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Letter to the Editor

Alert and surveillance on H5N1 influenza virus: risks to agriculture and public health

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Dear Editor,

Bird flu, primarily caused by avian influenza A viruses, poses significant pandemic threats due to antigenic drift and shift.[1] The highly pathogenic avian influenza (HPAI) A(H5N1) virus has caused global outbreaks in birds, killing millions of wild birds and poultry, with sporadic cases in humans often being fatal with a case fatality rate of 52% (893 cases in 24 countries between 2003 and 2024, with 463 deaths)[2] reaching all continents.[3] The 2009 H1N1 pandemic demonstrated the risks of reassortment between human, avian and swine influenza viruses.[4] Recent H5N1 outbreaks in mammals raise concerns about potential human transmission. Effective cooking is one step toward critical control. In an experiment cooking study cooking ground beef at 120°F (48.9°C), the temperature of a rare steak was not able to inactivate the virus, but it was not detected at 145°F–160°F (62.8°C–71.1°C), suggesting sufficient cooking temperatures are required to inactivate HPAI A(H5N1) virus in meat.[5] Although cows routinely contract other forms of influenza viruses, one study had shown that they could potentially contract A(H5N1) virus following an experiment in four calves inoculated with A(H5N1) virus isolated from a cat.[6] It is concerning that for the first time, HPAI A(H5N1) virus, clade 2.3.4.4b has been identified in 145 dairy herds across 12 US states (Colorado, Idaho, Iowa, Kansas, Michigan, Minnesota, New Mexico, North Carolina, Ohio, South Dakota, Texas, Wyoming; as of July 8 2024; Figure 1).[7] Cows show symptoms of infection including sharply reduced milk supply, changes in milk thickness and lethargy. Of particular concern is the recent detection of the A(H5N1) virus in humans who had direct contact with dairy cattle, marking the first recorded instances of transmission from cows to humans. On 1 April 2024, a case was reported in Texas, followed by two cases in Michigan on 22 May and 30 May 2024 and one case in Colorado on 3 July 2024 (Figure 1).[8–11] Previously, in 2022, a single case in the United States involved transmission from poultry, bringing the total number of human A(H5N1) cases in the country to five. In 2024, the first two cases reported conjunctivitis (clade 2.3.4.4b), the third case (clade 2.3.4.4b) reported typical symptoms of acute respiratory illness, and, the recent case in Colorada only reported conjunctivitis (clade not known yet).[12] These four recent cases have raised concerns about viral mutations enhancing infectivity in mammals and humans. Infected cattle increase the risk due to higher human–animal interactions. Genetic analysis of the Texas case shows mammalian adaptation with the PB2 E627K mutation. The Michigan case lacks changes in hemagglutinin but has a PB2 M631L mutation, indicating mammalian adaptation and suggests direct cow-to-human transmission. These mutations are known to enhance replication and pathogenicity. This does not imply that an outbreak will occur, but the presence of infected cattle increases the risk due to more frequent human–animal interactions compared to wildlife. As per USDA, out of 96 muscle samples from culled dairy cows, only 1 tested positive for viral particles and no contaminated meat has entered the food supply.[5]

Wild aquatic birds (geese, ducks) are regarded as the original reservoir of A(H5N1) virus, which was first detected in 1996 in China, which spread to domestic chickens in 1997. The clade 2.3.2.1c of A(H5N1) has led several outbreaks in poultry

