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Perspective

## Will influenza A(H3N8) cause a major public health threat?

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## ABSTRACT

The diversity of zoonotic influenza viruses and their ability to cross the species barrier has always been alarming and requires continuous surveillance in both human and animal populations. Avian A(H3N8) influenza viruses are frequently detected in animals and represent one of the most common subtypes in wild birds. Cross-species transmission of avian A(H3N8) influenza viruses has been reported for multiple mammalian hosts, including the outbreaks in horses and dogs by the equine and canine lineages of A(H3N8), respectively. In humans, there was no evidence of influenza A(H3N8) infection until 25 April 2022, when the Chinese health authority reported the first-ever human H3N8 case in a 4-year-old boy from Henan province. Although there is no information that this virus can sustain human transmission, additional epidemiological and virological studies are needed to better assess the replication potency of the virus in human cells as well as the risk posed to public health. In this study, we briefly discuss the influenza A(H3N8) interspecies transmission of the virus, with emphasis on human transmission.

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## Introduction

Since the start of the COVID-19 pandemic, influenza has recorded the lowest numbers in decades worldwide. Currently, two subtypes of influenza A (H1N1 and H3N2) and two influenza B lineages (Victoria and Yamagata) are circulating in the human population. H2N2 is another influenza subtype that circulated in humans between 1957 and 1968, causing the Asian flu pandemic. All three subtypes (H1, H2, and H3) originated from birds, resulting in three pandemics that claimed the lives of millions of people. In addition, sporadic cases with other subtypes, specifically H5, H6, H7, and H9, are reported from time to time. Most of these cases are reported in individuals who work in close contact with infected birds. The latest sporadic case was reported on April 28, 2022, when the Centers for Disease Control and Prevention confirmed the detection of the first avian influenza A(H5) virus case in the US, in a person who had direct exposure to poultry ([Case of Human Avian Influenza AH5 Virus Reported, 2022](#)). So far 863, one, 1568, and 74 cases, have been reported worldwide for H5, H6, H7, and H9 respectively, with a fatality rate ranging from 2.7% to 53% for H9 and H5, respectively ([Reported Human Infections with Avian Influenza A Viruses, 2022](#)). Fortunately, none of these subtypes has gained the ability to sustain human-to-human transmission, although sev-

eral studies have identified mutations that might promote better transmission among humans. Swine also harbor viruses (H1 and H3) that may infect humans, one of which was the origin of the latest H1N1 2009 pandemic.

## Influenza A(H3N8) in humans

China reported the first-ever human infection with H3N8 in a 4 year old boy from the Henan province on April 27, 2022. This raised a major public health concern worldwide. Similar to the previously mentioned scenario, the boy had been in contact with chickens and crows raised at his home. None of the patient's close contact was infected with the virus, providing a relief sign for public health officials. The boy developed flu-like symptoms before getting hospitalized 10 days after the onset of the symptoms. Of interest, H3N8 is known to infect horses (equine influenza), dogs (equine origin), and seals in addition to waterfowls which are the natural reservoir of the virus ([He et al., 2019](#)). The equine influenza lineages seem to have diverged from avian influenza lineages of the same subtypes ([Chambers, 2022](#)). Hence, this subtype, in particular, has shown flexibility to cross the species barrier and infect mammals, which raises public health concerns.

More importantly, according to the sequence analysis of the hemagglutinin (HA) protein, the sequence of the HA from the recent human H3N8 virus was found to be most closely related to avian H3 sequences. Amino acid sequence comparison of the HA

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## Ethical approval statement

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## Author contributions

HMY designed and study. MKS did the analysis and wrote the first draft of the manuscript. HMY read and approved the final draft.

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