eMicrobe
https://www.sciltp.com/journals/eMicrobe

Editorial

Emergence of Fatal Influenza A Virus H5N5 Infection in Human

Patrick C. Y. Woo [1,2]

[1] Doctoral Program in Translational Medicine and Department of Life Sciences, National Chung Hsing University, Taichung 402, Taiwan; pcywoo@hku.hk; Tel.: +886-4-22840370 (ext. 19); Fax: +886-4-22860164
[2] The iEGG and Animal Biotechnology Research Center, National Chung Hsing University, Taichung 402, Taiwan

How To Cite: Woo, P.C.Y. Emergence of Fatal Influenza A Virus H5N5 Infection in Human. *eMicrobe* **2026**, *2*(1), 2. https://doi.org/10.53941/emicrobe.2026.100002.

In November 2025, a patient from the Grays Harbor County, Washington State, USA, died of influenza A virus H5N5 infection (https://www.latimes.com/science/story/2025-11-21/washington-state-resident-dies-of-new-h5n5-form-of-bird-flu; accessed on 4 December 2025). This was, in fact, the first known case as well as the first fatal case of human H5N5 infection. The patient had a backyard flock consisting of mixed domestic poultry.

Influenza A viruses represent a vast and evolutionary dynamic group of pathogens capable of infecting a high diversity of avian and mammalian hosts [1–3]. They have a segmented RNA genome composed of eight negative-sense strands, enabling genetic reassortment when two different influenza viruses co-infect a host cell. This reassortment capacity is a defining feature of influenza virus evolution. Influenza A viruses are classified into different subtypes by two surface glycoproteins: hemagglutinin (H) and neuraminidase (N). Some of the subtypes (e.g., H1N1, H3N2) have been well-known to be circulating in humans for a long time, others are restricted only to birds; while a few of them were occasionally transmitted from birds to humans, sometimes causing devastating outbreaks [4].

Among the different influenza A viruses, the H5 lineage, particularly influenza A virus H5N1, has attracted considerable global attention due to its potential for high pathogenicity. Since the first reported outbreak of H5N1 infection in humans from Hong Kong in 1997, more than a thousand cases have been reported, mostly from patients in Southeast Asia who have been linked to direct contact with infected poultry, sick or dead birds, or environments contaminated by them [4]. H5N1 infection in humans was associated with a high case fatality rate of around 50%, although this figure was influenced by limited surveillance and the likelihood that mild cases go undetected. Sustained human-to-human transmission has not been established, although limited, non-sustained transmission has been reported in rare family clusters. In addition to H5N1, H5N8 is another H5 influenza A virus that has been confirmed to cause human infection. In 2021, a number of workers in a poultry farm in Russia had asymptomatic H5N8 infections, without any evidence of human-to-human transmission [5]. The workers were exposed during a large outbreak among egg-laying hens.

Influenza A virus H5N5 has appeared multiple times independently rather than descending from a single lineage. Many strains emerged when an H5 lineage virus, such as clade 2.3.4, 2.3.4.4, or related subclades, reassorted with viruses carrying the N5 segment [6]. Such reassortment events typically occur in wild waterfowl, which act as natural reservoirs for nearly all known H and N subtypes. Particularly, the clade 2.3.4.4 H5 viruses, which have demonstrated extraordinary reassortment diversity, have produced numerous combinations with various neuraminidases, including N2, N6, N8, and N5 [7–9]. H5N5 sublineages have therefore appeared in different geographical regions at different times, often sharing genetic backbones with better-known H5 strains but differing in their neuraminidase segment and sometimes internal genes. Since the early 2010s, H5N5 has been detected in Asia, Europe, the Middle East, and occasionally Africa, usually aligning with waterfowl migratory routes. The distribution of H5N5 is sporadic, with periodic introductions rather than sustained global circulation. Many detections have been associated with migratory bird populations, which can transport the virus across continents. However, unlike some H5 subtypes (e.g., H5N1) that have become well-established in poultry, H5N5 has more often remained a spillover virus, appearing in wild birds or causing limited outbreaks in domestic flocks.

The natural hosts of H5N5 are wild aquatic birds. Similar to other influenza viruses in aquatic birds, transmission occurs through the classical fecal-oral route associated with waterborne influenza ecology. In these species, infection may be asymptomatic or mild, allowing the virus to spread silently across long distances. Occasional spillover to domestic poultry can occur, particularly in areas where wild birds and domestic flocks interact around shared water sources or open-air environments. The pathogenicity of H5N5 varies widely. Some early H5N5 detections involved low-pathogenicity avian influenza strains, causing minimal diseases in birds. However, many more recent strains have been classified as high-pathogenicity influenza strains, particularly those emerging from clade 2.3.4.4 [6,9]. Some H5N5 strains have demonstrated the molecular hallmarks of high pathogenicity in poultry, such as polybasic cleavage sites in the hemagglutinin protein, enabling systemic infection in chickens and turkeys. Outbreaks in poultry can cause sudden death and a variety of other symptoms, depending on the particular strain. Evidence of infections in mammals is limited but not absent. Like many avian influenza viruses, H5N5 has occasionally been detected in scavenging or predatory mammals that consume infected birds. However, these cases do not necessarily indicate sustained mammalian transmission; instead, they usually reflect isolated spillovers facilitated by ingestion of contaminated animal.

