

**The Public Health Risk from Highly Pathogenic Avian Influenza
Viruses Emerging in Europe with Specific Reference to type A/H5N1**

Interim ECDC Risk Assessment – Revision 20th May 2006
(previous versions from 19th October 2005 and 5 January 2006)

Preamble

The objective of this revised document is to further determine the risk to human health in Europe from highly pathogenic avian influenza viruses in birds and animals. Specifically the additional risk that arises from the recent emergence and extension of A/H5N1 viruses into the European Union and elsewhere in the world, and the changed biology of the viruses among wild and domestic birds. In addition the document identifies areas requiring additional scientific and public health work both as single pieces of work and for risk monitoring by ECDC and its partners. Given the rapidly developing epidemiology in Europe and elsewhere the document remains an interim assessment, that will be regularly updated. The document should be considered along with other relevant publications concerning Avian Influenza produced by ECDC and other authoritative bodies such as WHO, the European Commission, the FAO, OIE etc. ECDC's collection of documents on H5N1 - the H5N1 Portfolio - is available at [/www.ecdc.eu.int/avian_influenza/index.php](http://www.ecdc.eu.int/avian_influenza/index.php).

Weekly updates are published in ECDC's Influenza Surveillance and Risk Monitoring summaries at www.ecdc.eu.int/influenza/update_influenza.php

Comments and contributions to the document continue to be welcomed to influenza@ecdc.eu.int

Executive Summary

Outbreaks of highly pathogenic avian influenza (HPAI) viruses in domestic poultry have been increasing since the late 1990s and have affected poultry in Europe as elsewhere.

Essentially there are two forms of risk to human health from these viruses:

- direct infection of humans with the avian virus
- the emergence of a new pandemic strain of type A influenza.

The human health impact of HPAI epizootics was very small, and almost unnoticed, until 1997. Infections were generally minor and usually self-limiting. The appearance of A/H5N1 in Asia, changed this perspective when infection of humans with a high mortality rate was detected during an outbreak in Hong Kong in 1997 after a pause until around 2003 this pattern of infection has continued as huge epizootics extended across the domestic poultry populations of South East Asia. However considering the massive exposure in Asia from one HPAI type (A/H5N1) there have been very few human infections resulting from HPAI. In the over 200 reported human infections since 2004 mortality is around 57%.

Compared to before 2003 there have been some significant changes in the behaviour of the H5N1 viruses in birds. One strain has stabilised and has been spreading more easily through a range of bird species and this is the strain that has spread to the EU. In some countries outside the European Union that strain could become endemic in some domestic birds as it has seemingly done in certain wild species. In the Asia-Pacific region, Indonesia is currently the most active site of H5N1 transmission but, in general, reported activity appears reduced compared to similar periods of 2004 and 2005.

In contrast in Africa, the Middle East and South Asia there is some evidence of significant levels of infection in domestic poultry. There has to be caution here as surveillance is weak. Equally weak are the veterinary services which mean that the prospects for control may be bleak in the short term.

Mild and asymptomatic human H5N1 infection seems to be rare and the indications are that transmissibility of A/H5N1 to humans is still very low even for those directly exposed. Most infections continue to be acquired from exposures to high doses of virus from sick domestic poultry in household

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settings. There is no evidence of transmission to humans from casual contact with infected wild birds. The clinical picture continues to be unusual for HPAIs in humans in that infections are usually severe and often affect not just the respiratory system. Though human outbreaks and cases have been occurring in settings where it has proved difficult to mount proper investigations and studies, there is no evidence of any recent significant change in the behaviour of the virus in humans. Human to human transmission occurs but there is no evidence that it has become more efficient, cluster size has not increased and the case fatality rate of human infection has remained extraordinarily high for a human influenza. There is thus, as yet no evidence that the viruses have become any better adapted to humans than they were nearly a decade ago. The few humans who are infected do so only when exposed to high doses of virus and are likely to become very ill. They are unlikely to be a major infection risk to their families and those providing care. However normal infection precautions must be taken and antivirals given to those most exposed, usually other household members. A notable feature has been the focus of infections in other family members which could indicate some genetic susceptibility.

