COMMENTARY

Is it safe to put the cat among the chickens?

Feline friend or potential foe?

What role do cats play in the epidemiology of H5N1 avian flu virus? We don't yet have all the answers, but it's time to consider new precautions, argue **Thijs Kuiken**, **Albert Osterhaus**, **Peter Roeder** and their colleagues.

There are increasing numbers of reports from Asia and Europe of domestic cats dying from avian influenza H5N1 virus. The available evidence, albeit incomplete, suggests that cats are more than collateral damage in avian flu's deadly global spread and may play a greater role in the epidemiology of the virus than previously thought. Here we recommend that new precautions are taken by nations and agencies fighting avian flu to minimize the risk of cats becoming infected and spreading the highly pathogenic virus to poultry, humans and other species.

The first report of domestic cats dying from H5N1 virus infections was in February 2004, when 14 out of 15 cats in a household near Bangkok, Thailand, became weak, started vomiting and coughed up blood before dying. One of the cats had eaten a chicken carcass on a farm where there was an H5N1 virus outbreak. The presence of H5N1 virus was confirmed in three of the cats following necropsies at Kasetsart University in Bangkok, Thailand[1]. Subsequent experiments in The Netherlands, by some of us, have experimetally confirmed the severity of H5N1 virus infections in cats[2] — with all eight cats exposed to the virus going on to develop the disease.

The jury's out

The 2004 outbreak in domestic cats showed striking similarities with an incident that occurred three months previously at a zoo in Suphanburi, Thailand, during a local outbreak of H5N1 virus infection in poultry. At this zoo, two tigers and two leopards died suddenly after feeding on fresh chicken carcasses. The probable cause of death was diagnosed as severe pneumonia due to H5N1 virus infection[3]. Also in 2004, there was a second outbreak of H5N1 virus infection at another zoo in Thailand, again involving consumption of virus-infected chicken. This time, a total of 147 tigers died or were killed[4]. These reports were surprising because both domestic cats and wild felids were considered to be resistant to disease from influenza A virus infection, of which H5N1 is a subtype.

Despite these unexpected events, the possible role of cats in the epidemiology of H5N1 virus infection has been largely overlooked by the human- and animal-health communities. As recently as 28 February 2006, a World Health Organization (WHO) press release[5] stated: "There is no present evidence that domestic cats play a role in the transmission cycle of H5N1 viruses." A March press release[6] from the World Organisation for Animal Health (OIE) stated: "The OIE stresses that as of today, all the natural cases in felines have not led to any change in the epidemiology of the disease that has fundamentally remained a bird disease, nor have they led to any recognized virus change in epidemiology or mutation leading to an increased virulence of the virus for felines or other mammals."

There are now several observations indicating a greater role for domestic cats than these cautious statements suggest. First, it has become evident that fatal infections among cats are common in countries such as Indonesia, Thailand and Iraq, where the virus seems to be endemic in poultry. For example, veterinarians conducting an epidemiology programme with the participation of the Food

and Agricultural Organization (FAO), recently reported a high incidence of sudden death among cats during fatal poultry outbreaks in several villages in Indonesia. The disease in cats is well-recognized by poultry keepers and is considered to be linked to the poultry disease. It is sufficiently well-known to have been given an onomatopoeic name in the local Javanese dialect — 'aargh-plop'[7].

Second, veterinarians in Iraq combating H5N1 virus outbreaks in poultry in collaboration with the FAO also report widespread and high mortality in cats, confirmed to have been caused by this virus. Third, dead or moribund cats were found to be infected with H5N1 virus soon after the virus was detected in wild birds in Germany. This suggests not only that H5N1 virus can be transmitted from wild birds to cats, but also that unusual mortality of cats in areas at risk of H5N1 virus infection may act as an early warning signal for the virus. Given the high number of infected cats in these areas, and considering their ability to excrete virus into their surroundings in sufficient quantities that transmission between cats takes place under both natural and experimental conditions (see below), cats could be more than a dead-end host for H5N1 virus.

"Cats may be involved in helping the virus to adapt to efficient human-to-human transmission."

An incomplete picture

What scientific data on H5N1 virus infection in cats are currently available? There are so far three publications[2,8,9] reporting experimental studies, all conducted at the Erasmus Medical Centre in Rotterdam, The Netherlands. Laboratory cats infected with H5N1 virus[2,8] by the respiratory tract (three in total), by feeding on virus-infected chicks (three), or through close contact between infected and non-infected cats (two) all excreted virus from the pharynx, nose and rectum. Excretion lasted from three days post-infection until the end of the experiment on day seven, when the cats were killed. The amount of excreted virus recorded from cats was much lower than the levels excreted by chickens.

