Avian influenza frequently asked questions

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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 viruses[1] have 16 H subtypes and 9 N subtypes[2]. 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^{o}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.

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[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