



Avian influenza (bird flu): an introduction

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. The disease, which was first identified in Italy more than 100 years ago, occurs worldwide. 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.

There are three influenza genera, A, B and C; only influenza A viruses are known to infect birds. Fifteen subtypes of influenza virus are known to infect birds, thus providing an extensive reservoir of influenza viruses potentially circulating in bird populations. To date, all outbreaks of the highly pathogenic form have been caused by influenza A viruses of subtypes H5 and H7. Although not all viruses of the H5 and H7 subtypes are highly pathogenic and not all will cause severe disease in poultry, viruses of low pathogenicity can, after circulation for some time in a poultry population, mutate into highly pathogenic viruses.

All birds are thought to be susceptible to infection with avian influenza, though some species are more resistant to

infection than others. Severity of infection in birds ranges from mild illness to a highly contagious and rapidly fatal disease resulting in severe epidemics. The terms highly pathogenic avian influenza and “fowl plague” refer to the severe infection with virulent strains of influenza A virus.

Migratory waterfowl, most notably wild ducks, are the natural reservoir



of avian influenza viruses, and these birds are also the most resistant to infection. Domestic poultry, including chickens and turkeys, are particularly susceptible to epidemics of rapidly fatal influenza. Direct or indirect contact of domestic flocks with wild migratory waterfowl has been implicated as a frequent cause of epidemics. Live bird markets have also played an important role in the spread of epidemics. Birds that survive infection excrete virus for at least 10 days, orally and in faeces, thus facilitating further spread at live poultry markets and by migratory birds. The quarantining of infected farms and destruction of infected or potentially exposed flocks are standard control measures.

Avian influenza viruses do not normally infect species other than birds and pigs. The first documented infection of humans with an avian influenza virus occurred in Hong Kong in 1997, when the H5N1 strain caused severe respiratory disease in 18 humans, of whom 6 died. The infection of humans coincided with an epidemic of highly pathogenic avian influenza, caused by the same strain, in Hong Kong’s poultry population. Studies at the genetic level further determined that the virus had jumped directly from birds to humans. That event alarmed public health authorities, as it marked the first time that an avian influenza virus was transmitted directly to humans and caused severe illness with high mortality.

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Among influenza virus subtypes, H5N1 is of particular concern for several reasons. H5N1 mutates rapidly and has a documented propensity to acquire genes from viruses infecting other animal species. Its ability to cause severe disease in humans has now been documented. 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.

Direct contact with infected poultry, or surfaces and objects contaminated by their faeces, is currently considered the main route of human infection. Exposure is considered most likely during slaughter, defeathering, butchering and preparation of poultry for cooking. The virus does not spread easily from birds to humans. 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.

The spread of infection in birds increases the opportunities for direct infection of humans. If more humans become infected over time, the likelihood also increases that humans, if concurrently infected with human and avian influenza strains, could serve as the “mixing vessel” for the emergence of a novel subtype with sufficient human genes to be easily transmitted from person to person. Such an event would mark the start of an influenza pandemic.

What is influenza?

Influenza is an acute viral disease of the respiratory tract. It is caused by a virus that attacks mainly the upper respiratory tract – the nose, throat, bronchi and, rarely, the lungs. The infection is spread through airborne transmission or direct contact with infected secretions. It is indicated that patients can transmit the infection 3 to 5 days from clinical onset in adults, and up to 7 days in children.

The disease usually lasts for about a week. It is characterized by sudden onset of high fever, myalgia, headache and severe malaise, non-productive cough, sore throat and rhinitis. Due to this non-specific presentation, influenza is often indistinguishable from other viral respiratory diseases such as the common cold or viral pneumonia. If no complications occur, recovery usually takes place within 2 to 7 days from the onset of clinical manifestations. Most people recover without requiring any medical treatment. In the very young, the elderly and people suffering from medical conditions such as lung diseases, diabetes, cancer, kidney or heart problems, influenza poses a serious risk. In these people, the infection may lead to severe complications of underlying diseases, pneumonia and death.

Influenza spreads rapidly around the world during seasonal epidemics and imposes a considerable economic burden in the form of hospital and other health care costs and lost productivity. In annual influenza epidemics, 5%–15% of the population is affected with upper respiratory tract infections. Hospitalization and deaths mainly occur in high-risk groups (elderly, chronically ill). These annual epidemics are thought to result in between 3 and 5 million cases of severe illness and between 250 000 and 500 000 deaths every year around the world. Most deaths currently associated with influenza in industrialized countries occur among people over 65 years of age.