Before the present incident, H5N5 was not considered a major zoonotic threat. Although several molecular characteristics limit its capacity to infect humans, such as receptor-binding preferences that strongly favor avian-type α2,3-linked sialic acid receptors, a recent study in fact described that a novel strain of highly pathogenic avian influenza clade 2.3.4.4b in North America may carry a key mutation (PB2-E627K substitution) which facilitated its adaptation in mammals [10]. The present alarming case of fatal human H5N5 infection implies that more active surveillance of H5N5, which relies on close monitoring of wild birds, particularly waterfowls, as well as in poultry farms, live markets, and other high-risk interfaces between wildlife and domestic animals and humans, is crucial [11]. In parallel with the emergence of fatal influenza A virus H5N5 infection in humans is the emergence of new bioinformatics tools and artificial intelligence algorithms for tracking and predicting the evolution of influenza viruses [12,13]. Such improvement of *in silico* technologies is of paramount importance in the prediction of possible interspecies jumping, development of vaccines, and timely implementation of public health measures for this centuries' old infection that has been associated with countless epidemics and outbreaks in the history of mankind [14].

Funding

This work was partly supported by the Feature Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE-114-S-0023-A) in Taiwan.

Conflicts of Interest

The author declares no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

References

1. Lau, S.K.; Chan, K.H.; Yip, C.C.; et al. Confirmation of the first Hong Kong case of human infection by novel swine origin influenza A (H1N1) virus diagnosed using ultrarapid, real-time reverse transcriptase PCR. *J. Clin. Microbiol.* **2009**, *47*, 2344–2346.
2. Naguib, M.M.; Kinne, J.; Chen, H.; et al. Outbreaks of highly pathogenic avian influenza H5N1 clade 2.3.2.1c in hunting falcons and kept wild birds in Dubai implicate intercontinental virus spread. *J. Gen. Virol.* **2015**, *96*, 3212–3222.
3. Martelli, P.; Teng, J.L.L.; Lee, F.K.; et al. Influenza A(H1N1)pdm09 Virus Infection in a Captive Giant Panda, Hong Kong. *Emerg. Infect. Dis.* **2019**, *25*, 2303–2306.
4. Yuen, K.Y.; Chan, P.K.; Peiris, M.; et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet* **1998**, *351*, 467–471.
5. Pyankova, O.G.; Susloparov, I.M.; Moiseeva, A.A.; et al. Isolation of clade 2.3.4.4b A(H5N8), a highly pathogenic avian influenza virus, from a worker during an outbreak on a poultry farm, Russia, December 2020. *Euro Surveill.* **2021**, *26*, 2100439.
6. Lewis, N.S.; Banyard, A.C.; Whittard, E.; et al. Emergence and spread of novel H5N8, H5N5 and H5N1 clade 2.3.4.4 highly pathogenic avian influenza in 2020. *Emerg. Microbes Infect.* **2021**, *10*, 148–151.

7. Herfst, S.; Begeman, L.; Spronken, M.I.; et al. A Dutch highly pathogenic H5N6 avian influenza virus showed remarkable tropism for extra-respiratory organs and caused severe disease but was not transmissible via air in the ferret model. *mSphere* **2023**, *8*, e0020023.
8. Beerens, N.; Heutink, R.; Bergervoet, S.A.; et al. Multiple Reassorted Viruses as Cause of Highly Pathogenic Avian Influenza A(H5N8) Virus Epidemic, the Netherlands, 2016. *Emerg. Infect. Dis.* **2017**, *23*, 1974–1981.
9. Fusaro, A.; Monne, I.; Mulatti, P.; et al. Genetic Diversity of Highly Pathogenic Avian Influenza A(H5N8/H5N5) Viruses in Italy, 2016–2017. *Emerg. Infect. Dis.* **2017**, *23*, 1543–1547.
10. Erdelyan, C.N.G.; Kandeil, A.; Signore, A.V.; et al. Multiple transatlantic incursions of highly pathogenic avian influenza clade 2.3.4.4b A(H5N5) virus into North America and spillover to mammals. *Cell Rep.* **2024**, *43*, 114479.
11. Woo, P.C.; Lau, S.K.; Yuen, K.Y. Infectious diseases emerging from Chinese wet-markets: Zoonotic origins of severe respiratory viral infections. *Curr. Opin. Infect. Dis.* **2006**, *19*, 401–407.
12. Cai, C.; Li, J.; Xia, Y.; et al. FluPMT: Prediction of Predominant Strains of Influenza A Viruses via Multi-Task Learning. *IEEE/ACM Trans. Comput. Biol. Bioinform.* **2024**, *21*, 1254–1263.
13. Jia, Q.; Xia, Y.; Dong, F.; et al. MetaFluAD: Meta-learning for predicting antigenic distances among influenza viruses. *Brief. Bioinform.* **2024**, *25*, bbae395.
14. Woo, P.C.Y. Rigorous analysis of microbes and infectious diseases using an expanding range of robust *in silico* technologies. *eMicrobe* **2025**, *1*, 1.