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1 **HIGHLY PATHOGENIC AVIAN INFLUENZA H5N1 VIRUS IN CATS AND OTHER**
2 **CARNIVORES**

3

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26

26

27 **Abstract**

28 The Asian lineage highly pathogenic avian influenza (HPAI) H5N1 virus is a known
29 pathogen of birds. Only recently, the virus has been reported to cause sporadic fatal disease in
30 carnivores, and its zoonotic potential has been dominating the popular media. Attention to
31 felids was drawn by two outbreaks with high mortality in tigers, leopards and other exotic
32 felids in Thailand. Subsequently, domestic cats were found naturally infected and
33 experimentally susceptible to H5N1 virus. A high susceptibility of the dog to H3N8 equine
34 influenza A virus had been reported earlier, and recently also HPAI H5N1 virus has been
35 identified as a canine pathogen. The ferret, hamster and mouse are suitable as experimental
36 animals; importantly, these species are also kept as pets. Experimental intratracheal and oral
37 infection of cats with an HPAI H5N1 virus isolate from a human case resulted in lethal
38 disease; furthermore, cats have been infected by the feeding of infected chickens. Spread of
39 the infection from experimentally infected to in-contact cats has been reported. The
40 epidemiological role of the cat and other pet animal species in transmitting HPAI H5N1 virus
41 to humans needs continuous consideration and attention.

42

42

43 **Introduction**

44 In 1997, the Asian lineage highly pathogenic avian influenza (HPAI) H5N1 virus spread
45 among poultry in Hong Kong and was directly transmitted to humans (Claas et al., 1998;
46 Webster et al., 2006). Then, after several years of silence, the virus re-emerged in Asia,
47 causing high-mortality outbreaks in poultry; in addition, it was responsible for acute
48 respiratory infection in human with lethality rates approaching 50% (Li et al., 2004). The
49 property of this virus to infect and kill mammals in addition to birds (Govorkova et al., 2005)
50 became particularly conspicuous during outbreaks in Thailand with many fatalities amongst
51 tigers, domestic cats and other felids (Kuiken et al., 2006a). This information did not
52 immediately alert the scientific community, and caused a stir only after decisive experiments
53 had proven the susceptibility of cats to a H5N1 virus isolated from a human case (Kuiken et
54 al., 2004; Rimmelzwaan et al., 2006). Earlier experiments with other human or avian
55 influenza (AI) A viruses had shown that the cat can be infected, but without clinical signs
56 (Hinshaw et al., 1981; Vahlenkamp and Harder, 2006). After the Asian endemics, two
57 outbreaks of AI in cats occurred in Europe in February/March 2006, on the Rügen isle,
58 Germany, involving three cats (Editorial team, 2006; Thomas Mettenleiter, personal
59 communication). In Graz, Austria, three cats were found infected in a rescue shelter by
60 demonstration of virus followed by seroconversion (Leschnik et al., 2007). These recent data
61 substantiate earlier reports (2004) of experimental HPAI H5N1 virus infection in household
62 cats in Thailand (Kuiken et al., 2006a; World Health Organisation, 2004). At least two
63 outbreaks of fatal disease in large felids, tigers and leopards, have occurred in Thailand
64 (Keawcharoen et al., 2004; Thanawongnuwech et al., 2005). Experimental infection with a
65 HPAI H5N1 virus isolated from a human case produced a highly lethal disease in cats
66 (Kuiken et al., 2004; Rimmelzwaan et al., 2006).

67
68 The current HPAI H5N1 viruses emerged from the Gs/Gd lineage isolated in China in 1996,
69 from which derived the virus that caused the first cases of human AI in Hong Kong in 1997
70 (Li et al., 2004). The continuous evolution of H5N1 virus through mutations, including
71 deletions and reassortment, gave rise to the dominant genotype Z in 2003 (Li et al., 2004;
72 Chen et al., 2006). Phylogenetic analyses of the haemagglutinin H5 gene revealed two
73 different lineages, also termed clades 1 and 2 (World Health Organization global influenza
74 program surveillance network, 2005). Clade 1 viruses were responsible for the regional
75 outbreak in Thailand, Vietnam, Cambodia and Malaysia where fatal human cases were
76 observed; and clade 2 spread in Indonesia and China, where several sublineages cocirculated.
77 One of those originated from lake Qinghai in China and spread in Asia and over Siberia to
78 Europe in 2005 (Chen et al., 2006). Reported mammalian (human and felid) cases of HPAI
79 H5N1 virus have been caused by clade 1 viruses in Vietnam (Amonsin et al., 2006) but
80 recently clade 2 virus infection was also demonstrated in a cat (Yingst et al., 2006). It is likely
81 that the 2006 European cat cases were also due to clade 2 viruses.

