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The Public Health Risk from Highly Pathogenic Avian Influenza Viruses Emerging in Europe with Specific Reference to type A/H5N1
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Interim ECDC Risk Assessment – Revision 20th May 2006
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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, he 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.

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

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 or 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 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

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

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.

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."*

- 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.[2] 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]

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* 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 pathogencity and it particularly affecting young adults.

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 haemaglutinin 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

57%)**. Apart from a single fatality attributed to A/H7N7 virus strain during the Netherlands / Belgium / German outbreak all the deaths and most of the severe disease have been due to A/H5N1 (Figure1).[4,5,15] Mild human infections have been reported in a number of outbreaks, for example in Italy and Western Canada.[7,9,16] In the Netherlands, during the epizootic of HPAI with a different virus (A/H7N7), up to 64% of persons exposed to the virus showed a serological response consistent with infection.[17]

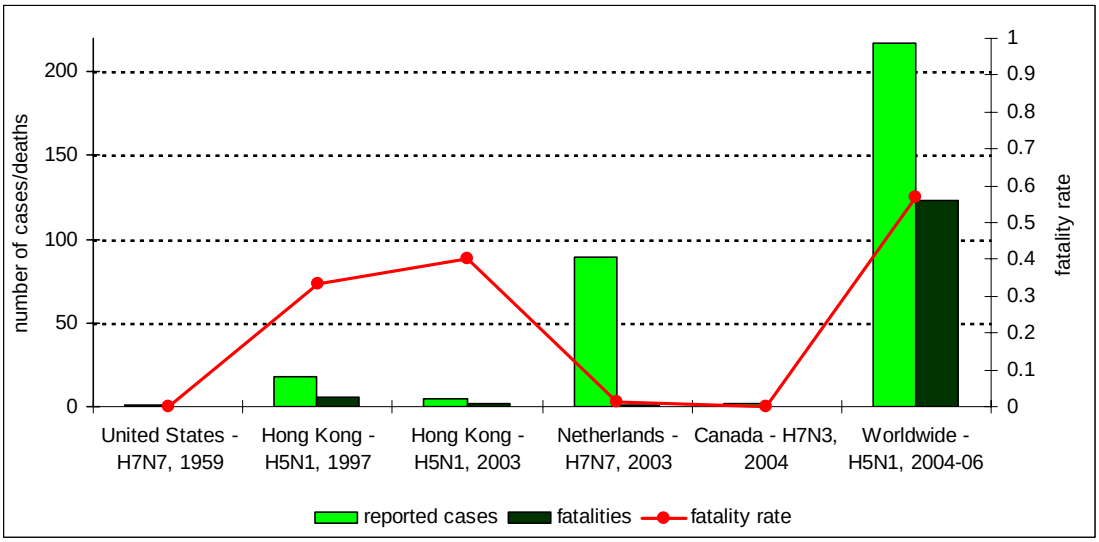

Figure 1. Reported human cases of infection and deaths with HPAI virus strains, 1959 – 2006.

** A/H5N1 data infections meeting WHO criteria as of 19 May 2006
http://www.who.int/csr/disease/avian_influenza/country/cases_table_2006_05_19/en/index.html

4. A/H5N1 - an unusual HPAI [††]

4.1 The Emergence of H5N1

In 1997 a series of poultry outbreaks of highly pathogenic avian influenza occurred in Hong Kong. An A/H5N1 strain was isolated both from chicken and humans (18 human cases, 6 fatalities). This included the first human to human transmission and the first occupational infection of a health care worker.[18,19,20,21] The outbreak was contained by the rapid culling of infected and at risk poultry and biosecurity measures. The virus strain is thought to have been circulating in Mainland China before 1997.[4,22,23]

These A/H5N1 viruses are a group of evolving viruses forming distinct strains some of which have achieved a degree of genetic stability. They have an ability to infect a surprisingly wide range of bird and even some animal species (for example the cat family with some cat-to-cat transmission in artificial circumstances).[22,24,25] This ability to transmit from mammal to mammal has raised concern of public health officials.[26]