For prevention and control of influenza, it is necessary to educate the public on personal hygiene practices related to coughing, sneezing and prevention of transmission from hand to mucous membranes. Specific vaccines are developed annually following WHO recommendations regarding the composition of the vaccine. Vaccination should be given every year before influenza spread is expected in the community. Antiviral drugs are also available and have proven to be effective for prophylaxis and treatment.

History of influenza pandemics

Historical overview

History suggests that influenza pandemics have probably occurred during at least the past four centuries, with a heavy toll on human life. The highly pathogenic avian influenza, which was first recognized in Italy in 1878, is extremely contagious in birds and is rapidly fatal, with a mortality rate approaching 100%. During the 20th century, three influenza pandemics have occurred among humans.

1918: Spanish flu [A (H1N1)]

The Spanish influenza pandemic is the catastrophe against which all modern pandemics are measured. It is estimated that approximately 20% to 40% of the population worldwide became ill, and that over 20 million people died. Between September 1918 and April 1919, approximately 500 000 deaths from the flu occurred in the United States alone. Many people died very quickly. Those who did not succumb to the disease within the first few days often died of complications from the flu, such as pneumonia or other opportunistic infections.

One of the most unusual aspects of the Spanish flu was its ability to kill young adults. The reasons for this remain uncertain. With the Spanish flu, mortality rates were high among healthy adults as well as the usual high-risk groups. The attack rate and mortality rate were highest among adults 20 to 50 years old. The severity of this pandemic flu virus has not been seen again.

1957: Asian flu [A (H2N2)]

In February 1957, the Asian influenza pandemic was first identified in the Far East. Immunity to this strain was rare in people under 65 years of age, and a pandemic was predicted. In preparation, vaccine production began in late May 1957, and health officials increased surveillance for flu outbreaks.

The pandemic resulted in an estimated 4 million deaths. Unlike the virus that caused the 1918 pandemic, the 1957 pandemic virus was quickly identified due to advances in scientific technology. Vaccine was available in limited supply by August 1957. Most influenza- and pneumonia-related deaths occurred between September 1957 and March 1958. The highest rates of death were among the elderly.

By December 1957, the worst seemed to be over. However, during January and February 1958 there was another wave of illness among the elderly. This is an example of the potential “second wave” of infections that can develop during a pandemic. The disease infects one group of people first; after infections appear to decrease, they may increase again in

a different part of the population. Although the Asian flu pandemic was not as devastating as the Spanish flu, about 69 800 people died in the United States alone.

1968: Hong Kong flu [A (H3N2)]

In early 1968, the Hong Kong influenza pandemic was first detected in Hong Kong. It is estimated to have claimed another 4 million lives. This virus was first detected in Hong Kong in early 1968 and spread to the United States later that year. Influenza A (H3N2) viruses still circulate today. Illness did not become widespread in the United States until December, but deaths from the virus peaked between December 1968 and January 1969.

Pandemic scares

Several pandemic scares have occurred since 1976. A novel virus identified at Fort Dix, United States, labelled as “killer flu” was thought to be related to the Spanish flu virus of 1918. The virus later came to be known as the “swine flu”. In May 1977, influenza A/H1N1 viruses isolated in northern China spread rapidly, and caused epidemic disease in children and young adults (< 23 years) worldwide. The virus was referred to as “Russian flu”. The most recent pandemic scares occurred in 1997 and 1999. In 1997, at least several hundred people became infected with the avian A/H5N1 flu. In 1999, another novel avian flu virus, A/H9N2, was found which caused illness in two children in Hong Kong.

Source: United States Department of Health and Human Services, National Vaccine Program Office, 2004



Inactivated influenza vaccines offer approximately 70%–90% protection against clinical disease in healthy adults, provided there is a good match between the vaccine antigens and circulating virus(es). Among elderly people not living in institutions, vaccination may reduce the number of hospitalizations by 25%–39% and has also been shown to reduce overall mortality by 39%–75% during influenza seasons. Inactivated influenza vaccine has been widely used for 60 years, with an excellent safety profile.

Live attenuated influenza vaccines, administered by the intranasal route, are available in the Russian Federation and United States of America. The temperature-sensitive vaccine virus will replicate well in the relatively cool environment of the nasopharynx, but poorly in the lower respiratory tract. This vaccine is reported to be safe and highly efficacious following one single dose. The Russian type is given to those over 3 years of age, while in the United States the vaccine is licensed only for healthy people aged 5–49 years.

