Highly Pathogenic Avian Influenza
(HPAI, Fowl Plague)

ANIMAL GROUP AFFECTED	TRANS-MISSION	CLINICAL SIGNS	FATAL DISEASE ?	TREATMENT	PREVENTION & CONTROL
All Birds, especially galliformes, anseriformes and struthioformes; occasionally in humans, captive, wild and domestic animals: felids, mustelids, pigs, horses, seals, dogs	Directly (aerosol, body fluids, feces) or indirectly (contaminated vehicles, material or persons, possibly wild birds) Feeding on infected animals	In non-domestic birds usually none or mild respiratory signs; in poultry very high morbidity and mortality with peracute to acute course. However, H5N1 2003-2006 caused death, respiratory and neurological signs in some wild and captive bird species	HPAI has a high morbidity and mortality in domestic poultry; mortality in non-domestic birds is rare in H5N1 2003-2006 or very rare in other HPAI viruses	No treatment currently allowed	Vaccination of all susceptible birds (currently requires special permit); quarantine of susceptible birds and potentially of susceptible mammals; notifiable disease. Measures of biosecurity. Vaccination of people in close contact with seasonal WHO vaccine

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Susceptible animal groups

Domestic birds: chicken, turkey, ostriches, peafowl, guinea-fowl, quails, ducks, geese

Non-domestic birds: order anseriformes, galliformes and struthioformes are the ones most likely to be susceptible to HPAI, but cases of high mortality in other orders have been described: the first documented outbreak of HPAI in the wild was in common tern (*Sterna hirundo*), order charadriiformes, in 1961 in South Africa; juvenile ostriches were affected by HPAI in the 1999/2000 outbreak in northern Italy. The H5N1 virus of 2002-2006 was atypical in that it caused noticeable mortality in wild birds (in China, Romania, Germany, others). In Hong Kong in December 2002, at the start of the H5N1 outbreak, wild ducks, geese, swans, as well as flamingos, egrets (*Egretta garzetta*) and gray herons (*Ardea cinera*) died (Guan *et al.*, 2004). Other mortalities included birds from the orders anseriformes, galliformes, ciconiiformes, columbiformes, falconiformes, gruiformes, passeriformes, pelecaniformes, phoenicopteriformes, psittaciformes, stringiformes, and struthioniformes.

In contrast, LPAI probably affects all birds and has been isolated most frequently from anseriformes and charadriiformes, but also from psittaciformes, passeriformes, struthioformes, cuculiformes and many others.

Others:

The H5N1 outbreak in 2002-2006 was also atypical in that this virus was capable of infecting and causing mortality in humans and several species of captive and domestic mammals (fed with infected birds) of the mustelidae (Owston palm civet *Chrotogale owstoni*, Ferret *Mustaela putoris furo*), and felidae (domestic and feral cats *Felis domestica*, leopard *Panthera pardus*, tiger *Panthera tigris*). Furthermore, several mammal species could be infected experimentally: mouse, rat, rabbit, cynomolgus monkey (*Macaca fascicularis*), and domestic cat.

Causative organism
The avian influenzaviruses are orthomyxoviruses of the influenza A type. They are further characterised and numbered by their 16 types of haemaglutinin (H) and 9 types of neuramindase (N). Any combination of these two protein types seems possible and most have been isolated from birds. A distinction is made between avian influenza viruses of low pathogenicity (LPAI) and of high pathogenicity (HPAI) with mortality in domestic birds up to 100%. The avian HPAI viruses have traditionally been of the subtypes H5 and H7, although not all viruses of these subtypes cause HPAI. In several cases, LPAI have mutated to HPAI, both in epidemics as well as in laboratory passaging of the virus. One study reported that highly pathogenic H5N1 avian influenza virus reversed into LPAI in domestic ducks (Hulse-Post *et al.*, 2005).
The current definition of HPAI differs in some details between the OIE and the EU.

Zoonotic potential
Avian influenza is a classical zoonosis and this threat needs to be considered seriously since infection, human-to-human transmission and fatal disease in humans has occurred. However, morbidity and clinical course, mortality, and inter-human transmission differ between different HPAI viruses. At the time of writing, the prevalent genotype z/Asia H5N1 virus is supposed to "not easily cross from birds to infect humans" (WHO, 2006). The epidemiology of human H5N1 remains poorly understood and does not follow predictions (WHO, 2006). For this subtype of AIV, more than 200 laboratory-confirmed human infections have occurred, with 80+ fatal cases in Asia and Turkey in the years 2003-2006.
Preventive medication with Tamiflu ® (oseltamivir) was recommended and used in several countries for those persons in close contact with infected birds. However, the efficacy and side effects of Tamiflu ® have been discussed recently (Sprenger, 2006; de Jong *et al.*, 2005).
Additionally, vaccination against human influenza with the seasonal human influenza vaccine, as recommended by the WHO, was recommended to reduce the risk of reassortment by coinfecting avian and human viruses.