The A/H5N1 viruses were not detected again until they reappeared in Hong Kong in February 2003 in humans (5 cases, 2 fatalities).[23] The infection was again controlled in poultry through vigorous culling, biosecurity measures and poultry vaccination. However this was the prelude to a vast expansion of the infection in the poultry populations in the Far East in Vietnam, Thailand, Cambodia and Indonesia and beyond.[23] The drivers for this rapid dissemination are unclear but commercial movements of chicks, birds and their products are as likely as dissemination through wild birds. By the end of 2005, over 140 human cases with a fatality rate close to 50% had been reported to the World Health Organization (WHO) from five counties.[23] It was on this basis of this spread and the possibility of A/H5N1 further adapting to humans that WHO raised its global influenza alert to Pre-Pandemic Alert Phase 3 in 2005.[27 ‡‡] To date that further adaptation has not been observed, specifically clusters of human H5N1 infection have not expanded in size as would be the case if there had been increases in human to human transmission.[28] However the potential may remain. It is thought by some that

†† The on-going history of A/H5N1 in animals and humans is well described in tabular form in the *WHO Time Line* available at http://www.who.int/csr/disease/avian_influenza/timeline.pdf
‡‡ In 2004 WHO changed its Pandemic Scale to a Six Point measure with three Pre-Pandemic Phases. Phase Three is when a novel influenza A virus has appeared can infect humans and cause disease, occasionally transmits from human to humans but has yet to show efficient person to person transmission.

a particular risk of pandemic emergence arises through recombination with circulating well-adapted (human) viruses through dual infections in humans and other mammals to produce a pandemic strain.[29,30]

By early 2005 H5N1 was causing special concern because it was becoming widely distributed in East and South East Asia.[23] The next major development, the dissemination of a particularly stable strain well adapted to birds beyond East and South East Asia seems to have started from an important natural event in China. This was at Qinghai Lake in West Central China where in April 2005 there was a large die-off of wild birds affecting an unusually diverse range of bird species.[23,31] Subsequent bird outbreaks across Asia, Europe and Africa have mostly been of the same strain as that observed at Qinghai, an unusual genetic stability for an avian influenza. When compared to earlier strains the virus has shown no diminution in its pathogenicity for chickens or humans.[23,32,33,34,35] The same virus then started to be seen in well migratory and non-migratory wildfowl and showed some indication of being somewhat more persistent in the environment though peer-review publications confirming this latter point have yet to appear.[36] Hence it became apparent in late 2005 that some H5N1 viruses could travel long distances quickly with wild birds as the vectors.[23,37]

Single cases or outbreaks in wild birds were subsequently detected in early 2006 in many European countries where wild bird surveillance was already in place.[23,38] Outbreaks were also detected in Middle Eastern, African and South Asian countries.[23] In these settings wild bird surveillance is unusual and so detection has usually taken place when either a domestic or commercial flock has been affected or when human deaths occur.[23]

The emphasis on wild birds does not mean that they have been the only source of dissemination though nobody could deny their role.[29,39,40] There are other important routes of local spread, notably through commercial practices and poor biosecurity (e.g. movements of infected poultry and people and vehicles with contaminated fomites). Control of these latter factors are crucial for protection of animals and humans at the local level.[29,40]

4.2 Increased Human Exposure to H5N1 2005-6 – the Implications

The range of the stable strain of H5N1 has extended considerably in 2005-6. Outbreaks in domestic poultry have expanded in some Regions where veterinary services are weaker than in the European Union. Therefore in

those places the likelihood of control of the infection is low and the numbers of people potentially exposed to H5N1 though domestic flocks has increased dramatically. That is in the Middle East, Africa and South Asia. This means that there will be more people who are at direct risk of H5N1 infection.[30] Equally there are many more governments that are needing to prepare for this eventuality. Though there may not have been any change in the pandemic potential the likelihood of any potential manifesting in the near future must have increased. This will be discussed in Section 5.

