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]

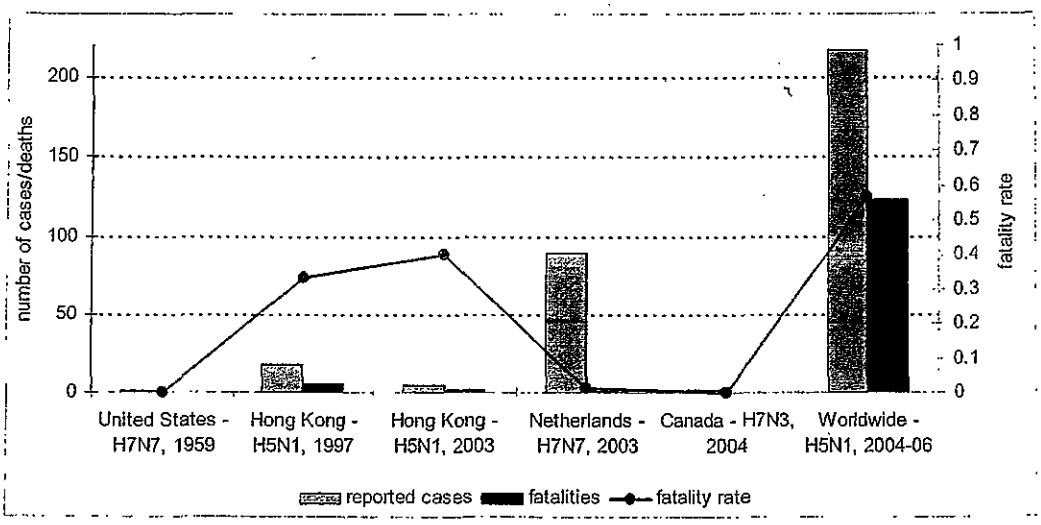

Figure 1. Reported human cases of infection and deaths with HPAI virus strains, 1959 – 2006.

** 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]

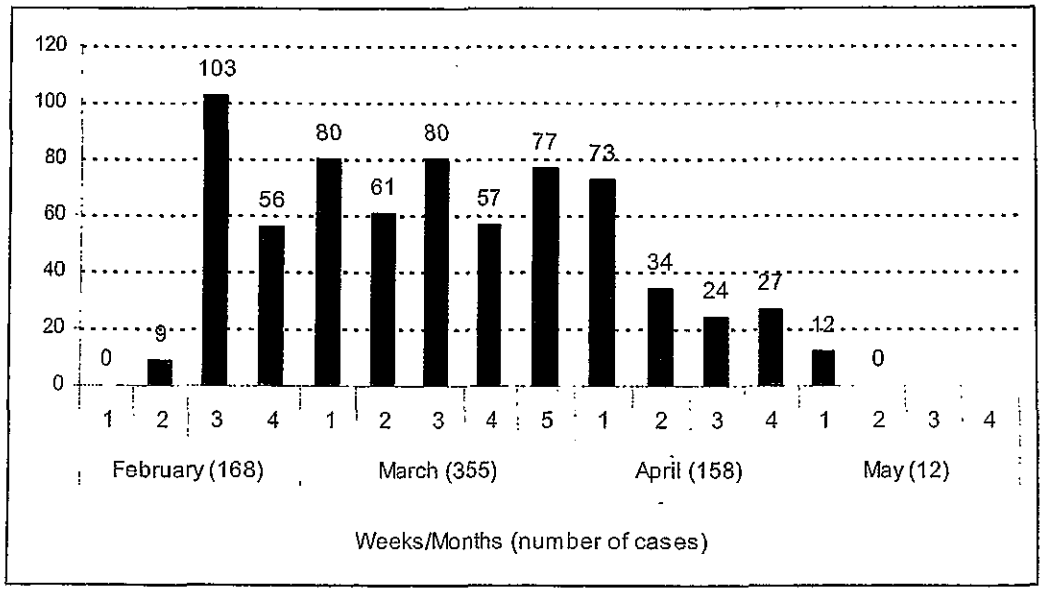

Figure 2. Highly Pathogenic Avian Influenza (H5N1) reported in the European Union through the Animal Disease Notification System February to May 2006 Source DG Sanco; http://europa.eu.int/comm/food/animal/diseases/adns/index_en.htm

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