

What is the pandemic potential of avian influenza A(H5N1)?



On March 25, 2024, a national authority in Viet Nam notified WHO of a case of human infection with highly pathogenic avian influenza (HPAI) A(H5N1) virus (clade unreported). Then on April 1, a second but unrelated human infection with HPAI A(H5N1) virus (clade 2.3.4.4b) was reported in Texas, USA. The two cases occurred under different circumstances with different outcomes. The case in Viet Nam followed exposure to infected birds and resulted in death. By contrast, the case in Texas was in a worker on a commercial dairy farm who presented with only mild illness and was treated outside hospital. Genomic analysis at the US Centers for Disease Control and Prevention (CDC) revealed that the virus from the patient in Texas was closely related to viruses detected in cattle and dead birds from the same farm. This case occurred in the midst of an outbreak of HPAI A(H5N1) in dairy farms across multiple US states. No evidence of human-to-human transmission could be detected in either case, and the CDC and WHO deemed the risk to human health as low. While transmission of this virus from an infected bird to a person is not unheard of, the spread of the virus to cows and the subsequent human case represents one of several concerning developments in recent years for this virus.

The HPAI A(H5N1) virus was originally discovered in domestic waterfowl in southern China in 1996 and subsequently caused human infections with high mortality (>50%). Over time, the virus evolved into multiple genetic clades and subclades through accumulation of mutations and genetic reassortment with other avian influenza viruses. The resulting viruses have only sporadically infected humans, with no evidence of sustained between-human transmission that would suggest human adaptation. As observed for the case in Viet Nam, the illness HPAI A(H5N1) causes is often severe, although the human case in Texas was associated with only conjunctivitis, and numerous reports of human exposure to HPAI A(H5N1) clade 2.3.4.4b in the European Union and European Economic Area since 2020 have described few symptomatic infections.

By contrast, since 2020, the virus has been associated with large and deadly outbreaks in wild and farmed bird populations across multiple continents. Many millions of birds have died, either through direct infection or as a result of culling to control the outbreaks. In Europe,

where the virus followed a seasonal epidemic pattern for many years, mainly affecting waterfowl, an enzootic pattern has emerged, coinciding with a switch in host range of the virus to infecting colony-breeding seabirds. This switch has also been linked to the spread of the virus from Europe to the Americas and, most recently, to the Antarctic, where an enormous vulnerable bird population exists. To date, Oceania is the only continent to have been spared the virus, although how long this will last is unclear.

Concurrently with this concerning geographical spread, there have been reports of infection in more than 40 mammalian species. These reports include large outbreaks in fur farms, in which transmission between mammals could not be excluded, and the recent outbreak in dairy farms in the USA. The increasing host range of the virus, potential spread among mammals and between a mammal and a human, its wide geographical spread, and the unprecedented scale of the outbreaks in birds raise concerns about the pandemic potential of HPAI A(H5N1).

For avian influenza viruses to cross the species barrier and become pandemic, they must become transmissible between and be able to replicate efficiently in humans. Usually, this requires reassortment with human influenza viruses, or the virus could undergo adaptation (a process that can take a long time, but which may be expedited by the frequent infection of mammals and humans).

What can be done to prevent an avian influenza pandemic? The European Centre for Disease Prevention and Control and the European Food Safety Authority outlined One Health mitigation measures in a report published on April 3, 2024. These measures include enhancing surveillance and data sharing, careful planning of poultry and fur animal farming (especially in areas with high waterfowl density), and preventive measures such as vaccination of poultry and at-risk people. Although sequencing of viruses from the patient and cattle in Texas did not ring alarm bells regarding the potential of HPAI A(H5N1) clade 2.3.4.4b for sustained human transmission, the next flu pandemic—whether caused by an avian influenza A(H5N1) virus or otherwise—seems inevitable. The threat of a pandemic remains high, and we urge international leaders to reach an agreement on a pandemic accord before it is too late.

■ *The Lancet Infectious Diseases*



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For more on the **case in Viet Nam** see <https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON511>

For more on the **human case in Texas, USA** see <https://www.cdc.gov/ncird/whats-new/human-infection-H5N1-bird-flu.html>

For the **ECDC/EFSA report** see <https://www.ecdc.europa.eu/en/publications-data/drivers-pandemic-due-avian-influenza-and-options-one-health-mitigation-measures>