4.3 Poultry Immunisation to protect against H5N1

At least three countries, China, Indonesia and Viet Nam are undertaking large-scale poultry vaccination programs against H5N1, seemingly as medium term strategies and with the objective of reducing disease and the need for culling in poultry. The impact of these strategies on human risk of infection and disease is unclear. If poultry immunization is efficient and well monitored it could reduce the population burden of H5N1 in poultry and hence the risk for humans.[40] Equally however if it leads to the silent circulation of H5N1 in poultry it could actually increase the threat to humans in those countries and the risk of co-infection with other influenzas. The closely studied programme in Viet Nam is perhaps most likely to reveal which of these alternatives is realized. One unintended effect of these programmes is that they may make surveillance for single cases and small clusters of human H5N1 more difficult. Outbreaks in poultry can become 'silent' and the marker of die-offs of domestic flocks could be lost when deciding which human pneumonias to investigate. Falling numbers of reported human cases in countries practicing large scale poultry immunization may therefore be misleading.

4.4 The Extension of A/H5N1 into Europe

H5N1 extended into Europe in wild birds in early 2006 (Figure 2) with outbreaks or single cases in 13 out of 25 EU countries. Prior to 2006 large scale wild bird surveillance and surveys had produced results that were entirely negative for H5N1. The outbreaks have been instructive. Almost all the H5N1 that has been seen in the European Union has been in wild birds with only a handful of outbreaks in commercial poultry.[38] This reflects generally high levels of biosecurity in the European Union in the commercial sectors. The presentations have sometimes been subtle with relatively few bird deaths, notable odd neurological behaviours and no striking die-off of poultry. This raises the possibility that the virus could spread to other areas

and not be immediately apparent. Die-offs in commercial flocks due to HPAI are unlikely to go unnoticed in Europe. However it is acknowledged that more could be known about the presence of HPAI in the wild bird population and especially migratory birds.[41] Commercial flocks of poultry in the European Union are on the whole more separated from wild birds than those in Asia and Africa and so are less likely to act as sentinels. After the pulse of H5N1 in the early spring of 2006 numbers of H5N1 wild bird cases are diminishing but has not gone away as shown by outbreaks in commercial and domestic poultry along the Danube (Romania) and in the Baltic (Denmark) (Figure 2). The threat may return later through further migrations. There is agreement that controlling H5N1 in wild birds is impossible and should the stability of the current H5N1 strains be maintained Europe may simply have to adjust to add A/H5N1 influenza as one of endemic or occasionally appearing zoonotic infections. Guidelines to that effect for human health have been developed by ECDC.[42]

