.

What is the status of vaccine development and production?

Vaccines effective against a pandemic virus are not yet available. Vaccines are produced each year for seasonal influenza but will not protect against pandemic influenza. Although a vaccine against the H5N1 virus is under development in several countries, no vaccine is ready for commercial production and no vaccines are expected to be widely available until several months after the start of a pandemic.

Some clinical trials are now under way to test whether experimental vaccines will be fully protective and to determine whether different formulations can economize on the amount of antigen required, thus boosting production capacity. Because the vaccine needs to closely match the pandemic virus, large-scale commercial production will not start until the new virus has emerged and a pandemic has been declared. Current global production capacity falls far short of the demand expected during a pandemic.

What drugs are available for treatment?

Two drugs (in the neuraminidase inhibitors class), oseltamivir (commercially known as Tamiflu) and zanamivir (commercially known as Relenza) can reduce the severity and duration of illness caused by seasonal influenza. The efficacy of the neuraminidase inhibitors depends, among others, on their early administration (within 48 hours after symptom onset). For cases of human infection with H5N1, the drugs may improve prospects of survival, if administered early, but clinical data are limited. The H5N1 virus is expected to be susceptible to the neuraminidase inhibitors. Antiviral resistance to neuraminidase inhibitors has been clinically negligible so far but is likely to be detected during widespread use during a pandemic.

An older class of antiviral drugs, the M2 inhibitors amantadine and rimantadine, could potentially be used against pandemic influenza, but resistance to these drugs can develop rapidly and this could significantly limit their effectiveness against pandemic influenza. Some currently circulating H5N1 strains are fully resistant to these the M2 inhibitors. However, should a new virus emerge through reassortment, the M2 inhibitors might be effective.

For the neuraminidase inhibitors, the main constraints – which are substantial – involve limited production capacity and a price that is prohibitively high for many countries. At present manufacturing capacity, which has recently quadrupled, it will take a decade to produce enough oseltamivir to treat 20% of the world's population. The manufacturing process for oseltamivir is complex and time-consuming, and is not easily transferred to other facilities.

So far, most fatal pneumonia seen in cases of H5N1 infection has resulted from the effects of the virus, and cannot be treated with antibiotics. Nonetheless, since influenza is often complicated by secondary bacterial infection of the lungs, antibiotics could be life-saving in the case of late-onset pneumonia. WHO regards it as prudent for countries to ensure adequate supplies of antibiotics in advance.

Can a pandemic be prevented?

No one knows with certainty. The best way to prevent a pandemic would be to eliminate the virus from birds, but it has become increasingly doubtful if this can be achieved within the near future.

Following a donation by industry, WHO will have a stockpile of antiviral medications, sufficient for 3 million treatment courses, by early 2006. Recent studies, based on mathematical modelling, suggest that these drugs could be used prophylactically near the start of a pandemic to reduce the risk that a fully transmissible virus will emerge or at least to delay its international spread, thus gaining time to augment vaccine supplies.

The success of this strategy, which has never been tested, depends on several assumptions about the early behaviour of a pandemic virus, which cannot be known in advance. Success also depends on excellent surveillance and logistics capacity in the initially affected areas, combined with an ability to enforce movement restrictions in and out of the affected area. To increase the likelihood that early intervention using the WHO rapid-intervention stockpile of antiviral drugs will be successful, surveillance in affected countries needs to improve, particularly concerning the capacity to detect clusters of cases closely related in time and place.

What strategic actions are recommended by WHO?

In August 2005, WHO sent all countries a document outlining [recommended strategic actions](#) for responding to the avian influenza pandemic threat. Recommended actions aim to strengthen national preparedness, reduce opportunities for a pandemic virus to emerge, improve the early warning system, delay initial international spread, and accelerate vaccine development.

Is the world adequately prepared?

No. Despite an advance warning that has lasted almost two years, the world is ill-prepared to defend itself during a pandemic. WHO has urged all countries to develop preparedness plans, but only around 40 have done so. WHO has further urged countries with adequate resources to stockpile antiviral drugs nationally for use at the start of a pandemic. Around 30 countries are purchasing large quantities of these drugs, but the manufacturer has no capacity to fill these orders immediately. On present trends, most developing countries will have no access to vaccines and antiviral drugs throughout the duration of a pandemic.