Surveillance for human cases may be becoming harder where poultry immunization is widely but inevitably imperfectly practiced as the marker of local poultry deaths for human case detection is being lost. Declines in the number of sporadic human cases in some countries should therefore be interpreted cautiously. It is also unclear as yet if massive immunization of poultry programmes increase or decrease the overall human population exposure to H5N1 viruses.

Despite the seeming lack of adaptation of H5N1 viruses a major caveat is the ability of influenza viruses to change, recombine, adapt and generally confound those attempting to control them. Though no H5 virus is known to have adapted to humans in the past it would be unwise to assume they cannot do so. Exposure of humans to H5N1 viruses must have increased considerably recently, for example in Africa. This does not necessarily change the pandemic potential of H5N1 viruses. However if through genetic recombination with human influenza or mutation the viruses can achieve any potential then they now must be more likely to do so sooner than when human exposure to H5N1 viruses was uncommon and localized.

The pattern of infection and disease seen in Asia for A/H5N1 may not be seen elsewhere and therefore close clinical and laboratory surveillance for and of

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human cases in Europe will be vital. That said, the Asian pattern of A/H5N1 has to be expected for planning purposes: a group of influenza viruses of birds, poorly adapted to humans whom they find hard to infect except at high doses. They are dangerous as they are highly pathogenic in those few humans that do become infected, but then they generally do not transmit on to other humans.

In the European Union, where surveillance for HPAI in wild-life is strong, this has detected steady extension of the virus in wild birds, including non-migratory species, and some domestic poultry. This peaked in early 2006 seemingly following migrations and numbers have declined but not fallen to zero. The risk of reintroduction through further migrations is significant though very difficult to predict.

The direct risk to the health of people in Europe from A/H5N1 is very low, but not zero. Human outbreaks in Turkey, Iraq, Azerbaijan, Egypt and elsewhere have indicated the potential of infection of humans from sick domestic poultry and probably also wild birds. The risk is mostly concentrated in one human group, those with domestic or pet poultry. Such groups exist in most European countries and they need to be informed of the risk and how to protect themselves. These pose particular challenges in terms of protection and risk communication as some of these groups are poor, marginalized or simply difficult to reach. There are occupational groups at lower and mostly theoretical risk who should take precautions. For those people who have no contact with domestic or wild birds or their products the risk must be almost non-existent.

Monitoring human H5N1 infections and other emerging influenza viruses is of crucial importance as probably it's only in the early phases of emergence of a pandemic that there is any hope of containment. Though such emergence could take place in the European Union that seems unlikely. Though there are places not far beyond the borders of Europe where this could occur as well as in Asia and Africa.

ECDC and its partners will continue to monitor the risk from H5N1 and other HPAIs actively. A surveillance system for human cases A/H5N1, compatible to that already in use by WHO elsewhere has been developed and adopted as part of surveillance of human influenza. In addition some specific pieces of work on immunisation with seasonal vaccines are recommended. Most crucial will be continuing and developing close working of those responsible for

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animal and human health at all levels, proper risk communication and dissemination of factual scientific data to the public including those few people at risk of infection.

It does not follow from any of the above that the next pandemic will necessarily be due to H5N1 or another HPAI. Equally since it is not fully understood how pandemics arise it does not follow that the risk of a pandemic is actually any higher now than it was say a decade ago. Though there is more H5N1 in circulation it does not follow that there has been an overall increase worldwide of the influenza viruses (of all H types) whose genetic material has pandemic potential.

Though there has been no increase in the pandemic potential of H5N1 the likelihood that it might achieve any inherent potential in the near future may have risen. There are many good reasons why the momentum of pandemic preparations in EU countries and preparations for possible outbreaks of H5N1 in birds and some human cases should continue and intensify. One implication for those determining policy is that if they are convinced that preparation should be made for a pandemic based on an H5N1 virus there are now reasons for speeding up those preparations.