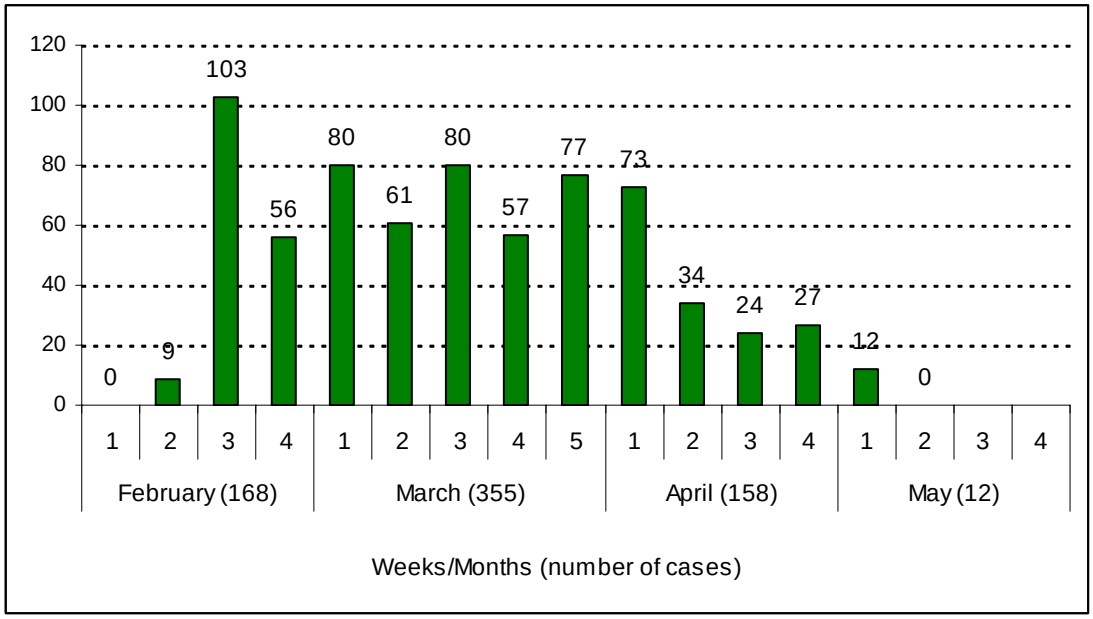

Figure 2. Highly Pathogenic Avian Influenza (H5N1) reported in the European Union through the Animal Disease Notification System February to May 2006 Source DG Sanco; http://europa.eu.int/comm/food/animal/diseases/adns/index_en.htm

4.5 Human A/H5N1 Cases - An Unusual Clinical and Epidemiological Profile

The only multi-country review of the clinical pattern of A/H5N1 in humans to date found that the infection and disease pattern differed significantly from any other human infections with HPAI.[30] Whilst it is certain that human cases have gone unrecognised and unreported, serological studies around cases to date have failed to identify mild or asymptomatic cases.[30] These serological studies have been criticized for being small scale and incompletely published. Also it has been suggested that the methods applied may only have the ability to detect serological responses in heavily ill hospitalized patients. However these findings are consistent with other results indicating that the H5N1 viruses are yet poorly adapted to humans.[23, 28]

A/H5N1 viruses do not transmit easily from birds to humans but when they do infect humans they cause severe disease.[30] It seems even less able to transmit on from human to human, which is typical of other poorly adapted zoonoses. [43,44,45] This combination of high pathogenicity and only occasional person to person transmission has changed little since the first observed infections in Hong Kong in 1997.[19,20,23]

4.6 Human Risk Groups and Risks of Transmission in Europe

See Table - Human Risk Groups in Europe (Annex 1)

While the routes of entry of H5N1 into humans remain poorly understood epidemiological data and the principles that follow from H5N1 being a virus as yet poorly adapted to humans indicate that the chances of humans becoming infected with an HPAI virus are small.[23] Equally the opportunity for transmission are confined to specific circumstances.
Human exposure to AI viruses occurs through contact with infected tissues, excretions, and secretions of infected birds, especially faeces and respiratory secretions.[30] The avian influenza viruses could seemingly be transmitted through various media: inhalation of contaminated dust, inhalation of fine water droplets, aerosols, hand-to-mucous membrane transfer of infected faeces or respiratory secretions and theoretically, mucous membrane exposure through consumption of raw or undercooked blood, organs or meat.[30] In general however, human cases have been principally related to close direct contact with high doses of virus from live or dead infected poultry

or occasionally wild birds.[46] Transmission probability is thought to be linked both to virus and host factors. Current efforts (genomic approaches, animal models, recombination approaches) are being undertaken in order to determine which characteristics allow viruses to infect humans.[30] However even though many millions of people in East and South East Asia have been directly exposed to H5N1 virus, only a very small percentage of them have become infected or ill.

Determining the exact routes of human infection and their risk factors has been beset with problems. Detailed field investigations have been rare and those with serological support even rarer.[30,46,47] Also in most cases there are multiple exposures and it is very difficult to determine if a person was infected by direct exposure to poultry, fomites, contaminated food or person to person transmission. There are a few case reports with seemingly reported unusual transmission (e.g. associated with bathing or consuming uncooked blood).[30,48] However further investigations of these have usually revealed multiple exposure and not evidence that the water or food was actually contaminated (R. Brown, WHO Vietnam, personal communication). Almost all of the A/H5N1 cases in Asia have been most closely associated with direct exposure to live or dead infected poultry.[30] Some cases suggest exposure only to raw poultry products. The handling and consumption of raw or undercooked products could be a source of human infection. This suggests there may be a need for a model for enteric transmission and mucous membrane exposure in addition to the usual respiratory models.