82
83 The recent emphasis on cat infections is understandable from the zoonotic perspective, but
84 other susceptible carnivores, like the ferret (Govorkova et al., 2005), have recently gained
85 popularity and become companion animals; the role of other household pets, like mice and
86 hamsters has been reviewed by Vahlenkamp and Harder (2006). Some thirty years ago, the
87 dog was recognized as infectable by H3N2 influenza A virus (Kilbourne and Kehoe, 1975-
88 1976), but without clinical significance. This changed only in recent years, when reports of
89 fatal cases due to H3N8 equine influenza A virus (Crawford et al., 2005) and HPAI H5N1
90 virus were published (Songserm et al., 2006b).

91

92 **Epidemiology**

93 At present, transmission of HPAI H5N1 virus to mammals only sporadically results in
94 disease. However, these infections are important because of their high morbidity and lethality
95 rates and zoonotic potential. The mammalian species shown to be naturally or experimentally
96 susceptible include man, non-human primates like the cynomolgus macaque, mouse, hamster,
97 pig, ferret, stone marten, dog, domestic cat, tiger, leopard and the civet (Choi et al., 2005; Gao
98 et al., 1999; Govorkova et al., 2005; Keawcharoen et al., 2004; Kuiken et al., 2004, 2006a;
99 Maines et al., 2005; Rimmelzwaan et al., 2001; Songserm et al., 2006b; Vahlenkamp and
100 Harder, 2006; Zitzow et al., 2002).

101
102 Apart from the cat, only ferrets transmit HPAI H5N1 virus within their own populations and,
103 as pets, could possibly also infect humans; upon experimental infection, these animals excrete
104 large amounts of virus (Govorkova et al., 2005; Vahlenkamp and Harder, 2006). In Asia,
105 HPAI H5N1 virus has been occasionally transmitted from birds to pigs, but this species seems
106 to be a dead-end host experiencing only subclinical infections (Choi et al., 2005).

107
108 Most prominently, felids suffer from H5N1 virus infections under natural conditions, and
109 their susceptibility has been confirmed in laboratory experiments. Chronologically and
110 geographically, AI in felids was correlated with outbreaks in poultry in Asia (Keawcharoen et
111 al., 2004; Songserm et al., 2006a) and with diseased aquatic wild birds in Europe (Editorial
112 team, 2006; Thomas Mettenleiter, personal communication; Leschnik et al., 2007).

113 Sometimes they led to small endemics, as observed in household cats and tigers in Thailand
114 (Kuiken et al., 2006a; Thanawongnuwech et al., 2005). Horizontal transmission is likely to
115 occur in such situations, but most affected animals are infected by direct or indirect contact
116 from a common source, namely infected birds. Cats, tigers and leopards can be infected by

117 eating infected birds, swans, goose, chicken or pigeons (Editorial team, 2006; Keawcharoen et
118 al., 2004; Rimmelzwaan et al., 2006; Songserm et al., 2006a). Indirect transmission could also
119 occur by passive virus carriage in the fur of a cat that had been in contact with infected birds'
120 faeces (Leschnik et al., 2007). Furthermore, infection can be transmitted from infected to in-
121 contact cats or tigers through contaminated saliva, urine and faeces (Kuiken et al, 2004,
122 Thanawongnuwech et al., 2005). Cat-to-cat transmission may depend on the level of virus
123 excretion: it is assumed to be higher in Thai tigers and in experimentally infected cats, both
124 having been exposed to high infectious doses (Kuiken et al., 2004; Thanawongnuwech et al.,
125 2005) than under the conditions in Europe (Leschnik et al., 2007).

126

127 **Pathogenesis**

128 It is still unknown which is the most efficient route of infection. Oral infection can be
129 suspected after feeding infected raw chicken but respiratory infection cannot be completely
130 ruled out by this way. Both routes can be suspected upon cat-to-cat virus transmission. Virus
131 has repeatedly been isolated from saliva, the trachea and intestinal contents as well as from
132 urine and faeces of infected cats (Rimmelzwaan et al., 2006; Songserm et al., 2006a; Yingst et
133 al., 2006). It is therefore assumed that first replication takes place in the upper respiratory and
134 digestive tracts. The virus is propagated in the lower respiratory tract after infection of type II
135 pneumocytes that line the alveoli (van Riel et al., 2006); replication in the lung leads to foci of
136 alveolar damage. The virus eventually reaches the liver, heart, brain, renal glomeruli, adrenal
137 gland and sometimes the spleen and pancreas (Rimmelzwaan et al., 2006; Songserm et al.,
138 2006a); it has also been found in the large intestine (Yingst et al., 2006). Infection of internal
139 organs suggests systemic spread through viraemia, but so far no virus has been isolated from
140 blood (Rimmelzwaan et al., 2006). Multifocal haemorrhages and necroses are found in

141 different infected organs, which - together with the extended pulmonary damage - are
142 responsible for acute death (Keawcharoen et al., 2004).