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New considerations since January

- It has become apparent that a strain of the H5N1 viruses has been able to affect a wide range of birds' species and has adapted well to certain migratory birds being able to travel widely with them extending its geographical range. These viruses have shown considerable stability over time.
- The range of these H5N1 viruses has greatly extended from being mostly confined to East and South East Asia to Europe including wild birds in the EU, the Middle East and parts of Africa and South Asia.
- Should the stability of the current H5N1 strains be maintained, Europe will have to adjust to add A/H5N1 influenza as one of endemic or occasionally appearing zoonotic infections. With H5N1 infections being in wild birds in all of Europe that risk will inevitably seem closer to home to EU citizens.
- Many more people worldwide are going to come into contact with H5N1. This will be less so in Europe than elsewhere because poultry in the EU are mostly segregated from humans.
- Though this does not mean any change in the pandemic potential of H5N1, if such potential exists at all it must now be more likely to become evident sooner rather than later.
- Certain other animal species notably cats can become infected naturally and in artificial conditions may occasionally transmit on the infection to other cats though no human infections have resulted.

Unchanged considerations

- There has been no indication of a significant change of behaviour of H5N1 viruses in humans. They currently remain *"a group of influenza viruses of birds, poorly adapted to humans whom they find hard to infect except at high doses. They are dangerous as they are highly pathogenic in those few humans that do become infected, but then they generally do not transmit on to other humans."*

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- Control of infection in poultry along with risk communication to those at risk and prompt response (case finding and management) to human cases remain the cornerstones of strategies for protecting human health from H5N1 viruses.
- Human to human transmission occurs but remains uncommon and there has been no increase in cluster size where human cases have occurred.
- A few human cases have been detected in most countries where outbreaks in domestic poultry have occurred.
- The groups at risk in Europe are the same as before with the most important group being people with domestic poultry.
- There is no risk of catching H5N1 from eating food that has been prepared properly.

1. Background – the Zoonotic Potential of Avian Influenza

Influenza is an infectious disease of certain animals including humans with mostly respiratory characteristics. It is a zoonosis, that is an infection originally of animals which has extended to infect humans.¹ It is caused by RNA viruses of the family *Orthomyxoviridae*. These viruses are unstable in their structure and are continuously evolving.* Some of the viruses are well adapted to humans which have become their hosts and are regarded as human influenza viruses.[†] While the human infection and resulting disease caused can be mild or even asymptomatic it can also be severe and sometimes lethal for all age groups. It can extend beyond the respiratory system and is especially dangerous in the elderly and those with underlying chronic medical conditions. The most significant sudden impacts of influenza viruses on humans are those arising from the influenza A pandemic strains. These are novel or re-emerging viruses to which a large proportion of the human population have little immunity. They are thought to emerge through genetic recombination of human viruses or through recombination of human and animal viruses or perhaps changes in an animal virus and its adaptation to humans.[‡] When pandemics emerge they quickly sweep world-wide before settling down to dominate the less severe seasonal influenza epidemics seen each winter. Since 1918 three strains have arisen causing major pandemics each resulting in millions of deaths. These were: H1N1 (1918) with an estimated forty million deaths world wide[‡], H2N2 (1957) and H3N2 (1968) both with estimated deaths of between one and four million. A lesser pandemic occurred in 1977 when an H1N1 strain emerged without major mortality and only partially replaced the H3N2 strain so that at present both H1N1 and H3N2 strains circulate currently along with less pathogenic influenza B strains.²

The natural reservoir of influenza A strains is a diverse pool of viruses among aquatic wild bird populations, so called avian influenza (AI) viruses. These viruses are well adapted to many aquatic bird species, less so to other bird species while most are not at all adapted to humans and other mammals.¹

* Influenza A viruses are classically characterized according to the serologic reaction to the surface glycoproteins into sixteen hemagglutinin subtypes (H1-16) and nine neuraminidase subtypes (N1-9). Not all potential combinations exist and of the 16 H types known, only subtypes H1, H2, H3, H5, H7, H9 and H10 seem capable of infecting humans.

† The families of influenza A viruses that are well adapted to humans are mostly in the subtypes H1, H2 and H3.

