

## Is H9N2 avian influenza virus a pandemic potential?

To the Editor:

H1N1 and H3N2 influenza virus subtypes continue to cause human disease (1,2), while avian influenza A H5 and H7 subtypes spread globally among birds with limited an inefficient transmission to humans (3,4). Results from recent ferret research on the H9N2 subtype has demonstrated an increased theoretical threat to humans from the potential emergence of novel subtypes of avian influenza.

In North America, there is no evidence of fixed lineages of the H9N2 avian influenza virus in land-based poultry; it is found in wild ducks and shore birds (5). In contrast, H9N2 remains endemic across Asia, mainly limited to outbreaks in domestic land-based poultry, but overshadowed as a pandemic threat by H5N1 bird flu, which has spread from Asia into Africa and Europe (6-9). However, there is evidence of interspecies transmission of H9N2 from land-based poultry to mammals, such as pigs and swine (10-13). Further evidence of an expanded mammalian host range includes efficient replication of H9N2 in mice without adaptation (14). H9N2 has already caused mild respiratory disease in humans in Hong Kong and mainland China in 1999 and 2003 (10,13,15,16). The six genes encoding the internal components of the H9N2 virus are similar to those found in a previous 1997 outbreak of H5N1 that caused several human deaths in Hong Kong (15). Furthermore, circulating H9N2 strains show human-like receptor specificity with amino acid leucine at position 226 at the receptor-binding site of human airway epithelial cells cultured in vitro (17). H9N2 isolated from live bird markets in Hong Kong possessed receptor specificity similar to human H3N2 viruses (18) and mutations similar to human H2N2 and H3N2 viruses, so the glycoproteins of the Hong Kong H9N2 viruses may potentially promote human infection.

In a ferret model of transmission (9), the H9N2 avian reassortment subtype appears to be evolving. The H9N2 virus replicates in the respiratory tract of ferrets and can spread to noninfected ferrets (9). The amino acid leucine residue located at position 226 in the hemagglutinin receptor-binding site (instead of glutamine), plays a key role in human virus-like receptor specificity, and promotes transmission of the H9N2 virus in ferrets. Airborne transmission has not been detected. Mixing the H9N2 viral genes containing the surface glycoprotein and the six internal genes of a human H3N2 virus resulted in increased transmissibility. The model and reassortment mixing results raises concern about viral

evolution as well as efficient pandemic transmission, and suggests that the H9N2 avian virus could be of pandemic importance (19). To conclude that H9N2 is the next human pandemic strain is premature at this time given the unfolding evidence. Yet, the possibility for competent nonavian intermediate reassorters generating novel and virulent pandemic strains of H9N2 (or other avian influenza strains) has increased given the recent raccoon influenza transmission findings (20). Additional study and timely surveillance of H9N2 is needed to identify any increments in viral adaptation to human beings. Studies should consider the widespread prevalence of the H9N2 virus in poultry, and co-circulation and mixing of avian H9N2 with human H3N2, H5, H7 and other avian and mammalian viruses.

**NOTE:** The conclusions drawn are those of the authors and not of their organizations.

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## LETTER TO THE EDITOR

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