143

144 A peculiar feature is a ganglio-neuritis of the intestinal plexus nervosus that could be
145 explained by infection of submucosal tissues from the intestinal lumen (Rimmelzwaan et al.,
146 2006). A non-suppurative encephalitis is observed in infected cats, which explains the
147 neurological signs observed in natural cases (Keawcharoen et al., 2004; Rimmelzwaan et al.,
148 2006).

149

150 Clinical signs appear after a short incubation period, when the virus had multiplied in the
151 primary and secondary replication sites. In clinically affected cats, virus excretion starts by
152 day 3 after infection and persists until day 7 after infection or longer (Rimmelzwaan et al.,
153 2006).

154

155 Subclinical infections have been identified in cats after contact with a dead swan, probably
156 after exposure to a low infectious dose of virus. These cats, in a shelter in Graz, Austria,
157 experienced a limited upper respiratory infection, as pharyngeal swabs were virus-positive
158 whereas rectal samples remained negative (Leschnik et al., 2007).

159

160 **Clinical signs**

161 The incubation period ranges from 2 days (as assessed in experimentally infected cats) to 3
162 days in large felids. In cats and tigers, the clinical signs are fever, decreased activity,
163 protrusion of the nictitating membrane, conjunctivitis and laboured breathing (Kuiken et al.,
164 2004). Serosanguinous nasal discharge and icterus in case of diffuse haemorrhagic lesions
165 can be observed (Thanawongnuwech et al., 2006; Rimmelzwaan et al., 2006). In severely

166 affected cats, sudden deaths may occur as soon as 2 days after the onset of illness (Songserm
167 et al., 2006a). Nervous signs including convulsions and ataxia are consistent with the brain
168 lesions (Songserm et al., 2006a). Subclinical infections also occur, as evidenced by the cases
169 in the animal shelter in Graz, Austria.

170

171 **Diagnosis**

172 A HPAI H5N1 virus infection can be suspected when high fever and acute respiratory distress
173 is seen in cats that have access to outdoors, and when this virus had affected poultry and/or
174 aquatic wild birds in the region. The clinical signs are not pathognomonic and may be taken
175 for the feline upper respiratory disease syndrome, caused by feline herpesvirus and
176 calicivirus, or for a bacterial pneumonia (due to *Bordetella bronchiseptica*, *Chlamydomphila*
177 *felis*, *Mycoplasma*). Feline infectious peritonitis may also lead to respiratory signs but the
178 disease course is rather subacute. Immunodeficiency caused by feline immunodeficiency
179 virus and immunodepression provoked by feline leukaemia virus also facilitate secondary
180 respiratory infections. It is therefore important to correlate the clinical signs observed in cats
181 with the epidemiological situation of HPAI H5N1 virus infection in birds in the region.

182

183 At necropsy, multifocal lung lesions and petechial haemorrhages in the lungs, heart, thymus,
184 stomach, intestine, tonsils, mandibular and retropharyngeal lymph nodes and liver, as well as
185 a haemorrhagic pancreatitis are seen macroscopically (Keawcharoen et al., 2004; Yingst et al.,
186 2006). Microscopically, the lesions are characterized by inflammation and necrosis. In large
187 felids, thrombocytopenia, haemorrhagic lesions in the lung and encephalitis characterised by
188 multifocal infiltration by neutrophils and macrophages have been reported (Keawcharoen et
189 al., 2004).

190

191 The virological diagnosis *in vivo* is made on oropharyngeal, nasal and rectal swabs or faecal
192 samples. At necropsy, affected organs, intestinal content and pleural fluid are sampled. After
193 nucleic acid extraction, a RT-PCR is performed using primers designed to identify the
194 haemagglutinin and neuraminidase genes (Keawcharoen et al., 2004) as well as the
195 nucleocapsid gene (Amonsin et al., 2006). H5N1 virus antigens are identified by
196 immunohistochemistry on sections of affected organs, using a monoclonal antibody specific
197 for the nucleocapsid of influenza A virus (Keawcharoen et al., 2004; Rimmelzwaan et al.,
198 2006); a polyclonal goat antiserum against H5N1 virus has also been used (Songserm et al.,
199 2006a). Virus isolation follows the influenza virus protocol of inoculating tissue homogenates
200 into the allantoic sac of embryonated chicken eggs (Keawcharoen et al., 2004; Songserm et
201 al., 2006a). For identification, RT-PCR can be applied on the isolated virus. In subclinical
202 cases, serological diagnosis is performed using the haemagglutination inhibition assay (World
203 Organisation for Animal Health, 2004).

