Avian influenza H5N1 – the global situation

The influenza A H5N1 virus, most commonly found in birds, has the potential to cross the species barrier and infect humans, as has occurred in south-east Asia. The recent outbreak of infection in turkeys in England has again raised concern about this particular serotype as the source of the next human influenza pandemic. Here, Richard A Collins provides an update.

Avian influenza H5N1 is perceived as the emerging infectious disease posing the greatest global threat.

The United Kingdom has become the third country in Europe to see infection by avian influenza A (H5N1) during the current winter season. Outbreaks previously had been reported in Hungary and Russia. It is timely, therefore, to examine the spread of H5N1 around the world and assess the risk for a pandemic caused by transmission of this virus that is deadly to humans.

Influenza is an infectious disease of birds and mammals caused by an RNA virus of the family *Orthomyxoviridae*. In humans, common symptoms of influenza infection are fever, nausea, vomiting, sore throat, muscle pains, severe headache, coughing and fatigue. In more serious cases, influenza causes pneumonia, which can be fatal, particularly in young children and the elderly. Influenza is sometimes confused with the common cold, but it is a much more severe disease and is caused by a different type of virus.

Influenza is transmitted from infected mammals through the air by coughs and sneezes, creating virus-laden aerosols, and from infected birds through their droppings. Influenza can also be transmitted by saliva, nasal secretions, faeces and blood. Infections occur through contact with these bodily fluids or with contaminated surfaces. Influenza viruses can remain infectious for about a week at 37°C, for over 30 days at 0°C, and indefinitely at very low temperatures. However, they are inactivated easily by disinfectants and detergents.

There are three genera of influenza virus: *Influenzavirus* A, *Influenzavirus* B and *Influenzavirus* C.[1] Influenza A and C infect multiple species, while influenza B almost exclusively infects humans. Type A viruses cause the most severe disease in humans. The influenza A virus can be subdivided into different serotypes based on antibody responses.

Influenza B virus is less common than influenza A. Apart from humans, the only other species known to be susceptible to influenza B infection is the seal. The influenza B genome mutates at a rate two to three times slower than that of type A. Consequently, influenza B is less genetically diverse and has only one serotype. As a result of this lack of antigenic diversity, a degree of immunity to influenza B is usually acquired at an early age. However, influenza B mutates sufficiently often to ensure that lasting immunity is not possible. This reduced rate of antigenic change, combined with its limited host range (inhibiting cross-species antigenic shift), ensures that pandemics of influenza B do not occur.

The influenza C virus infects humans and pigs, and can cause severe illness and local epidemics. However, influenza C is less common than the other types and usually seems to cause only mild disease in children.

> 'Influenza A virus causes the most severe disease in humans, and can be can be subdivided into different serotypes based on antibody responses'

The influenza A virus particle (virion) is roughly spherical and 80–120 nm in diameter.[1] The influenza A genome contains eight pieces of segmented negative-sense RNA (total size: 13.5 kb), which encode 11 proteins (HA, NA, NP, M1, M2, NS1, NEP, PA, PB1, PB1-F2, PB2). The best characterised of these viral proteins are haemagglutinin and neuraminidase, two large glycoproteins found on the outside of the viral particles.

Neuraminidase is an enzyme involved in the release of progeny virus from infected cells, by cleaving sugars that bind the mature viral particles. Haemagglutinin is a lectin that mediates binding of the virus to target cells and entry of the viral genome into the target cell. These proteins are recognised by antibodies. The responses of antibodies to these proteins are used to classify the different serotypes of influenza A viruses – hence the H and N in H5N1. All avian influenzas (H1–H16) can be low-level pathogens but only H5 and H7 are known to become highly pathogenic.

The influenza virus lacks RNA proofreading enzymes. As a result, the viral RNA-dependent RNA transcriptase makes a nucleotide insertion error about once every 10,000 nucleotides, which is the approximate length of the influenza RNA genome. Hence, nearly every newly manufactured influenza virus is a mutant. The separation of the genome into eight separate segments of RNA also allows mixing or re-assortment of gene segments if more than one strain of virus has infected a cell. This shuffling of gene segments produces antigenic shifts that allow the virus to infect new host species and quickly overcome protective immunity.

SUMMARY OF THE GLOBAL SITUATION

Currently, avian influenza H5N1 is perceived as the emerging infectious disease posing the greatest global threat. Enhanced global surveillance has been in place since 2003, when human infections and deaths from this serotype were reported in parts of Asia. The current global situation in the major geographic regions is described below.

