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POTENTIAL ROLE OF CERTAIN FREE LIVING AVIAN AND FREE LIVING AND DOMESTIC ANIMAL SPECIES IN THE EPIDEMIOLOGY OF HIGHLY PATHOGENIC AVIAN INFLUENZA (H5N1)

A Commentary

Working Document

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1 Summary

In addition to wild waterfowl, natural infections with H5N1 virus have also recently been reported in other free living avian species and free living and domestic animals. The issue has been raised as to whether these species also play a role in the epidemiology of the H5N1 virus in avian species in general and in animals.

This risk assessment concludes:

a) The currently available evidence indicates that exposure of various free living avian species and free living and domestic animals to HPAI H5N1 virus is likely to result in death following close and direct exposure to the virus.

b) In epidemiological terms, this development is consistent with the concept of a self-limiting disease (a ‘dead-end’ host).

c) The recent pattern of the virus detection in these species indicates that these species became infected because of localised introduction and exposure to the virus from other species rather than horizontal transmission within the species concerned.

These conclusions are based on the following facts:

- There were a large number of wild birds that died of HPAI H5N1 in the area where dead free living avian species and free living and domestic animals were found. It is likely that these species have become infected having been in close contact with infected wild birds shedding the virus, scavenged the carcasses of dead infected birds or preyed on sick or dead birds.

- Published observations in poultry and some other species indicates that infection with H5N1 virus only occurs as a result of very close direct exposure.

- A number of other avian species and mammals have been shown to be susceptible to natural (and experimental) infection with the H5N1 strain. Evidence of H5N1 virus strain variation with respect to the susceptibility of some species is also consistent with the known epidemiology of all avian influenza (AI) viruses.

- It is epidemiologically notable that the recent detection of highly pathogenic avian influenza (HPAI) H5N1 virus in other avian species and mammals has been associated with a high prevalence of uncontrolled infection, either in wild waterfowl (e.g. Europe) or commercial poultry (e.g. some countries in Asia). It is also worth noting that in the majority of cases the virus has been detected as isolated cases where wild birds of

prey and scavenging birds have been found dead and submitted for testing or in the case of big cats (tigers and leopards) in zoos that have been fed infected poultry.

- Recent reports on HPAI H5N1 virus in avian and mammal species correlate with the known epidemiology of AI viruses and its ability to infect a variety of species following exposure. Therefore, these recent detections are not unexpected and need to be interpreted with care, particularly when referring to the virus's ability to infect 'new species'.

This risk assessment acknowledges that the conclusions above are based on much uncertainty. Nevertheless, these conclusions will be subject to revision when more detailed epidemiological information becomes available on the differences related to species susceptibility, the ecology of the virus and the pathways of introduction and subsequent spread. It is encouraging to note that there have recently been initiatives at the international level for the open sharing of data on H5N1 virus isolates.

We continue to monitor the situation.

2 Introduction

This qualitative risk assessment considers the potential role of certain avian and mammalian species in the epidemiology of highly pathogenic avian influenza (HPAI) H5N1 virus. The following information has been received from the European Commission (European Commission, 2006) and the World Organisation for Animal Health (OIE, 2006) unless otherwise stated.

The information presented here is current as of 15 March 2006. However, the situation has been changing rapidly and further developments are likely.

3 Hazard identification

3.1 Official Disease Reports - HPAI (H5) in pigeons and doves

H5N1 virus has been reported in wild pigeons in Turkey, Iraq and Romania.

3.1.1 Turkey

Turkey reported the confirmation of H5 avian influenza virus in 11 wild pigeons and 2 doves between January and March 2006 in eight provinces (Amasya, Aydin, Bitlis, Erzincan, Karabuk, Mardin and Samsun)

3.1.2 Iraq

Iraq reported an outbreak of H5 HPAI in village pigeons in Missan (Maysan) on 9 February with two deaths in a population of 980 pigeons. The remaining birds were destroyed.

3.1.3 Romania

Romania reported the finding of a dead wild pigeon infected with H5 HPAI in Constanta on 23 February.

3.2 Official Disease Reports - HPAI (H5) in mammals

3.2.1 Germany

H5N1 virus has been reported in several cats in the in the island of Rügen in Germany.

An HPAI H5 infection is suspected in a Stone Marten (*Martes* spp) that was found in the same area as three cats that were previously confirmed as having H5N1. The Stone Marten was found alive with clinical signs in the Rügen area of Germany. It was euthanized and submitted for testing. A regional laboratory on Rostock carried out the first tests for Influenza virus. Further characterisation and confirmation for H5N1 is awaited from the National Reference Laboratory at Reims.

