

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

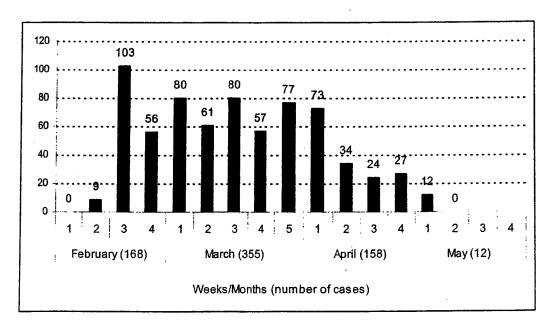


Figure 2. Highly Pathogenic Avian Influenza (H5N1) reported in the European Union through the Animal Disease Notification System February to May 2006 Source DG Sanco;

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. 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. 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. 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. 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. 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. 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}

 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. 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. 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. 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. 123,28 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. 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. 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 <u>highest risk</u> 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.