Africa

Bird flu has been detected in domestic and wild birds in Africa and transmission of H5N1 from birds to humans has resulted in several infections and deaths (Table 1). Egypt and Nigeria have experienced outbreaks of avian influenza with human fatalities in 2006–2007. Although bird flu was presumed to be under control in Nigeria by the end of 2006, there has been a resurgence in recent months, according to UN scientists monitoring the country.[2]

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Avian influenza used to be found mainly in large poultry farms, but now it is being found on small farms and in backyard flocks. There is good circumstantial evidence to show that illegal poultry imports and transport were responsible for bird flu problems in Egypt and Nigeria, particularly of eggs and chicks. Such trade is very hard to trace and control, if only because of the volume. The poultry sector is the most globalised in agriculture and there is a significant movement of chicks and other products.

Nigeria, Africa's most populous country, reported its first human fatality from H5N1 in January 2007 – one year after the virus was first detected in domesticated poultry flocks in that country. Nigeria is among countries regarded by experts as the weakest links in the global attempt to stem infections of birds. The virus has spread to more than half of Nigeria's 36 states over the past year, despite measures such as culling, quarantine and bans on transporting live poultry.[3] Highly pathogenic H5N2 was also reported in commercial ostrich farms in South Africa in July 2006.[4]

Australia

During the current period of enhanced surveillance for avian influenza, beginning in 2003, Australia has not been affected significantly by H5N1 in domestic flocks or from the large numbers of migrating birds visiting the continent from potential hotspots in Asia. Indeed, scientists now conclude that the current outbreaks of avian influenza are linked to global trade in poultry, and migrating birds are no longer seen as culprits.

Asia

Asia has been the focus of attention in the spread and control of avian influenza H5N1 since 2003. Most countries in south-east Asia, from the poorest and least developed (Laos and Cambodia) to the most highly developed (Japan), have seen outbreaks of the disease. The current outbreak of human infection with H5N1 began in Vietnam in 2003 and peaked there in 2005, since when there have been no further cases reported (Table 1). The global community has commended Vietnam for the effectiveness of its control efforts since the initial outbreak was detected there in 2003. A lethal outbreak in Thailand also appears to be have been brought under control.

Indonesia, however, continues to give cause for concern. It has a large population, extensive poverty and a predominantly rural economy, especially in the more remote provinces. The country is wracked by political instability and ineffective local government. Expenditure on healthcare is among the lowest in the region (US$113 per capita compared with $260 per capita in Thailand and $2244 per capita in Japan).[5] Resources for the advanced testing needed to confirm whether an influenza-like illness is due to H5N1 or not is scarce. The lack of timely and effective intervention is reflected in the case fatality rate from H5N1 in Indonesia (63/81 [78%]) compared with Vietnam (42/93 [45%]) (Table 1).

Europe

A large outbreak of H5N1 in Suffolk in February 2007 that resulted in the death and slaughter of nearly 160,000 turkeys has now been contained. Thirteen European Union (EU) countries have been affected by avian

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Table 1. Cumulative number of confirmed human cases of avian influenza A/(H5N1) reported to the World Health Organization (1 March 2007).

Country	2003		2004		2005		2006		2007		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
EURASIA												
Azerbaijan	0	0	0	0	0	0	8	5	0	0	8	5
Cambodia	0	0	0	0	4	4	2	2	0	0	6	6
China	1	1	0	0	8	5	13	8	1	0	23	14
Indonesia	0	0	0	0	19	12	56	46	6	5	81	63
Iraq	0	0	0	0	0	0	3	2	0	0	3	2
Laos	0	0	0	0	0	0	0	0	1	0	1	0
Thailand	0	0	17	12	5	2	3	3	0	0	25	17
Turkey	0	0	0	0	0	0	12	4	0	0	12	4
Vietnam	3	3	29	20	61	19	0	0	0	0	93	42
AFRICA												
Egypt	0	0	0	0	0	0	18	10	5	3	23	13
Djibouti	0	0	0	0	0	0	1	0	0	0	1	0
Nigeria	0	0	0	0	0	0	0	0	1	1	1	1
TOTAL	**4**	**4**	**46**	**32**	**97**	**42**	**116**	**80**	**14**	**9**	**277**	**167**

Total number of cases includes number of deaths.
WHO reports only laboratory-confirmed cases.
All dates refer to onset of illness.
Reproduced from www.who.int/csr/disease/avian_influenza/country/cases_table _2007_03_01/en/index.html

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influenza since the beginning of 2006, and the Standing Committee on the Food Chain and Animal Health – a panel of senior government veterinary surgeons from 27 countries – requires member states to ring-fence outbreak sites and impose strict controls on the movement of poultry. Following notification of a suspicion of an outbreak of a highly pathogenic avian influenza of any type, EU legislation requires that rapid containment measures be applied in the affected premises, including the culling of the flocks. Targeted surveillance for highly pathogenic H5N1 avian influenza and other avian influenza viruses in wild birds is in place throughout the UK and is ongoing.