3.2.2 Austria

H5N1 virus has been reported in three cats that have been in a same animal shelter in Austria where a case of the virus infection was first reported in a rescued swan which died.

3.3 Hazards to be considered

The virus has been recently reported in dead wild birds that have been collected where die-offs of waterfowl have been reported in Europe. The virus has been detected mainly in dead Mute Swans (*Cygnus olor*). Furthermore, the infection has also been reported in either single or a few Whooper Swans (*Cygnus cygnus*), Cormorants (*Phalacrocorax carbo*), Grey Herons *(Ardea cinerea*), Mallards (*Anas platyrhynchos*), Common Pochard (*Aythya ferina*) and Red-breasted Goose (*Branta ruficollis*).

Natural infection with H5N1 virus has also recently been reported in other avian species and mammals.

With regard to other free living avian species, natural infection was detected in either single or a few and Goshawk (*Accipiter gentilis*), Seagulls (*Larus* sp.), buzzards (*Buteo buteo*), Feral pigeons (*Columbia livia*), Doves (*Streptopelia* spp), Eurasian Tree sparrows (*Passer montanus*), Jungle crows (*Corvus macrorhynchos*), Black drongo (*Dicrurus macrocercus*) Scaly-breasted Munia (*Lonchura punculata*), Black-billed Magpies (*Pica pica*) and Rook (*Corvus frugilegus*) (National Wildlife Health Center, 2006).

With regard to free living and domestic animals, infection with the virus in either experimental or natural conditions has been reported in either in a single or a few domestic and feral cats (*Felis domestica*), Tigers (*Panthera tigris*), Leopards (*Panthera purdus*), Pigs (*Sus domesticus*), Ferrets (*Mustela putoris furo*), Monkeys (*Macaca facsicularis*), Owston's Palm civet (*Chrotogale owstoni*), Rats (*Rattus norvegicus*) and New Zealand white rabbit (*Oryctolagus cuniculus*) (National Wildlife Health Center, 2006).

A concern has been raised that other free living avian species and free living and domestic animal species may also play a role in the epidemiology of H5N1 virus. Therefore, they have been identified as a hazard for consideration.

4 Risk assessment

4.1 Release Assessment

4.1.1 Terms and definitions

For the purpose of the release assessment (Section 4.1) the following definitions will apply:

Term	Definition
HPAI	*"HPNAI viruses have an IVPI in 6-week-old chickens greater than 1.2 or, as an alternative, cause at least 75% mortality in 4-to 8-week-old chickens infected intravenously. H5 and H7 viruses which do not have an IVPI of greater than 1.2 or cause less than 75% mortality in an intravenous lethality test should be sequenced to determine whether multiple basic amino acids are present at the cleavage site of the haemagglutinin molecule (HA0); if the amino acid motif is similar to that observed for other HPNAI isolates, the isolate being tested should be considered as HPNAI"* (OIE, 2005)

For the purpose of the release assessment (Section 4.1) the following terminology* will apply (OIE, 2004):

Term	Definition
Likelihood	Probability; the state or fact of being likely
Likely	Probable; such as well might happen or be true; to be reasonably expected
High	Extending above the normal or average level
Highly	In a higher degree
Low	Less than average; coming below the normal level
Negligible	Not worth considering; insignificant
Remote	Slight, faint

* This risk assessment uses the OIE recommended terminology. This is important to maintain consistency in expressing estimates. Defra is aware of some concerns that have been expressed lately about the appropriateness of this terminology for practical purposes (ie. clarity for the purpose of understanding by wider non-technical audience). Defra will consider this issue in the near future.

4.1.2 Epidemiological considerations

4.1.2.1 Free living avian species

Recent events show that the virus has been detected in a number of species of birds of prey or scavenging birds. Presumably, these birds have become infected because of exposure and close contact with a number of dead wild waterfowl available as food.

4.1.2.1.1 Birds of prey and scavenging birds

Susceptibility of birds of prey to the infection with H5N1 virus has been demonstrated in the past. In most cases, the virus was isolated from dead birds.

As far as we are aware, in only one instance was the virus suspected in live birds and subsequently confirmed. The virus has been isolated from two crested hawk-eagles (*Spizeatus nipalensis*) from Thailand that were seized at the Brussels International Airport in 2004. The birds showed no apparent clinical signs of the disease. Subsequent post-mortem examination indicated that both eagles had enteritis and one of them had bilateral pneumonia. It remains unknown when and how birds become infected (Van Borm and others, 2005). Therefore, it remains unknown how long the incubation period is in raptors following exposure. However, detection of pathological changes in the respiratory and intestinal tracts suggest that the infection does have the potential to lead to a fatal outcome.
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4.1.2.1.2 Free-living pigeons

Free-living pigeons live in contact with people and a variety of species of birds and animals all over the world.