¹ Influenza viruses are grouped into three types, designated A, B, and C. Influenza A and B viruses are of concern for human health. Only influenza A viruses can cause pandemics.

² The H subtypes are epidemiologically most important, as they govern the ability of the virus to bind to and enter cells, where multiplication of the virus then occurs. The N subtypes govern the release of newly formed virus from the cells



Avian influenza – situation in Indonesia – update 36

16 October 2006

The Ministry of Health in Indonesia has confirmed an additional three cases of human infection with the H5N1 avian influenza virus. All three cases were fatal.

The first newly confirmed case occurred in a 67-year-old woman from West Java Province. She developed symptoms on 3 October, was hospitalized on 7 October, and died on 15 October. Diagnosis was complicated by the presence of chronic diseases. Chickens reportedly died in her household and neighbourhood prior to symptom onset.

The second case was an 11-year-old male from South Jakarta, Jakarta Province. He developed symptoms on 2 October, was hospitalized on 5 October, and died on 14 October. His recent history included exposure to dead chickens in his neighbourhood.

The third case was a 27-year-old female from Central Java Province. She developed symptoms on 8 October, was hospitalized on 12 October, and died on 13 October. The source of her exposure is currently under investigation.

Of the 72 cases confirmed to date in Indonesia, 55 have been fatal.

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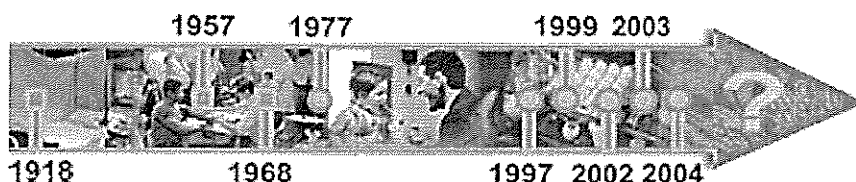


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Focus on the FluTimelineTimeline of Human Flu Pandemics



■ Major pandemic

● The appearance of a new influenza strain in the human population

1918 ■ Pandemic

"Spanish flu" H1N1

The most devastating flu pandemic in recent history, killing more than 500,000 people in the United States, and 20 million to 50 million people worldwide.

1957-58 ■ Pandemic

"Asian flu" H2N2

First identified in China, this virus caused roughly 70,000 deaths in the United States during the 1957-58 season. Because this strain has not circulated in humans since 1968, no one under 30 years old has immunity to this strain.

1968-69 ■ Pandemic

"Hong Kong flu" H3N2

First detected in Hong Kong, this virus caused roughly 34,000 deaths in the United States during the 1968-69 season. H3N2 viruses still circulate today.

1977 ● Appearance of a new influenza strain in humans

"Russian flu" H1N1

Isolated in northern China, this virus was similar to the virus that spread before 1957. For this reason, individuals born before 1957 were generally protected, however children and young adults born after that year were not because they had no prior immunity.

1997 ● Appearance of a new influenza strain in humans

H5N1

The first time an influenza virus was found to be transmitted directly from birds to people, with infections linked to exposure to poultry markets. Eighteen people in Hong Kong were hospitalized, six of whom died.

1999 ● Appearance of a new influenza strain in humans

H9N2

Appeared for the first time in humans. It caused illness in two children in Hong Kong, with poultry being the probable source.

Highlights

Oct. 17, 2006

[Experimental Vaccine Protects Mice Against Deadly 1918 Flu Virus](#)

Oct. 12, 2006

[Updates on Pandemic Flu Vaccine Trials to be Presented at 44th Annual IDSA Meeting](#)

Sept. 27, 2006

[Mouse Study Reveals New Clues about Virulence of 1918 Influenza Virus](#)

Sept. 25, 2006

[H9N2 Avian Flu Vaccine Paired with Adjuvant Provokes Strong Human Immune Response at Low Doses](#)

May 2006

[Q&A: H5N1 Avian Influenza](#)

March 29, 2006

[H5N1 Avian Flu Virus Vaccine Induces Immune Responses in Healthy Adults](#)

See Also

[PandemicFlu.gov](#)

The Official U.S. Government Web Site for Information on Pandemic Flu and Avian Influenza

2002 ● **Appearance of a new influenza strain in humans**
H7N2

Evidence of infection is found in one person in Virginia following a poultry outbreak.

