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LETTER

Cats as a potential source of emerging influenza virus infections

Dear Editor,

Historically, the influenza virus has not been regarded as a major pathogen of cats. However, since 2003, natural infections of domestic cats with highly pathogenic H5N1 avian virus causing fatal cases have been reported (Songserm et al., 2006; Yingst et al., 2006; Klopfleisch et al., 2007). Furthermore, infections of this animal with A (H1N1) pdm09 virus, causing respiratory illness with some fatal cases, have also been reported in various parts of the world (Fiorentini et al., 2011; Campagnolo et al., 2011; Pigott et al., 2014). These reports revealed that cats are susceptible to influenza A viruses, resulting from bird-to-cat or human-to-cat transmission, and were supported by the detection of several virus subtypes in domestic cats through serological studies (McCullers et al., 2011; Ali et al., 2011; Zhao et al., 2014; Su et al., 2013). In other reports, the H3N2 dog virus was also transmitted to cats in Korea and China, causing respiratory illness (Song et al., 2011; Lei et al., 2012). These findings provide further evidence that cats should be included among the animals that are responsible for interspecies transmission of influenza A virus. Moreover, the findings of these reports suggest that cats may play a role as an intermediate host in which a mutant virus with pandemic potential could emerge. To validate this possibility, here we conducted a serological survey of human and avian influenza virus infections in cats, from either H5N1 virus-endemic or non-endemic areas.

We used a total of 15 serum samples, which were collected from stray cats between April 2010 and February 2012, most of which roamed in the markets where birds are sold on Java Island, Indonesia, which has been an H5N1 virus-endemic area since 2005. Additionally, we tested sera from another group of cats (26 samples), collected from in-door, domestic cats at animal hospital in Kanagawa Prefecture, Japan between April 2009 and July 2010. H5N1 viruses have never been detected before in wild birds, poultry, and mammals including human in this prefecture. The cats were brought to the hospital with various symptoms, and their serum samples were randomly collected for the study with the pet owner's permission. To detect antibodies specific to influenza viruses in the sera, we performed a standard virus-neutralization (VN) test (Horimoto et al., 2011) with human viruses (former seasonal H1N1 virus, seasonal H3N2 virus, A (H1N1) pdm09 virus, and influenza B virus) and H5N1 highly pathogenic avian viruses, after receptor-destroying enzyme treatment (RDEII: Denka) and heat-inactivation (56 °C, 30 min) of the sera to remove non-specific inhibitors. VN antibody titers ≥ 16 were considered positive reactions, because sera with these titers could specifically react to the same viral antigens in an immunoblot assay, confirming the reaction specificity (Horimoto et al., 2011).

In these VN assays, 2 sera (#CP1 and #CP2) of Indonesian cats were positive for the H5N1 virus-specific VN antibody, representing 13.3% positivity (Table 1), although the number of cats tested in the present study may be statistically insufficient to show the exact seroprevalence. VN cross-reactivities to a panel of H5N1 viruses belonging to different clades or subclades revealed that both sera reacted with the highest titers to clade 2.1.3 viruses isolated in Indonesia in 2010, confirming that these stray cats must be infected with the H5N1 virus that spreads endemically in this country. Two H5N1 virus-seropositive cats were found to be roaming in the same market in Jakarta, suggesting that the virus was transmitted to them from the infected poultry, brought into the market from backyard farm, and also that cat-to-cat transmission could occur. Although previous studies including experimentally induced infection (Küiken et al., 2004; Vahlenkamp et al., 2010) showed that H5N1 is a highly pathogenic virus causing systematic infection in cats, asymptomatic or disease-recovered infection was also suggested in another report (Leschnik et al., 2007). The 2 seropositive cats identified in this study fell into the latter category. Notably, another serum sample (#GD7) was positive for VN antibody to A (H1N1) pdm09 virus, albeit a weak reaction, which suggested a human-to-cat transmission of the human virus.

In contrast, sera obtained from Japanese cats were not positive for the VN antibody specific to H5N1 virus; however, 2 sera (#210 and #213) were positive for VN antibody specific to human viruses; one positive for the seasonal H3N2 virus and the other positive for A (H1N1) pdm09 virus. However, none of these seropositive cats showed any typical signs of acute respiratory illness according to the clinical records, suggesting that they were asymptomatic or had minor infections. Nevertheless,

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Table 1. Cats seropositive of VN antibodies to influenza viruses.

Country	Sample #	Collection time	Location	Virus										
				H1N1	H1N1 pdm	H3N2	H5N1 cl.1	H5N1/05 cl.2.1.3	H5N1/10 cl.2.1.3	H5N1 cl.2.2	H5N1 cl.2.3.2.1	H5N1 cl.2.3.4	H5N1 cl.2.5	B
Indonesia	GD7	March 2010	Bandung	< 16	16	< 16	ND	< 16	< 16	ND	< 16	ND	< 16	< 16
	CP1	April 2010	Jakarta	< 16	< 16	< 16	< 16	256	512	128	16	128	256	< 16
	CP2	April 2010	Jakarta	< 16	< 16	< 16	< 16	32	64	32	< 16	16	64	< 16
Japan	210	June 2009	Kanagawa	< 16	< 16	32	ND	ND	ND	< 16	ND	ND	ND	< 16
	213	August 2009	Kanagawa	< 16	16	< 16	ND	ND	ND	< 16	ND	ND	ND	< 16

Following influenza virus strains were used for VN test; H1N1, A/Kawasaki/UTK4/09; H1N1pdm, A/Osaka/364/09; H3N2, A/Kawasaki/UTK20/08; H5N1 clade 1, A/Vietnam/1194/04; H5N1 clade 2.1.3, A/Indonesia/3006/05 and A/chicken/East Java/UT551/10; H5N1 clade 2.2, A/whooper swan/Mongolia/4/05; H5N1 clade 2.3.2.1, A/Tundra swan/Tottori/12-002/10; H5N1 clade 2.3.4, A/Hanoi/30850/05; H5N1 clade 2.5, A/chicken/Yamaguchi/8/04; and influenza B virus, B/Tokyo/UT-E2/08. ND: not determined.

human-to-cat transmission of the human virus likely occurred in these in-door pet cats, as reported in other countries (Campagnolo et al., 2011; Pigott et al., 2014).

Based on the findings of the present study, we conclude that cats can be infected with human influenza viruses as well as avian influenza viruses. Actually, the recent study has shown that both human-type (α2,6-linked sialic acid) and avian-type (α2,3-linked sialic acid) influenza virus receptors were extensively detected in the respiratory organs such as trachea, bronchus, and lung of the domestic cats (Wang et al., 2013). Therefore, cats may act as a vector for human influenza virus transmission within households, posing a potential public health concern. Furthermore, we detected both H5N1 and human virus-seropositive cats in neighboring areas at similar sampling times, suggesting that cats can be simultaneously infected with both avian and human viruses in H5N1 virus-endemic areas. Thus, cats, like pigs, may act as an intermediate host for the emergence of new, potentially pandemic viruses. Although our study was a small-scale surveillance of influenza virus infections in cats, these findings evidence the need for continued and large-scale surveillance of influenza viruses in cat populations will be important to achieve the "One Health" concept for this zoonotic disease.

FOOTNOTES

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