Based on published data on AI detection in various bird species until 2005, birds of the order *Columbiformes* have been cited in 20 publications (1.8%) out of 1080 publications. Most AI detections have been cited in *Anatiformes* (geese, duck and swans)(~65%); *Phasianiformes* (pheasants, partridges quails, etc)(~12%); *Charadiformes* (lapwings, plovers)(~12%), *Passeriformes* (perching birds)(~4%), *Psittaciformes* (parrots)(~2%) and others (~3%) (Kaleta and others, 2005).

In one experiment, free-living pigeons have been shown to be resistant to infection and no virus has been reisolated following the challenge with the strain of the virus obtained in Hong Kong in 1997 (Perkins and Swayne, 2002). In another experiment, experimental inoculation of pigeons with two different H5N1 isolates from Thailand resulted in the death of one pigeon while a few others become infected but showed no clinical signs. In this experiment, about half of the pigeons did not become infected following the challenge with the virus (Swayne, D.E., – personal communication, March 2006).

4.1.2.2 Mammals

It has been long known that influenza A viruses can infect a variety of animals, including humans, pigs, horses, sea mammals (seals, whales). In experimental conditions, pigs, ferrets, cats, mink and monkeys had also been infected with influenza viruses originating from avian species (Easterday and others, 1997).

4.1.2.2.1 Cats

There are anecdotal reports of domestic cats succumbing to natural H5N1 infection in Thailand, but there is only evidence of confirmed infection in three domestic cats which died in January 2004 (Morris and Jackson 2005). This was at the height of the first epidemic wave when “big cats” in zoological collections (see below) also became infected.

A recent news feature in *Nature* reports rather vague unpublished findings on the serological examination of 111, presumably healthy, cats in the Suphanburi district of (central) Thailand of which 8 (7.2%) were seropositive (Butler 2006). This area had the greatest incidence of H5N1 infection in poultry in the second epidemic wave in Thailand in October 2004.

The first confirmed case of H5N1 infection in Europe in a domestic cat was in three cats found dead in the Baltic Sea on the coast of the Island of Rügen, North Germany in February 2006. Two more affected cats have been reported so far. These cats were found in an area with an unusually large prevalence of H5N1 infection in dead wild birds. Surveillance within EU member states so far has not revealed other areas with such a large number of infected birds. These cats were apparently part of an ecological niche of infected waterfowl and predatory species and had access to carcasses of dead birds with a high prevalence of H5N1 infection. This is consistent with the findings from Thailand and Cambodia of incidents of infection in big cats (tigers and leopards).

Official reports indicate that cats were present in the animal shelter in Graz, Vienna, Austria which “took in” dead and dying swans, subsequently resulting in chickens in the shelter becoming infected. Samples from more than 70 apparently healthy cats in the shelter have been tested. We understand that tonsil swabs collected from 40 cats have been tested in the first instance by polymerase-chain reaction (PCR) and three cats tested positive. Subsequently, 34 out of these 40 cats have been resampled eight days later and tested with negative results. Only one positive cat has not been re-tested and follow up is underway.

A recent experimental study also demonstrated that domestic cats may be at risk of disease or death from H5N1 virus through feeding on carcasses of infected poultry or wild birds and that secondary cat-to-cat transmission may be possible. The study considered that the role of cats in the spread of the disease between poultry farms and from poultry to other susceptible species needs to be reassessed (Kuiken and others, 2004). Subsequent experimental studies by this Dutch group indicated that experimentally infected cats excreted virus (H5N1) in faeces and from the respiratory tract (Rimmelzwaan and others, 2006).

There is obviously considerable variation in the surveillance capabilities in countries in south-east Asia, but two points emerge from the accumulated data and information.

The first is that the veterinary authorities in Japan did not identify infection in cats. From the available evidence Japan appears to have one of the most efficient surveillance systems in South-East Asia. In Japan, wild birds were known to be infected as spill over hosts, in addition to commercially kept chickens. Infection of commercial poultry with H5N1 virus was restricted to only four premises. On the other hand, there is no evidence from Thailand to indicate that H5N1 infection has been transmitted from domestic cats to any other species.

H5N1 virus was detected for the first time in a dead tiger in the People's Republic of China in 2002 (Xia Xian-zhu and others, 2003).