2003 ● **Appearance of a new influenza strain in humans**
H5N1

Caused two Hong Kong family members to be hospitalized after a visit to China, killing one of them, a 33-year-old man. (A third family member died while in China of an undiagnosed respiratory illness.)

H7N7

In the first reported cases of this strain in humans, 89 people in the Netherlands, most of whom were poultry workers, became ill with eye infections or flu-like symptoms. A veterinarian who visited one of the affected poultry farms died.

H7N2

Caused a person to be hospitalized in New York.

H9N2

Caused illness in one child in Hong Kong.

2004 ● **Appearance of a new influenza strain in humans**
H5N1

Caused illness in 47 people in Thailand and Vietnam, 34 of whom died. Researchers are especially concerned because this flu strain, which is quite deadly, is becoming endemic in Asia.

H7N3

Is reported for the first time in humans. The strain caused illness in two poultry workers in Canada.

H10N7

Is reported for the first time in humans. It caused illness in two infants in Egypt. One child's father is a poultry merchant.

2005 H5N1

The first case of human infection with H5N1 arises in Cambodia in February. By May, WHO reports 4 Cambodian cases, all fatal. Indonesia reports its first case, which is fatal, in July. Over the next three months, 7 cases of laboratory-confirmed H5N1 infection in Indonesia, and 4 deaths, occur.

On December 30, WHO reports a cumulative total of 142 laboratory-confirmed cases of H5N1 infection worldwide, all in Asia, with 74 deaths. Asian countries in which human infection with H5N1 has been detected: Thailand, Vietnam, Cambodia, Indonesia and China.

2006 H5N1

In early January, two human cases of H5N1 infection, both fatal, are reported in rural areas of Eastern Turkey. Also in January, China reports new cases of H5N1 infection. As of January 25, China reports a total of 10

cases, with 7 deaths. On January 30, Iraq reports its first case of human H5N1 infection, which was fatal, to the WHO.

In March, the WHO confirmed seven cases of human H5N1 infection, and five deaths, in Azerbaijan. In April, WHO confirmed four cases of human H5N1 infection, and two fatalities, in Egypt.

In May, the WHO confirmed a case of human H5N1 infection in the African nation of Djibouti. This was the first confirmed case in sub-Saharan Africa.

WHO confirmed human cases of avian influenza A (H5N1)

WHO timeline of human and animal H5N1 infections since 1996 (PDF)

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Pandemic Resource Websites

Websites to keep up to date on useful information about avian influenza.

<http://www.pandemicflu.gov>

U.S. Government

http://www.who.int/csr/disease/avian_influenza/en

World Health Organization

<http://www.cdc.gov/flu/avian/index.htm>

Center for Disease Control

Several Websites offer access to useful documents on the general issue of preparing for a widespread outbreak of the “avian flu”:

ftp://www.nerc.com/pub/sys/all_updl/cip/Influenza%20Pandemic%20Summary.doc

for *Electricity Sector Influenza Pandemic Threat Summary* prepared by the North American Electric Reliability Council

ftp://www.nerc.com/pub/sys/all_updl/cip/Influenza%20Pandemic%20Reference%20Guide.doc

for *Electricity Sector Influenza Pandemic Planning, Preparation, and Response Reference Guide* prepared by the North American Electric Reliability Council

<http://www.whitehouse.gov/homeland/nspi.pdf>

for *The National Strategy for Pandemic Influenza*

<http://www.pandemicflu.gov/plan/pdf/businesschecklist.pdf>

for a *Business Pandemic Influenza Planning Checklist* prepared by the Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC)

<http://www.pandemicflu.gov/plan/states/texas.html>

for *Texas State And Local Pandemic Influenza Planning and Response Activities*

Other websites of interest:

http://www.ems-solutionsinc.com/handouts_materials.html

“**Pandemic Influenza – What are you doing to get ready?**” Excellent primer on influenza, past threats, current pandemic threat, public health law, modern medicine, pandemic economics and what you can do. Presentation at DJR Fall World Conference, September 2006.

<http://www.pandemicflu.gov/plan/maskguidancehc.html>

Interim Guidance on Planning for the Use of Surgical Masks and Respirators in Health Care Settings during an Influenza Pandemic – October 2006 update