Vaccine availability

Influenza pandemics are unique infectious disease events that can spread to every country in the world within months, resulting in a high and universal demand for preventive and

treatment measures. Given the characteristics of influenza viruses, influenza vaccines can't be stockpiled and vaccine production will start only after preparing the seed viruses of the appropriate composition. During inter-pandemic times, and once the WHO recommendation has been made, vaccine production processes can actually begin immediately, if the vaccine is multivalent and contains at least one previously used strain. In a pandemic situation, it is likely that monovalent vaccine would be made; in this case, efforts to reduce time for development of seed viruses would be desirable, since all other activities must await completion of this phase.

Current global manufacturing capacity (estimated at 300 million doses of regular trivalent influenza vaccine per year) is inadequate to meet the expected global needs during a pandemic and cannot be rapidly augmented. At present, 90% of production capacity for all influenza vaccines is concentrated in Europe and North America, in countries that account for only 10% of the world's population. Based on past experience, countries with local manufacturing capacity are likely to meet domestic demand for vaccines and other critical resources fully before freeing supplies for the export market.

Antiviral drugs

Improvements in medical care and the introduction of new anti-influenza antiviral drugs since the last pandemic offer the potential of reducing the impact of the next one. Antiviral drugs are effective for both prevention (chemoprophylaxis) and early treatment of influenza. If available in sufficient supply, antiviral agents could potentially play a valuable role in the initial response to pandemic influenza, particularly in the likelihood that an effective vaccine is unavailable. Wide-scale use could reduce influenza-related morbidity, complications, hospitalizations and other demands on the health care system during a pandemic and might possibly reduce mortality.

There are two classes of antiviral drugs: neuraminidase inhibitors and M2 inhibitors. The neuraminidase inhibitors, oseltamivir (commercially known as Tamiflu) and zanamivir (commercially known as Relenza), have been shown to reduce the severity and duration of illness caused by seasonal influenza. Their efficacy depends on their administration within 48 hours after the onset of symptoms. The H5N1 virus is expected to be susceptible to the neuraminidase inhibitors. These drugs may reduce the severity of human disease caused by H5N1, and improve prospects of survival, if administered early. However, clinical data are limited. Currently, the main constraints for the neuraminidase inhibitors, which are substantial, involve limited production capacity and a price that is prohibitively high for many countries.

The M2 inhibitors amantadine and rimantadine could potentially be used against pandemic influenza, but resistance to these drugs may develop rapidly and this could significantly limit their effectiveness. Some currently circulating avian H5N1 strains are fully resistant to the M2 inhibitors, while others remain fully susceptible.

The available agents can be administered once daily for prophylaxis and twice daily for treatment, but they have important differences in mechanism of action, pharmacology and ease of administration, side effect profiles, cost and potential for emergence of drug resistance. The two M2 inhibitors (amantadine, rimantadine) and one neuraminidase inhibitor (oseltamivir) are taken orally, whereas the other neuraminidase inhibitor (zanamivir) is self-administered by oral inhalation and requires a specific delivery device. The M2 inhibitors are more likely than the neuraminidase inhibitors to have clinically significant issues with emergence and spread of drug-resistant influenza viruses.

At present the overarching limitation to antiviral use in a pandemic is inadequate availability. The high demand over the short period anticipated during the initial wave or waves of a pandemic would likely deplete supplies of antivirals unless stockpiles were in place or markedly enhanced surge production capacity was possible. Ethical dilemmas regarding fair access and rationing of available resources need to be addressed both within and between countries.

The anticipated pandemic

Influenza viruses undergo frequent changes in their surface antigens. Immunity resulting from infection by one influenza virus does not protect fully against antigenic or genetic variants of the same virus subtype (influenza A viruses) or other types (influenza B viruses). Influenza pandemics occur when a novel virus appears. A novel virus might appear as a result of an assortment process or an adaptive mutation mechanism. Once it appears, it will produce epidemics on a large scale extending across the globe, i.e. a pandemic.