During the outbreak in Thailand in December 2003, two tigers (*Panthera tigris)* and two leopards (*Panthus pardus*) at a zoo died after exhibiting clinical signs suggestive of avian influenza, but there was no virological confirmation. At this time a large number of chickens were dying in this area which had respiratory and neurological signs which were, retrospectively, identified as likely to have been caused by H5N1 infection (Keawcharoen *et al*. 2004). Subsequently, isolates from a dead Clouded Leopard, in the Khao Khiew Open Zoo, in the Chon Bhuri province, in January 2004, were confirmed as H5N1.

Then in October 2004, at the Sri Racha Tigers Zoo, Thailand, the deaths of tigers were attributed to HPAI. This was also in the central region. In the event, 147 of the 441 tigers at risk either died or were euthanased. Whole chicken carcasses and chicken bones were fed to these tigers.

There was a possible common source of infection for these tigers, but investigations also suggested that there had been horizontal (tiger-to-tiger) transmission (Thanawongnuwech *et al.* 2005).

Big cats (tigers and leopards) also apparently succumbed to H5N1 infection in Cambodia. This was at the PhnomTamao Wildlife Rescue Centre. This was identified as an infected premises at the time of the identification of the first outbreak of H5N1 infection, perhaps belatedly, in Cambodia on 23 January 2004. The outbreak in this Rescue Centre had probably started in December 2003, when retrospectively infection in commercial poultry flocks most probably first occurred. A wide range of avian species were affected in addition to tigers, leopard, clouded leopard, golden cat and lion. The feeding of infected poultry was a possible source of infection for these big cats.

4.1.2.2.2 Dogs

The news feature in *Nature* claims the isolation of H5N1 from at least one dog, which was serologically positive (Butler 2006). As indicated above, for the report of serological surveillance of cats, it is not known whether the 629 dogs, which were also examined serologically in the Suphanburi district were healthy or fatalities. However, 160 (25,4%) of these dogs were seropositive. The interpretation of these second-hand findings is difficult. One presumes that dogs were exposed orally to infected chickens either deliberately as a source of food or from their predatory activities. There are no published reports of confirmed infection in domestic dogs. Therefore, there is no virus available from this species to develop reliable serological tests. Caution must be exercised when interpreting serology using standard serological methods to test for this virus in dogs.

4.1.2.2.3 Ferrets

In experimental conditions, Zitzow and others (2002) also succeeded in infecting ferrets with H5N1 virus isolates obtained from humans in Hong Kong in 1997. The ferrets showed severe clinical signs similar to those recently observed in tigers and cats. The virus was also isolated from the brains of these ferrets.

4.1.2.2.4 Pigs

Early in 2005, an independent researcher in Indonesia tested ten pigs from Banten in western Java that had been kept near a chicken farm that had been infected with HPAI last year. Although the pigs that were tested showed no signs of illness, H5N1 virus was found in five of the pigs. There was also no evidence presented that the virus was replicating in the pigs. Subsequently, three official surveys in pigs were conducted during February and April 2005. In each survey the presence of H5N1 virus was detected, However, none of the infected pigs showed clinical signs of avian influenza. Further investigations have been made in seven provinces (Central Java, West Java, West Kalimantan, South Sulawesi, Bali, Riau and North Sumatra). The results of the serological testing of 250 samples of pigs (sera and swabs) were all negative.

Further analysis indicated that this virus appeared to be the same as that isolated from infected poultry across east Asia. These pig farms were adjacent to backyard chicken farms. It is suspected that the infection in pigs was due to contamination with chicken manure. It is, however, also possible that pigs were fed on carcasses of infected poultry and could therefore have been exposed to a high viral load (as occurred in the H7N7 outbreak in the Netherlands in 2003) (Alexander and Brown, VLA, Weybridge, personal communication, 2005)

Cyranoski (2005) considers that "*concerns over the presence of a strain of avian flu virus in Indonesia's pigs are growing, as government tests confirm the existence of infection. In some areas, the H5N1 virus could be infecting up to half of the pig population, without causing any signs of disease*." However, there is no substantive evidence to support these assertions. In fact infection has not been conclusively proven in pigs since detection by RT-PCR in nasal swabs does not constitute absolute proof of infection. Theoretically exposure of pigs to high viral load may result in the detection of viral RNA in the snout (similar results were obtained in early 2004 in Vietnam)(Alexander and Brown, VLA Weybridge, personal communication, 2005).

The report of H5N1 findings in pigs in Indonesia is not the first of this kind in the region. Chinese researchers have reported on the isolation of H5N1virus in southeast China's Fujian province (a pig in 2001and a pig in 2003) (Chen and others, 2005). According to the Chinese authorities, detailed analysis of these two isolates indicated that they are highly homologous to the duck-derived H5N1virus isolated recently in birds in China. No variation in the virus has been observed. Therefore, the Chinese authorities (Embassy of the Peoples Republic of China in India, 2004) consider that this was an "incidental infection" of pigs by the AI virus of duck origin.