Distribution
Worldwide. Believed by some researchers to have become endemic in Asian regions (Li, 2005)

Transmission
By direct contact (aerosol, body fluids and excrements) and by indirect transmission (contaminated instruments, vehicles and persons) and ingestion. Indirect transmission by vehicles and persons, by contaminated feces and by commercial bird transport was proven to be important in the 2003 outbreak in The Netherlands and Germany, and in other outbreaks. Transmission from carrier wild birds to domestic birds is very often discussed, but the 2003-2006 outbreak has shown that little transmission occurred during the migration of wild birds in fall of the year 2005. However, the WHO published in January 2006 that "at least some species of migratory waterfowl are thought to be carrying the H5N1 virus in its highly pathogenic form and introducing it to new geographical areas located along their flight routes" (WHO, 2006). Contrary to this, many researchers believe that wild birds are largely "victims" and not responsible for transmission. Transport of infected birds or their products, or of other infectious material by man is currently believed to be the most important source of transmission (Lubroth, cited in Stoddard, 2006). No hard evidence exists for either theory: outbreaks along the flyways are highly suggestive (and some birds do excrete virus), but equally suggestive and known are outbreaks along trade routes (Philippa, personal communication)
The 2003-2006 outbreak is considered the largest and most severe outbreak of HPAI on record, affecting Korea, Vietnam, Japan, Thailand, Cambodia, Laos, Indonesia, China, Malaysia, Russian Federation, Kazakhstan, Mongolia, Azerbajan, Iran, Iraq, Turkey, Romania, Croatia, Ukraine, Greece, Italy, Germany, Austria, Bosnia and Herzegovina, France, Switzerland, Niger, Hungary, Egypt, Serbia and Montenegro, Pakistan, Slovakia, Sweden, Poland, and others (currently continuing).

Incubation period
Highly variable, from few hours to 14 days; OIE definition (for declaring a country status "free") is 21 days.

Clinical symptoms
Domestic birds: clinical symptoms are very variable, depending on virus strain, species infected, age, and environmental conditions. Infections of poultry with HPAI are characterized by signs associated with the gastrointestinal and respiratory tracts, and the CNS (also oedema and cyanosis of comb and wattles), with very high morbidity and mortality reaching up to 100%. Also domestic turkeys, quails, pheasants and peafowl succumb to HPAI. Pigeons were previously believed to be resistant or only minimally susceptible (Panigrahy *et al.*, 1996), but feral pigeons (*Columba livia*) and Red-collared doves (*Streptopelia tranquebarica*) were affected by H5N1 in the 2003-2006 outbreaks (Ellis *et al.*, 2004a, ProMed 20041214.3303).
Non-domestic birds: Until recently -before the 2003-2006 outbreak of H5N1- most species, especially waterfowl, showed no symptoms at all and some evidence exists that this is due to the lack of an enzyme – except in intestine and lungs- for cleavage of the haemaglutinin precursor, necessary for pathogenicity; however, evidence for replication of the virus in all major target organs has been proven for one duck species: muscovy ducks, *Cairina moschata*, (Capua & Mutinelli, 2001b). Farmed ostriches, and wild common tern and wild muscovy ducks were among the few wild bird species to become clinically ill with associated

mortalities before the H5N1 outbreak (2003-2006); however, in the latter outbreak many wild and captive avian species were clinically affected and died (see above "Susceptible animal groups"), symptoms usually were respiratory signs, excessive lacrimation, head edema, diarrhea, neurological symptoms and (sudden) death; mortality was high (de Jong & Hien, 2006, Ellis *et al.*, 2004a).

Post mortem findings

Congestion, focal and diffuse haemorrhages and necrosis in multiple organs, especially pancreas, liver, spleen, kidneys; enteritis, encephalitis. See Capua & Mutinelli (2001a), Ellis *et al.* (2004a) and Swayne & Halvorson (2003) for very detailed descriptions.

Diagnosis

In clinical cases: By suspicion, followed by culling, pathology and virology by recognised methods in national reference laboratories.

For screening: Swabs from cloaca and trachea/oropharynx, as well as fecal samples can be analysed by some laboratories by rt-PCR; special medium is required for the swabs (e.g. PBS, pH 7-7.4, containing antibiotics and 5-10% serum or BSA). Serum can be tested for titres against haemaglutinins (best by haemaglutinin inhibition) and neuraminidases (by neuraminidase inhibition, often only possible to OIE laboratories). Rapid tests (ELISAs) are being developed and marketed.

Any laboratory diagnosis requires confirmation by the National Reference Laboratory or the OIE/EU reference laboratory by EU and OIE standard methods.

Material required for laboratory analysis

Samples of trachea, lung, intestine, CNS, blood ("acute sera") plus cloacal and tracheal swabs. Send moribund and dead birds for pathological investigation. Send samples cooled and well protected to avoid any leakage and any potential spread of the virus (see reference "Centro Regionale per l'Epidemiologia Veterinaria, 2000").

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Italy	See OIE reference laboratories		

Relevant diagnostic laboratories

Treatment

Usually not allowed by law. Amantadine has been used in birds but resistance is claimed to develop rapidly. Broad spectrum antibiotics, supportive therapy and increasing surrounding temperature (virus is less resistant to higher temperatures) may help to reduce mortality.