It has been suggested that these findings could have implications for Europe from environmental exposure to humans for example where wild migratory birds gather, for example at and around lakes. Certainly some studies of environmental contamination with HPAI where people and wild birds co-exist would be justifiable and risk assessments have been undertaken or are underway.[49,50] However it needs to be remembered that H5N1 remains poorly adapted to humans and that the greater risk for human infection (Table - Risk Group 1) is direct exposure to poultry raised or kept outdoors and those who have direct close contact with wild birds.[46] Poultry are highly susceptible to A/H5N1 Asian viruses and the expressed virus load grows to very high titres making the probability of exposure, infection and amplification and human infections greater through contact with outdoor-reared domestic poultry than indoor commercial or industrial poultry where biosecurity and worker protection is generally higher. There are also those who may theoretically be at risk though exposure (Table – Risk Group 2) but among

whom clinical infections have been very rare even in the Far East where exposure has been considerable.[23,30]

Three striking epidemiological features of human A/H5N1 infections have been

- how few infections have taken place considering the massive exposure to humans,
- the focus of infections in small household clusters involving family members
- the almost total absence of infections among those controlling the disease or caring for infected persons.

It has been suggested that a genetic susceptibility may partially explain some of these observations. Some comments have been made that children are more at risk (though the age structure of the human cases in the Far East is close to that of the population living in close proximity with poultry). This contrasts with the experience with the other HPAIs where those working to control the disease have been more at risk.[14,15,16,17]

This has implications for Europe as there is a risk, albeit very small to those who live closely with poultry and will probably not be so used to biosecurity considerations as those in the commercial farming sector – so called 'Sector 4' poultry owners, those with backyard or hobby poultry. This is especially so where those poultry may mix with migratory wild birds.

4.7 Risk to humans from Wild Birds

The experience from Azerbaijan indicate that there are rare circumstances where wild birds can pose a risk, for example if people attempt to handle and defeather sick or dead birds without taking precautions.[46] The public will be concerned but they need only follow simple measures already specified by European authorities and WHO such as not handling birds found dead and avoiding unnecessary contact with live birds when A/H5N1 has been shown to be present in a country. [42,46]

Finally however for the vast majority of people in Europe who do not have any of the above contact there can be hardly any risk at all of acquiring H5N1 infection while it remains in its present poorly adapted form.

Since unlike Asia, Africa and the Middle East most of the European Union's poultry flocks are segregated from humans the population risk is low. Those

working to control outbreaks of H5N1 are an obvious risk group. Good guidance for protection of this group already exists from the ECDC and also from other international and national sources in Europe and elsewhere.[51,52,53]

4.8 Risk from Food

Acquisition through food is a theoretical risk and has been demonstrated in the field and experimentally with tigers acquiring infection in Thailand from eating raw chicken and artificially infected cats.[24,25] However since cooking destroys the virus it should only be people consuming raw poultry products that would be at risk in Europe and there is already standard guidance to avoid such products including eggs.[54]

4.9 Identifying and Communicating with the Groups at Highest Risk

Because of the potential entry of the virus from migratory birds away from commercial flocks, the humans more at risk may be those with small flocks and a few backyard poultry (chickens, turkeys, ducks etc) and they also require guidance based on what has already been developed by WHO and UNICEF.[55,56] It is especially important to establish where there are such groups in Europe who are living with more intimate contact with domestic poultry and perhaps near migration sites. These groups can be hard to define and reach (e.g. families in poor circumstances without access to electronic communication). Those most at risk may be women who care for domestic poultry and children who play with them. However the extremely low transmissibility of A/H5N1 to people living like this observed in Asia is reassuring.

4.10 Preventing infection of Humans by H5N1 Viruses.

There is no single strategy that will uniformly prevent human infection with HPAI viruses though the most important strategy is control in poultry, the most likely way that people will be exposed. Three approaches seem sensible and have been supported internationally by WHO, OIE and FAO [29,40]

i. **Control the infection in birds which people will come into contact with – usually domestic poultry**.

ii. **Community mobilisation and education to reduce risk of human exposure to infected birds**

iii. **Case finding, surveillance, laboratory confirmation, treatment, patient isolation and infection control** Bearing in mind he people at highest risk are those living with other cases of H5N1 and after that people living intimately with domestic poultry

Most people in Europe will not be at risk (Table Risk Groups) though the potential widespread dissemination in the environment means that certain sensible precautions should be taken universally, most of these are around good general hygiene and should be being applied already and that is the basis of ECDC's advice to people living where H5N1 has been found.[42] The little risk that exists is mostly in groups that come into direct contact with birds. These groups need to take certain special precautions.