Following confusion regarding reports on isolation of H5N1 in pigs in China in 2004, the Chinese authorities clarified that 1.1 million samples including 4447 from pigs have been collected and analysed between April and August 2004. These samples were collected as part of their ongoing epidemiological surveillance programme from 10 provinces including Fujian. No H5N1 virus was detected in these pig samples. (Xinhua News Agency, 2004).

Experimental studies using the isolate from Hong Kong in 1997 demonstrated that pigs supported the replication of the H5N1 virus to only modest titers. However, there was no detectable transmission to contact animals (Shortridge and others, 1998).

4.1.2.2.5 Mice and rats

Experimental studies demonstrated that H5N1 viruses are pathogenic for mice. One study with the isolate obtained in Hong Kong in 1997 demonstrated that high titers of virus have been detected in the lungs of infected mice and that all inoculated mice died. A group of mice that have not been inoculated but kept in cages with infected mice did not become infected (Shortridge and others, 1998) indicating an absence of horizontal transmission.

An experimental study with an isolate obtained from Hong Kong in 1997 showed that H5N1 influenza virus isolates obtained from humans, chickens, and ducks all replicated to low titers in the lungs of rats. No rats have died while only a portion of them shed virus. Virus was detected in the lungs on day 3 but not on day 5, postinfection. The goose strain failed to replicate in rats. Chicken isolates appear to have replicated to higher titers (5.0 log10/ml) than did the other viruses (Shortridge and others, 1998).

4.1.2.3 General comment

Wild waterfowl are the major reservoir of avian influenza (AI) viruses. All influenza viruses in other animal species are thought to be derived from these birds. Historically, the highly pathogenic avian influenza (HPAI) viruses of H5 or H7 subtypes have been associated with most severe outbreaks of avian influenza in domestic poultry (Easterday and others, 1997). However, transmission of the AI viruses from waterfowl to other avian or mammalian species appear to be intermittent demonstrating that host specificity also include a limited ability to infect and generate diseases in aberrant (incidental hosts) (Perkins and Swayne, 2002).

The clustering of isolations of the virus in dead scavenging birds, birds of prey and carnivores in time with reported H5N1 infection of wild waterfowl in Europe or in some other countries is notable epidemiologically. This is most likely as a result of exposure due to close contact to a number of dead wild waterfowl available as food. While the virus detection in this species is a definitive proof of their susceptibility, it is also apparent that exposure will result in death. This is in line with the evidence so far that the virus has not been isolated from live and apparently healthy birds or carnivores.

It is considered that interspecies transmission of viruses does not necessarily result in a net gene flow between host-specific virus gene pools. Reassorted new virus progenies with new genes may have lower fitness (reduced replication and virus shedding) relative to virions that have host adapted genes and thus may not persist" (Webster and others, 1992).

5 Conclusions

A number of free living avian species and free living and domestic animal species have been shown to be susceptible to natural (and experimental) infection with the H5N1virus. There is evidence of H5N1 virus strain variation with respect to the susceptibility of some species which is consistent with the known epidemiology of all avian influenza (AI) viruses.

The currently available evidence indicates that exposure of various free living avian species and free living and domestic animal species to HPAI H5N1 virus is likely to result in death following close and direct exposure to the virus. In epidemiological terms, this development is consistent with the concept of a self-limiting disease (a 'dead-end' host). The recent pattern of the virus detection in these species indicates that these species became infected because of localised introduction and a high level of exposure to the virus from other species rather than horizontal transmission within the species concerned.

Published observations in poultry and some other species indicates that infection with H5N1 virus only results from very close direct exposure. It is epidemiologically notable that the recent detection of highly pathogenic avian influenza (HPAI) H5N1 virus in other avian species and mammals has been associated with a high prevalence of infection, either in wild waterfowl (e.g. Europe) or commercial poultry (e.g. some countries in Asia). It is also worth noting that in the majority of cases the virus has been detected as isolated cases where wild birds of prey and scavenging birds have been found dead and submitted for testing or in the case of big cats (tigers and leopards) in zoos that have been fed infected poultry.

Recent reports on HPAI H5N1 virus in avian and mammal species correlate with the known epidemiology of AI viruses and its ability to infect a variety of species following exposure. Therefore, these recent detections are not unexpected and need to interpreted with care, particularly when referring to the virus's ability to infect 'new species'.

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