Clinical signs were observed several days earlier in cats infected by direct respiratory and oral routes, than by cat-to-cat transmission. The signs included raised body temperature, decreased activity, conjunctivitis and laboured breathing. One of the cats died at day six. In some cats, virus excretion started before clinical signs were noted. Post-mortem examination demonstrated multiplication of the virus not only in the respiratory tract[2], but also in a number of other organs[8]. The presence of virus in most tissues was associated with cell death and inflammation. Viral infection in the nervous tissues of the intestinal wall was found only in cats fed on virus-infected chicks. This suggests that the virus reached these tissues directly from the guts — a novel route of entry for influenza virus in mammals.

Another recent paper of ours[9] shows that H5N1 virus attaches abundantly to the cells lining the lungs of domestic cats, but not to those in upper parts of the respiratory tract. This pattern of H5N1 virus attachment closely mirrors that in the human respiratory tract, identifying the cat as a suitable model for viral pneumonia caused by H5N1 in humans. Some of the above findings, such as infection by feeding on virus-infected chicken carcasses, transmission of H5N1 virus between cats and infection of extra-respiratory tissues, were also observed in the H5N1 virus outbreaks in tigers and leopards and in a naturally infected domestic cat[3,4,10].

Although the above data shed some light on the epidemiology, major gaps in our knowledge still remain. Most important, we do not know the minimal infectious dose for cats by either the oral or the respiratory route, how long cats excrete virus from the digestive and respiratory tracts, whether cats can excrete virus without developing clinical signs, and whether virus transmission from cats to poultry, humans and other species is possible. In the absence of these data, it is difficult to assess the overall risk posed by infected cats.

Apart from the role that cats may play in H5N1 virus transmission to other species, they also may be involved in helping the virus to adapt to efficient human-to-human transmission. H5N1 virus is basically an avian pathogen, and although humans can be infected, evidence for further spread of the virus among humans is rare. In the few suspected cases[11], it seems that close physical contact, for example between mother and child without the use of precautions such as gloves, nose-mouth masks, or antiviral treatment, was responsible. We have previously suggested that cats may provide the virus with an opportunity to adapt to efficient transmission within and among mammalian species, including humans, thereby increasing the risk of a human influenza pandemic[2]. Although our preliminary data from experimentally infected cats do not reveal important mutations in excreted viruses, at least within the haemagglutinin gene (the 'H' in H5N1), such mutations cannot be ruled out.

"The potential role of cats should be considered in official guidelines for controlling the spread of H5N1 virus."

Time for action

Collectively, the data so far show that domestic cats can become infected by contact with domestic or wild birds and possibly their droppings, develop severe to fatal disease, excrete the virus from the respiratory and digestive tracts, and transmit the infection to other cats. Consequently, these data indicate a possible role for cats in the epidemiology of H5N1 virus in poultry, humans and other species.

Despite the uncertainties, we believe that the potential role of cats should be considered in official guidelines for controlling the spread of H5N1 virus infection. Most international guidelines currently lack such considerations. In areas where H5N1 virus has been detected in either poultry or wild birds, we recommend taking steps to prevent contact between cats and infected birds or their droppings, and to quarantine and test cats suspected of such contacts, or cats showing clinical signs suggestive of H5N1 influenza. In most urban areas and in temperate climate zones, where most felids are domestic cats, prevention of contact could be achieved by keeping cats indoors. In other parts of the world, such measures may be more difficult, if not impossible, to implement.

Finally, we now know that H5N1 virus has the ability to infect an unprecedented range of hosts, including carnivores. In addition to felids, we can expect other domestic and wild carnivores, such as dogs, foxes, mustelids and seals, to be vulnerable to infection with H5N1 virus and to contribute to its epidemiology. Accordingly, we recommend increasing surveillance in areas where H5N1 virus is endemic, to include testing for H5N1 virus infections in felids and other carnivores showing unusual morbidity or mortality.

Only last month, H5N1 virus infection was detected in Germany in yet another mammalian species: a stone marten, belonging to the family Mustelidae. A nocturnal predator, the marten is presumed to have acquired its infections after feeding on a diseased bird. A WHO press release responding to this report states: "To date, only domestic poultry are known to have played a role in the transmission cycle of the virus from animals to humans." But given the potential contribution of these carnivore hosts to both virus transmission and its adaptation to mammals, we believe the time for increased surveillance and precaution is here. ■

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