4.11 The importance of small household clusters – Person to Person Transmission

One paradox arising from the human data is that while the risk of H5N1 in any individual is very low once a case appears the risk of cases other household members rises considerably. There have been many small household clusters in China, South East Asia, Turkey, Iraq and Azerbaijan. Hence the emphasis on case finding and then early treatment of other household members in public health guidance.[57]

This observation has been misinterpreted as implying there is more person to person transmission than appreciated. The cause of these small clusters is unclear. They include shared exposure, some genetic susceptibility as well as person to person transmission. Occasional transmissions to very close contacts have been seen since 1997 but remain rare.[23,30] Those who have become infected were generally blood relatives providing care at home. Apart from one case there have been no onward transmissions to those providing care in a health setting and taking normal precautions.[23] Probably the most important observation is that the clusters are no bigger now in 2006 than they were in 1997 in contrast to what would have occurred should the virus have adapted to humans and become more transmissible.[23,28] It that occurs it which would be an indication that the world was entering WHO's Phase 4 or

Phase 5 of a pandemic at which point there would probably only be a single opportunity to contain the pandemic through early containment.[58]

5. The Potential for generation of a pandemic strain from H5N1.

A/H5N1 viruses have been circulating with occasional human exposures for nearly a decade. While the infection can infect and cause disease no change in behaviour of the virus in humans have been detected (in stark contrast to all the changes in birds) and no pandemic strain has appeared.[23] There must be some restriction on widespread transmission in humans of the H5N1 virus since the AI virus strains that infect humans seems to be limited to a restricted genotype and there have been few infections, even though millions of exposures and very close contact is required to infect other humans. Hence most evidence indicates a difficult adaptation process for A/H5N1 viruses among humans.

An enduring concern is that a "normal" seasonal flu virus will infect an H5N1-infected human, the two viruses will recombine and a new efficient H5N1 strain will emerge.[2,59] Equally there might be recombination with another animal influenza or the H5N1 could simply mutate to form a pandemic strain.[2] Previously it was thought that due to the low number of H5N1 infected humans, this would be statistically unlikely though the risk might increase as the epizootic continues. Given that normal human influenza has been circulating world wide, including in Asia, the extension of A/H5N1 to birds in Europe, Africa and South Asia must have increased the numbers of people potentially exposed to H5N1 and human influenzas. At the same time it is unknown whether poultry immunization in the Far East will decrease or increase human exposure.

The reduced amounts of contacts between infected birds and humans in European countries compared to elsewhere makes it unlikely that Europe will be the starting point for an H5N1 pandemic though there are countries on the edge of the European Union to the East and South where those conditions exist and where WHO's Early Containment Strategy might be needed.[58]

The extension of range does not mean that there has been any change in the pandemic potential of H5N1 itself.[30] However the increased exposure of humans to H5N1 means that if this virus does have pandemic potential that potential must be more likely to be expressed in the near future than it was previously. Conversely if H5N1 shows no ability to adapt better to humans despite such exposure confidence is likely to increase that its genetic pandemic potential is low. 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 good reasons for speeding up those preparations.

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.

However certainly there is absolutely no room for complacency. The first pandemic of the 20th century is thought to have emerged at least in part from an avian influenza either in Europe or North America.[60] It has been suggested that other mammals may act as the 'vessel' for dual infection and recombination.[2]

There are reasons for recommending extending seasonal influenza vaccination to wider groups. It has been suggested to include those involved in control measures when seasonal influenza is circulating. This is already a standard recommendation by one of WHO's Regions.[53] The case for immunisation of the wider number of people in Europe who live with domestic poultry either in commercial farms or with just a few chickens in the backyard is a much more difficult decision and requires a measured scientific public health view. A major consideration will be the difficulty of identifying those at risk. It probably will be preferable to further expand the use of seasonal vaccinations in the general population at least in the risk groups as recommended by WHO's Executive Board.[61] Given the need to expand European capacity for production of influenza vaccine there are other reasons why this will be desirable.