Some scientists have called for vaccination against avian influenza in all poultry flocks in Europe in the wake of the recent UK outbreak. The Netherlands vaccinates 90% of each flock, leaving 10% unprotected. Theoretically, the unprotected birds show signs of illness if exposed to avian influenza. However, UK scientists fear vaccination could mask the start of an epidemic because it reduces the infectiousness of birds and stops them dying, but it does not halt the spread of disease. The UK holds 10 million doses of influenza vaccine to be used to create a buffer zone should further outbreaks occur, but it has no plans to introduce routine vaccination.

North America

Owing to its vast size, large numbers of migrating birds, industrial-scale poultry farming operations coupled with sophisticated surveillance and monitoring programmes, the USA continues to report a number of outbreaks of avian influenza in both its domestic and wild bird populations. Canada also monitors extensively for avian influenza. In 2004, authorities in British Columbia ordered a cull of 19 million poultry in the Fraser Valley area, the centre of an outbreak of H7N3 bird flu that had been found on 40 farms and 10 small poultry operations (Table 2).

Central and South America

The last significant outbreak of avian influenza in South America was highly pathogenic H7N3 in Chile in June 2002 (Table 2). It was not associated with any human infections. A massive outbreak of H5N2 in Mexico in 1994–1995 swept the country and took months to bring under control (Table 2).

Outbreaks of avian influenza are more difficult to control in developing countries for many reasons. Lower education standards and a poorer communications infrastructure mean that information on the seriousness of the disease is difficult to disseminate. In regions where backyard farms are common and there are insufficient government resources to compensate smallholders for their losses, people often are reluctant to cull healthy birds in order to prevent a more serious outbreak, even when ordered by authorities to do so. Deliberate evasion of control measures is a significant barrier to the rapid control of avian influenza outbreaks and potentially could lead to the outbreak escalating in size.

FUTURE OUTBREAKS

In 2003, an outbreak of H7N7 in The Netherlands resulted in a single human fatality and nearly 100 other human infections. Human infection with avian influenza H9 also has been reported. This indicates that the next human pandemic may not necessarily originate from an avian influenza H5N1 source.

Table 2. Previous outbreaks of highly pathogenic avian influenza worldwide (1959–2004).

Year	Country	Serotype
1959	Scotland	H5N1
1963	England	H7N3
1966	Ontario, Canada	H5N9
1976	Victoria, Australia	H7N7
1979	Germany	H7N7
1979	England	H7N4
1983–1985	Pennsylvania, USA	H5N2
1983	Ireland	H5N8
1985	Victoria, Australia	H7N7
1991	England	H5N1
1992	Victoria, Australia	H7N3
1994	Queensland, Australia	H7N3
1994–1995	Mexico	H5N2
1994	Pakistan	H7N3
1997	New South Wales, Australia	H7N4
1997	Hong Kong	H5N1
1997	Italy	H5N2
1999–2000	Italy	H7N1
2002	Hong Kong	H5N1
2002	Chile	H7N3
2003	Netherlands	H7N7
2004	Pakistan	H7N3
2004	Texas, USA	H5N2
2004	British Columbia, Canada	H7N3
2004	South Africa	H5N2

Data extracted from: *Avian influenza: assessing the pandemic threat*. WHO/CDS/2005.29. January 2005.

www.who.int/csr/disease/influenza/H5N1-9reduit.pdf (accessed 21 February 2007).

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PRECAUTIONS AGAINST INFECTION

Avian influenza is a disease of birds and while it can pass very rarely and with difficulty to humans, this requires extremely close contact with infected birds and in particular their faeces. Cases of human infection with H5N1 frequently have been linked to the home slaughter and subsequent handling of diseased or dead birds prior to cooking. These practices represent the highest risk to human infection and are the most important to avoid. When handling raw poultry or live or dead birds, it is imperative to disinfect hands and surfaces with soap and water. Consumers also need to be sure that poultry reaches temperatures of at least 70°C in all parts during the cooking process, and that eggs are fully cooked throughout. Advice from the Food Standards Agency remains that properly cooked poultry and poultry products, including eggs, are safe to eat. ■

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