The current highly pathogenic H5N1 strain, which is producing widespread episodes in several countries of South-east Asia is, in particular, a candidate for the

anticipated pandemic virus. It is highly pathogenic in poultry, producing outbreaks in large areas. It has also crossed the species barrier and produced disease in humans, although it has not yet developed the capacity for sustainable human-to-human transmission. The likelihood that this will happen is a matter of opportunity and probability. A pandemic is predictable, but it is difficult to say when it will happen. The main issue is that no virus of the H5 subtype has ever circulated widely among humans. Therefore, when and if widespread transmission occurs, the world community will have no immunity at all to the novel virus (the new subtype), and no existing vaccine can confer protection against it.

Preparing for the anticipated pandemic

Combating avian influenza will be difficult without a comprehensive and collaborative framework for providing human resources, training and supervision and for strengthening health services and logistics with regard to antiviral and laboratory supplies. Developing a pandemic preparedness plan is therefore an important requirement for all countries.

The table below shows the different phases of an avian influenza pandemic with the strategic actions for each phase.

	Phase	Transmission	Objectives	Strategic actions
Inter-pandemic period (planning and preparedness)	1	Influenza virus subtype in animals only (risk to humans low)	Strengthen pandemic preparedness at all levels	<ul style="list-style-type: none"> • Prepare pandemic preparedness plan • Establish surveillance in animals • Establish human influenza surveillance • Establish collaboration between human and animal sectors
Pandemic alert (emergency and pre-emptive response)	2	Influenza virus subtype in animals only (risk to humans substantial)	Minimize the risk of transmission to humans Detect and report rapidly, if it occurs	<ul style="list-style-type: none"> • Enhance animal surveillance and aggressive response to animal outbreaks • Strengthen human surveillance • Stockpile antiviral drugs, protective equipment, etc. • Strengthen collaboration between different sectors and WHO/OIE/FAO • Develop and implement risk communication strategy • Prepare health and essential contingency plan
Pandemic (minimizing impact)	3	Human infection (transmission in close contacts only)	Ensure rapid characterization of new virus Detect, notify and respond to additional cases	<ul style="list-style-type: none"> • Enhance animal surveillance and aggressive animal outbreak containment • Enhance human surveillance and aggressive outbreak management • Implement early strategic use of antiviral drugs
	4	Limited human-to-human spread; small clusters <25 cases lasting <2 weeks	Contain the virus or delay its spread	<ul style="list-style-type: none"> • Encourage social distancing • Implement risk communication strategy • Issue alert for quick implementation of health and essential service contingency plan
	5	Localized human-to-human spread; larger clusters 25–50 cases over 2–4 weeks	Maximum efforts to contain or delay the spread	<ul style="list-style-type: none"> • Implement health and essential services contingency plan
	6	Widespread in general population	Minimize the impact of the pandemic	<ul style="list-style-type: none"> • Continue risk communication • Treat cases and contacts with antivirals, if available • Enforce social distancing: close schools, ban gatherings • Administer vaccine, if available

Avian influenza: global concern

With the rapidly spreading, highly pathogenic avian influenza H5N1 and high potential for production of a pandemic virus, the world recognizes that this is a major public health challenge that requires strong, coordinated preparedness. Several global and regional meetings are being held in order to identify key components of a global action plan to control avian influenza in animals and simultaneously limit the threat of a human influenza pandemic. During such meetings, experts and officials set out key steps that must be taken, plan for organization and coordination of efforts and share expertise and experiences to fine-tune ways of working in response to the threat.

Avian influenza: International partnership to meet global threat, U.S. Department of State, Washington DC, United States, 6–7 October 2005

The meeting's main objective was to affirm the commitment of participating countries to work together to fight avian influenza and jointly develop a plan of action to supplement international efforts.

Global pandemic influenza readiness: an international meeting of ministers of health, Ottawa, Canada, 24–25 October 2005

A key outcome of the meeting was the commitment to ensure global engagement and collaboration on this issue among developed and developing countries as well as international organizations that deal with human health and animal health issues. The meeting concluded with unanimous support for the Ottawa Statement, which identifies four priority policy areas for pandemic influenza preparedness.

Meeting on avian and pandemic influenza preparedness and response, Brisbane, Australia, 31 October to 1 November 2005

The meeting aimed to identify ways in which APEC economies might further cooperate in responding to an outbreak of avian influenza, by:

- improving communication between the key experts leading the fight against avian influenza in the Asia-Pacific region;
- sharing information about and improving transparency of regional and national strategies for responding to an outbreak;
- identifying gaps in regional preparedness; and
- developing mechanisms to better coordinate the regional fight against outbreaks.