There are two crucial caveats to end this section. Firstly the ability of influenza viruses to adapt, change and surprise is well established. Just because the A/H5N1 viruses have been behaving in one way in Asia up to now that does not mean they cannot and will not and so become a greater threat to human health. Secondly it is important in this section to acknowledge that in focusing so much on HPAI in general and A/H5N1 in particular the next pandemic infection may actually arise from a low pathogenic strain, or the already human adapted A/H2N2 virus that caused a

previous pandemic because almost no community immunity exists against this virus anymore.

6. Final Considerations

6.1 The Need for Close Co-operation of Veterinary and Human Health Services

Much of the reduction of risk to humans from A/H5N1 will depend on the outcomes of veterinary control programs and how safely they are conducted.[29,40] While it would be difficult to justify large-scale public health expenditures in preventing a few sporadic human cases, it is justifiable to support expenditures to solve the problem in animals with such potentially significant public health implications as development of a pandemic. Increasing cooperation between the veterinary and human health agencies within Europe will be a crucial component to control avian influenza. Unified national and local planning is an imperative and is already part of the assessment exercises that ECDC, the European Commission and WHO Europe is assisting national authorities in making. Especially important will be unified approaches to any outbreaks of human H5N1 in the EU including vulnerable accession and candidate countries notably Romania.

6.2 The Importance of Risk Communication

Though strictly outside the remit of this paper it is impossible to ignore the evident confusion in the minds of the public between avian, seasonal and pandemic influenza. The perception of risk can be massive while as demonstrated above the actual risk to the individual from Avian Influenza is extremely low, even if they are exposed to infected poultry. Partially this confusion is understandable since avian influenza can lead onto pandemic influenza and the two issues are commonly tackled together in publications. However this is leading to disproportionate anxiety and needs to be addressed. Otherwise when the pandemic of 'bird flu' fails to materialize the case for preparing for the next pandemic will be undermined. Equally there will be unwarranted and disproportionate anxiety in the minds of the public and fear of harmless birds, both wild and domestic.

6.3 Adapting to H5N1

Though there is no sign that H5N1 is adapting to humans Europe needs to adapt to H5N1. The detection of H5N1 in wild birds in many European Union Countries and the seeming stability of the virus suggest that countries may

need to adjust to this being added to the current list of zoonoses present in animals that occasionally infect humans.

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Annex 1. Table: Who is at risk of getting "Bird Flu" - Highly pathogenic H5N1 avian influenza?

Broadly speaking there are two types of Risk Groups:-

Group 1 - Low but Real Risk

The risk of infection is almost entirely confined to the small numbers of **people who have close and intense contact with sick H5N1 infected domestic poultry (chickens, ducks etc) or their droppings or sometimes wild birds. For example through having sick and H5N1 infected poultry in the house.**
Human cases have almost entirely been in this category.
In these circumstances **children** may be at higher risk than adults. This probably represents behavioral rather than constitutional susceptibility. In these setting children being more play with or look after poultry and are less likely to practice good persona hygiene than adults.

People traveling to countries where H5N1 is prevalent can sometimes enter this category if they are staying with families with domestic poultry.

The people who are **at highest risk of acquiring H5N1** are the very small number of **people living in the same household as cases of H5N1 in humans**. It is thought that this is through shared exposure. Though person to person transmission also occasionally happens. This is why early identification of human cases and early treatment of them and their household contacts is crucial.

Group 2 Theoretical Risk – Precautions Required

There are also those at theoretical risk who may be exposed to the virus and should take appropriate precautions. This includes the following where H5N1 may be present:

- Health care workers caring for those with H5N1 infection though there have been no cases in this group for nearly a decade the risk is there and preventive measures should be taken. A related group are those working in laboratories with H5N1 viruses
- Veterinarian and people involved in controlling outbreaks in birds (culling)
- People who work on industrial poultry farms,
- People who may have close contact with infected wild birds e.g. some ornithologists and hunters,
- People who deal with sewage which is contaminated with H5N1

For the majority of people who have no contacts with domestic or wild birds or their droppings, the risk of acquiring H5N1 is almost non existent.