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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.

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 several 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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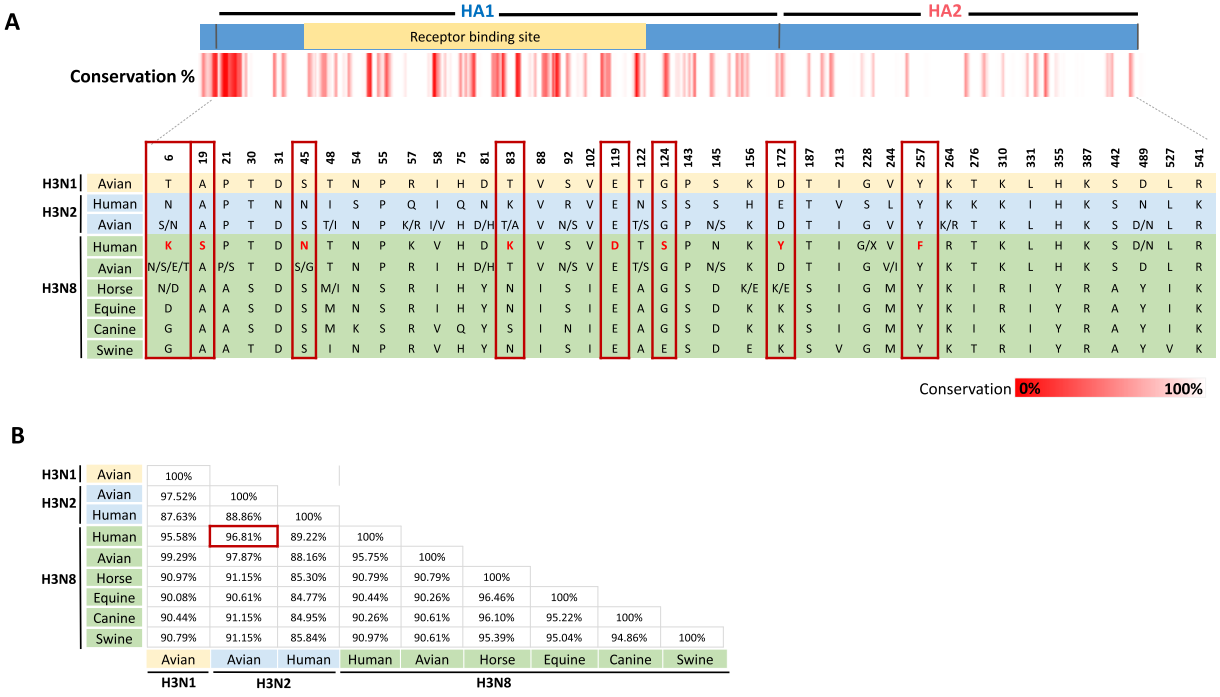

Figure 1. Comparison of the full-length HA protein sequence of the human H3N8 with the HA form H3N1, H3N2, and other H3N8 viruses. (a) Summary of selected unique aa that are present in different H3 hosts: Representative protein sequences (n = 142) from H3N1 (avian), H3N2 (avian and human), and H3N8 (human, avian, horse, equine, canine, and swine) were obtained from the Influenza Research Database and Global initiative on sharing all influenza data. Alignment was done using CLC software. The highest similarity was found between the HA from human H3N8 and avian H3N2, which differed at only eight aa sites (marked with red borders). A representation of cross-species sequence conservation of the full-length H3 is shown at the top. (b) Similarity statistics of H3 from different influenza strains and hosts. Protein sequences (n = 142) from H3N2 (avian and human), H3N1 (avian), and H3N8 (human, avian, horse, equine, canine, and swine) were aligned separately and the consensus sequence of each group was used to calculate the similarity index (SIAS tool, provided by UCM).
aa, amino acids; HA, hemagglutinin

from human H3N8 with that from H3N2 (avian and human), H3N1 (avian), and other H3N8 viruses (avian, horse, equine, canine, and swine) is presented in Figure 1a. Sequence similarity index of the HA amino acid sequences from different H3 hosts is shown in Figure 1b.

Influenza-like illnesses have been reported in horses since the 1870s. However, the first actual isolation of the H3N8 from horses was in the mid-1950s. The capacity of H3N8 transmission from horse to dog has been reported on several occasions. However, its transmissibility to humans has been debatable. In 1965, seroarchaelogical studies revealed the presence of reactive antibodies to H3N8 in an elderly population, whose exposure must have occurred around 1890, hypothesizing that H3 had entered humans from horses to cause the 1889 (or 1896) human influenza pandemic. Notably, the antigen used in these studies was of equine H3N8 origin, as H3N2 did not emerge in humans and swine until 2011 and 1998 respectively. Although this finding has not been validated by phylogenetic evolution analyses, it still indicates a possible circulation of an H3 subtype virus in humans in the 1890s.

In experimental studies (1965-1966), approximately two-thirds of equine influenza-vaccinated volunteers reported infection at low to subclinical levels, indicating possible infection of humans with the H3N8 (Alford *et al.*, 1967). Furthermore, recent serological studies from different nations, including the USA, Australia and others, revealed the presence of anti-equine H3N8 antibodies in 3-10% of the participants, mainly in those exposed to horses (Burnell *et al.*, 2014; Larson *et al.*, 2015). However, low antibody levels were measured, indicating acute infection with the virus, possibly due to cross-reactivity with human H3 influenza. Nonetheless, equine H3N8 was shown to infect pig cell lines and respiratory explants (Patrono *et al.*, 2015). Moreover, clade II equine H3N8 strains were isolated from pigs in China in 2009 (Tu *et al.*, 2009). Experimentally, equine and canine H3N8 viruses did not replicate well in the respiratory systems of pigs, whereas avian and seal counterparts replicated substantially and caused noticeable lesions in inoculated pigs. The viruses were used to inoculate pigs without any previous adaptation (Solórzano *et al.*, 2015). These results indicate that mammals are prone to infection with avian H3N8 viruses, as the distribution of sialic acid receptors in pig's respiratory tissue resembles that in humans, with abundance of α-2,6-linked sialic acid receptors in the trachea and other parts of the respiratory tract. This similarity had been clearly demonstrated with the emergence of the novel pandemic H1N1 virus in 2009.

Concluding remarks

In summary, the ability of the H3 influenza subtype to infect humans is documented. This subtype has been shown to infect different mammalian species, including pigs. The ability of avian H3N8 to infect pigs raises significant concern about its ability to infect humans. Urgent studies are needed to understand the phenotypic characteristics of the recent H3N8 in humans, including receptor specificity, as well as the replication in human airway cells. It is unlikely that immunity against H3N2 will protect from H3N8, considering the significant antigenic changes. Cross-reactivity studies of the different H3N8 lineages are needed in this regard. Currently, an inactivated vaccine against H3N8 is available for use in horses. Whether this vaccine produces immunity against avian H3N8 remains to be studied. The availability of such resources might speed up the production of human vaccines if needed.

Declarations of Competing Interest

The authors have no competing interests to declare.

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Ethical approval statement

Approval was not required.

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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