Joint WHO/FAO/World Bank/World Organisation for Animal Health meeting on avian influenza and human pandemic influenza, Geneva, Switzerland, 7–9 November 2005

The aims of this meeting were to define the strategies at the national, regional and international levels and to help coordinate efforts by all groups so that available resources will be used most effectively to support national, regional and global programmes to control avian influenza in animals and prepare for human pandemic. The overall objectives were to:

- confirm the two-pronged strategy: to control avian influenza at source in animals for the short- and medium-term and simultaneously prepare for pandemic influenza;
- support national plans in line with the above strategy through commitment at national, regional and global levels;
- discuss shared responsibilities of the international community and technical organizations and agencies in assisting affected countries and countries at risk;
- assess national, regional and global needs with broad indications of resources required in the short and medium term, review current bilateral and multilateral initiatives to avoid duplication and identify potential synergies;
- discuss and outline coordination mechanisms necessary at national, sub-regional, regional and global levels to ensure effective and rapid mobilization of resources and oversee the impact and progress in implementation;
- identify key next steps based on an agreed strategy with the political support and backing of the international community.

Intercountry meeting on avian influenza and preparedness for human pandemic influenza, Cairo, Egypt, 28–30 November 2005

The objectives of the meeting are to:

- promote epidemiological, laboratory and response capacities for pandemic influenza in public and animal health sectors in the Region;
- discuss non-pharmaceutical public health interventions, vaccines and antiviral treatment related to pandemic influenza;
- assist Member States in developing their own preparedness plans for pandemic influenza; and
- ensure rapid sharing of appropriate technical information related to pandemic influenza among national, regional, global and other relevant stakeholders.

An outbreak of yellow fever in South Kordofan, Sudan

On 21 October 2005, the Federal Ministry of Health of Sudan received the first report of the occurrence of haemorrhagic fever cases in South Kordofan state, about 800 kilometres south of the capital city of Khartoum. Based on preliminary results of laboratory investigations, the Ministry declared a dengue fever outbreak in the area. The laboratory investigations had used a rapid test and ELISA testing of 11 blood samples taken from the cases, of which five tested positive for dengue. However, further advanced laboratory testing at the laboratories of the U.S. Naval Medical Research Unit No. 3 (NAMRU-3), a WHO collaborating centre in Cairo, Egypt, confirmed a diagnosis of yellow fever. Lack of awareness about the gravity of the threat, poor communication systems and inadequate laboratory facilities contributed to the delay in detection of the outbreak.

Field investigation showed that the first probable death from yellow fever occurred on 20 September 2005, and the first probable case was admitted to a hospital was on 23 September. As of 17 November 2005, 424 cases of yellow fever have been reported, including 121 deaths (case fatality rate = 28.5%). The highest case fatality rate occurred among children under 5 years of age (9 out of 19 cases, 47.4%). Preliminary data show that all age groups are affected; however more cases were reported among males. The main affected areas (mostly central and eastern parts of South Kordofan) are Delling, with an attack rate (AR) of 80 per 100 000 population, Rashad (AR=18), Abu Jubaiyah (AR=10), Kadugli (AR=10) and Talodi (AR=3). On 17 November, a case of yellow fever was diagnosed in a new town in the western part of South Kordofan, Al Fula. About

half of the cases (47.5%) were diagnosed among a nomadic tribe (Shanabla), which could have contributed to the wide spread of the disease within a relatively short period.

An active sentinel disease surveillance system has been initiated in 8 hospitals and 3 health centres in the affected areas. Institution of control measures to contain the outbreak is led by the health authorities in Sudan. The WHO country office in Sudan, Regional Office for the Eastern Mediterranean and headquarters, as well as the partners of the Global Alert and Response Network (GOARN), are actively participating in containment efforts by providing technical assistance. With generous support from donors, a mass vaccination campaign against yellow fever is currently taking place, targeting about 5 million people living in South Kordofan and neighbouring states. Yellow fever vaccination is not routine in Sudan. Other control measures being instituted include vector control, training of health personnel on medical management of cases and social mobilization.

Documented outbreaks of yellow fever in Sudan in the past include outbreaks in the Nuba Mountains of South Kordofan in 1940 (15 000 cases, 1500 deaths), Blue Nile state in 1959 (120 cases, 88 deaths) and southern Sudan in 1999 and 2003 (178 cases, 27 deaths). Yellow fever is one of three diseases subject to the International Health Regulations (IHR) adopted in 1969. In the revised IHR 2005, yellow fever is still considered to be a public health emergency of international concern.



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