204

205 **Control and vaccination**

206 Highly pathogenic avian influenza H5N1 virus infection of the cat and other pet carnivores
207 could be controlled by preventing any contact with affected poultry or wild birds. The
208 European Commission has therefore recommended to keep cats indoor in the areas where
209 cases of HPAI H5N1 virus were recorded in poultry or wild birds (Anonymous, 2006;
210 Council of the European Union, 2006).

211

212 When HPAI H5N1 virus infection is suspected in a cat, the veterinary practitioner must take
213 measures to minimise the risk of transmission, like avoiding direct physical contact with the
214 cat by wearing gloves, mask and goggles. The suspected cat is kept in isolation in a cage.
215 Surfaces are decontaminated using a household detergent or standard medical disinfectant.

216 The owner and his relatives are instructed to minimise contacts with the cat and about the
217 disinfection of litter trays, drinking bowls, etc. Detailed measures have been published by the
218 European Advisory Board on Cat Diseases (2006) and can be consulted at [http://www.abcd-](http://www.abcd-vets.org/guidelines/)
219 [vets.org/guidelines/](http://www.abcd-vets.org/guidelines/).

220

221 Antiviral treatment with Oseltamivir (Tamiflu Roche, Basel, Switzerland) has been tried at a
222 dose of 75 mg/60 kg, twice daily in healthy tigers (Thanawongnuwech et al., 2005). The
223 dosage was obtained by extrapolating from human use, but evidence of protection was not
224 obtained. The bioavailability of Oseltamivir may vary with the animal species: indeed, the
225 effective dose in mice is 5x that of that in humans (Ward et al., 2005).

226

227 It can be debated whether there is a place for the vaccination of cats against HPAI H5N1
228 virus. An experimental challenge protocol has been established, and the safety and efficacy of
229 such vaccines could be tested in cats (Kuiken et al., 2004; Rimmelzwaan et al., 2006). In a
230 pilot experiment, the fowlpox virus vector Trovac expressing the H5 gene of AI virus induced
231 high levels of antibodies to the homologous haemagglutinin. The serological response rose as
232 early as one week after one vaccination, and a booster allowed cats to develop antibodies
233 cross-reacting with a recent, HPAI H5N1 Asian isolate (Karaca et al., 2005). Another vector,
234 based on canine adenovirus 2 expressing the H5 haemagglutinin of a tiger isolate, was able to
235 induce an antibody response in a cat (Gao et al., 2006).

236

237 **Conclusions**

238 Acute AI in cats is the consequence of an efficient crossing of the host barrier to infect a
239 susceptible species (Kuiken et al., 2006b). Contacts between birds and cats are a precondition
240 for transmission and have occurred on different continents. Although the epidemiological

241 situations are quite different in Asia and Europe, the same pattern was observed, the incidence
242 in cats being indeed proportional to the prevalence of infected birds. The sporadic cat-to-cat
243 transmission of HPAI H5N1 virus allowed some prediction to be made. In the putative case of
244 a human epidemic, the cat could play a role in virus transmission to other cats, other pet
245 animals, like ferrets, mice and hamsters, and to their owners (Kuiken et al., 2006a). In such an
246 epidemiological situation, infections of exotic felids in zoological gardens, safari parks and
247 circuses can also be expected. It is obviously unknown to what extent felids will play a role in
248 the epidemiology of the infection.

249
250 The high susceptibility of cats must be balanced against the discovery of subclinical
251 infections in the Austrian cases (Leschnik et al., 2007). These could be related to low
252 infectious doses that are insufficient to reach the lower airways and cause an acute illness.

253 The lower respiratory infection induced by HPAI H5N1 virus in cats could serve as an
254 experimental model to investigate the human infection, which appears to have a similar
255 pathogenesis (van Riel et al., 2006).

256
257 Other susceptible carnivores should not be disregarded in epidemiological considerations,
258 especially the ferret, which is becoming increasingly popular as a companion animal species.

259 More information will certainly become available about the infection of dogs with HPAI
260 H5N1 virus; recently a fatal canine disease case has been reported from Thailand (Songserm
261 et al., 2006b).

262

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267

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