‡ The 1918 pandemic is considered exceptional in its high pathogenicity and it particularly affecting young adults.

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Adaptation means the viruses' ability to infect a host, reproduce and be transmitted onto fresh hosts. The AI viruses are divided on the basis of their impact on birds into those of high and low pathogenicity avian influenza (hence HPAI and LPAI) mostly on the basis of their biological characteristics. Highly pathogenic avian influenza (HPAI) viruses are those that when injected into chickens cause a high mortality (over 75%). All are H5 or H7 influenza A subtypes and an alternative criteria not requiring biological testing is any H5 or H7 virus with a haemagglutinin proteolytic cleavage site compatible with an HPAI virus.^{3§}

2. Risk to Human Health from Avian Influenza Viruses - Principles

Essentially there are two mechanisms of risks to the physical health of humans from avian influenza viruses,

Direct or indirect^{*} infection causing disease and sometimes death.⁴

Pandemic Potential from the potential for the emergence of new pandemic strains either directly from avian viruses, or from their recombination of their genetic material (RNA) with RNA from human or other animal viruses.²

To realise any inherent genetic potential to cause a pandemic an influenza virus has to have three attributes. It has to be able to infect humans, to produce disease and most crucially to be efficiently transmitted from one human to another. Whilst HPAI infections as a whole carry a somewhat higher risk of producing infection in humans through direct or indirect infection it does not follow that because avian influenza is 'highly pathogenic' for birds that it has any greater risk of forming or contributing to a pandemic virus for humans.

§ On occasions in the last decade HPAI viruses have arisen that have a cleavage site that has not been seen before. Hence, the in vivo pathogenicity index is still necessary to judge an AI virus highly pathogenic if it has a cleavage site that has never been associated before with HPAI.

‡ Indirect meaning from the environment of fomites whereby live virus is deposited and survives for a short while. E.g. on hands, a towel or another surface and then is transferred to a human e.g. by shaking hands or sharing towels.

3. The History and Development of Highly Pathogenic Avian Influenza

3.1 Infections among Animals

Between 1959 and 2005 twenty-four HPAI epizootics (epidemics in animals) have been documented worldwide. These are all due to the A/H5 and A/H7 groups with types A/H5/N1-N3, N8, N9 and A/H7/N1, N3, N4, N7 respectively.^{4,5} Many million birds have died in these epizootics either directly from the infection or from culling undertaken to control the infection. Outbreaks have sometime been due to the introduction of HPAI from wild birds. Equally some low pathogenicity A/H5 and A/H7 strains have mutated to become HPAI viruses following circulation among domestic poultry.⁶

Since 2000 there have been more and larger outbreaks of HPAI in poultry.^{4,5} The reason for this is unknown and the subject of speculation. Both large and small outbreaks have taken place in Europe. Notable very large outbreaks have occurred in densely populated commercial bird populations such as in Italy in 1999 (type A/H7N1)⁷, the Netherlands, Belgium and Germany in 2003 (type A/H7N7) and Canada in 2004 (H7N3).^{8,9,10,11}

3.2 Human Infections due to Avian Influenza

The first documented human infection with an avian influenza (A/H7N7) goes back to 1959.⁴ Cases occur in association with both large and small outbreaks in birds but not all animal influenza infections in humans have come from birds. For example in the late 1970s some workers dealing with infections in seals developed eye infections (conjunctivitis).¹² However infected birds seem to have been the major source of risk to humans.⁴ There have been human infections with both low pathogenicity and high pathogenicity strains. Human infections with LPAI are recorded only occasionally but these have all been with minor self-limiting illnesses so it may be that they are under-recognised. For example there was one infection of a woman in the UK in 1996 receiving an eye infection from her domestic poultry which had mixed with wild birds and in 2006 a single case in a person seemingly exposed occupationally.^{13,14} No LPAI virus has been reported connected with severe disease or death in a human.⁴ In contrast the HPAI outbreaks in birds have resulted in at least 217 human cases and 123 deaths (a case fatality rate near