The officially recommended strategy of the WHO for domestic birds (WHO, 2006) is to cull, restrict movement of birds (“stand still”) and in some cases, to use preventive vaccination. See also EU Council Directive 2005/94/EC.

Prevention and control in zoos

National governments and the EU dictate general preventive and control measures, depending on the distance to the nearest outbreak and situation of the epidemic; frequent measures at present are housing of

susceptible birds inside of closed quarantine buildings at times of wild bird migration, stand still, and culling in the vicinity of an outbreak. For zoos, preventive vaccination is probably the most effective single measure, next to implementation of **general biosecurity measures** which are the first line of defense. Permits for preventive vaccination and exceptional quarantine measures can be requested and have been obtained in some cases and in certain EU countries. This is due to the fact that in 2005, the EU has officially changed its non-vaccinating strategy and exceptionally and explicitly permits protective vaccination of zoo birds (EU Council Directive 2005/94/EC). An inactivated H5N2 vaccine (Nobilis Influenza H5N2, Intervet) has been used in Singapore Zoo with promising results (Oh *et al.*, 2005); evaluation of the 2003 vaccination with an inactivated H7N1 vaccine (Nobilis Influenza H7N1, Intervet) in Dutch zoos resulted in 81.5% of birds developing a serum titre ≥40; vaccination efficacy seemed to depend on the taxonomic order and size of the bird species (Philippa *et al.*, 2005). An adaptation of the dosage for birds with higher body weight might be necessary. Nine German zoos which vaccinated zoo birds in 2003 with the same vaccine were informed of "negative haemaglutination inhibition(HI)" results before and "positive HI" results after vaccination (n=139). Several experimental vaccines have been developed and tested for their efficiency (Tian *et al.*, 2005, Capua *et al.*, 2003, Ellis *et al.*, 2004b, Quiao *et al.*, 2003).However, vaccination is not without problems and its use and the choice of the vaccine requires very careful consideration (Mettenleiter, 2005). The application of the DIVA vaccination strategy ("Differentiating infected from Vaccinated Animals") is considered in the 2005 EU Council Directive (EU Council Directive 2005/94/EC; Capua *et al.*, 2003, Capua & Marangon, 2003) and the risk assessment of the German National Reference laboratory on 04.03.2006 stated that evaluating vaccination against H5N1 of both domestic and zoo birds, the vaccination of zoo birds was the most viable option (FLI, 04.03.2006).

Other measures to be taken in zoos include (1) the segregation of animal species ("mixed exhibits"), especially of birds from mammals, (2) the reduction of food supply for wild birds which will reduce the potential risk of transmission from wild birds, (3) avoidance of direct contact between susceptible birds and public; other contacts with birds should be minimized and performed under adequate protective measures, (4) avoidance of the introduction of new birds into the collection, (5) permit only essential workers and suppliers on the premises, and control all suppliers, enterprises, and personnel for their contacts with potentially infected premises (*cave*: food suppliers are believed to have transferred the virus in The Netherlands and Germany in 2003, and journalists from wild birds to a poultry farm in France in early 2006), (6) cleaning and disinfecting all vehicles and equipment entering the premises and (7) quarantining of susceptible birds and animals in closed buildings in case of a nearby outbreak. Avoid feeding animals potentially infected meat/chicks.

In case of an outbreak inside the zoo: increase general biosecurity measures, complete isolation of the zoo, culling of all potentially infected birds according to official instructions, subdivide the zoo into epidemiological (quarantine) units, protect personnel by vaccination and preventive treatment with the appropriate antiviral drugs, report to authorities. Prepare for cases of human disease.

It is wise to implement all general measures of epidemiological control, like increased rodent control etc.

Suggested disinfectant for housing facilities

The use of disinfectants is regulated by national authorities and only specific disinfectants registered for use in HPAI outbreaks may be used (see also Appendix VI of EU Council Directive 2005/94/EC). Citric acid at 10% concentration –being effective and not costly- has been used as a preventive disinfectant during past HPAI outbreaks in Germany.

Notification

Any suspicion of HPAI has to be notified to the national veterinary authorities (OIE list A disease)

Guarantees required under EU Legislation

Guarantees required by EAZA Zoos

Measures required under the Animal Disease Surveillance Plan

Measures required for introducing animals from non-approved sources

Measures to be taken in case of disease outbreak or positive laboratory findings

First positive laboratory findings (usually performed by a local laboratory) need to be confirmed by haemaglutination inhibition (HI) test, which is specific for the haemaglutinin (H) involved. Only H5 and H7 strains with "genome sequences codifying for multiple basic amino acids at the cleavage site of the haemaglutinin site similar to that observed for other HPAI viruses" or "with an intravenous pathogenicity index in six-week old chickens greater than 1.2" are considered HPAI with the current EU-definition (EU Council Directive 2005/94/EC and OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, 2004).

It is suggested to subdivide the zoo into quarantine units with birds of different susceptibility housed separately. Clinically ill birds shed virus and therefore should be euthanised –with adequate protection of the

personnel.

Conditions for restoring disease-free status after an outbreak

This status can only be restored by the official veterinary service of the national government.

Contacts for further information

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