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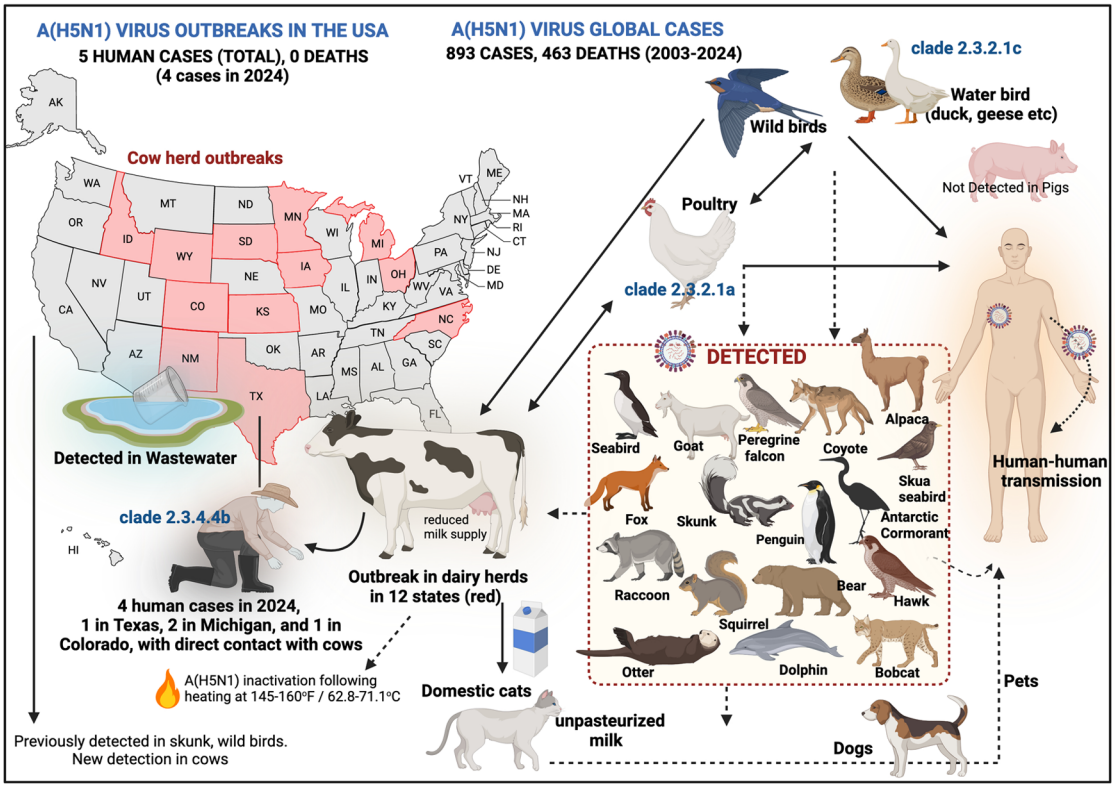

Figure 1. Is H5N1 the next pandemic? Since 2003, A(H5N1) has accounted for 893 global human cases with 463 deaths in 24 countries, including 11 cases in 2024. Antarctica has seen the first-ever cases of A(H5N1) virus in animals. In 2024, a man in Texas, two in Michigan, and one in Colorado, contracted H5N1 after contact with dairy cattle. H5N1 has been detected in several states across United States in wastewater, and there have been 145 cowherd outbreaks in 12 states across the United States (as of 8 July 2024), as shown. Cats contracted H5N1 from infected cow's milk, and hunting dogs have also been found to be positive after retrieving wild waterfowl. The virus's ability to infect pets is concerning, as wild birds transmit it to poultry and cattle. Other animals, as shown in the inset, have also been detected with A(H5N1) virus infection, but their role in transmission remains unclear. Solid lines depict confirmed transmission routes, while dotted lines depict uncertain transmission pathways.
Source: The bio-render (https://www.biorender.com/) was used for developing this figure.

and humans in Southeast Asian countries, including infections to five humans in Cambodia and one in Vietnam in 2024. The clade 2.3.2.1a has been identified in poultry and in a returned traveller to Australia from India. A(H5N1) virus was also detected in unpasteurized clinical samples of milk.[13] However, a recall is not required for commercial milk supplies as pasteurization inactivates the virus, and consumption of raw milk is generally not recommended. It is unclear if pigs can contract A(H5N1) virus, but if they do, it is particularly concerning as they can serve as mixing vessels for avian and human influenza viruses. This can lead to the emergence of new, potentially more virulent strains capable of human-to-human transmission, significantly increasing the risk of a pandemic. Since 2022, A(H5N1) has also been identified in 20 mammal species including, mink, goats, bears, foxes, sea lions, mountain lions, dolphins, seals, coyotes, otters, raccoons, skunks and squirrels.[14] To add to the concern, wastewater testing in several states across the United States identified H5N1 avian flu in 9 different Texas cities,[15] and A(H5N1) virus was detected in 59 wastewater treatment plants across the United States (from 190 wastewater treatment plants located in 41 states),[16] including California, Idaho, Iowa, Minnesota, Michigan and Texas. This suggests that A(H5N1) virus may spread in wild or domestic animals (cats, dogs) and enter residential areas. Several domestic cats have recently died due to H5N1 infections in a Texas farm and in Kansas, which had consumed unpasteurized raw milk from symptomatic

cows.[17] Hunting dogs in Washington state, particularly those frequently in contact with waterfowl in regions experiencing A(H5N1) outbreaks, have been detected with A(H5N1) virus.[18] Given the infection in cats and dogs, there is a high possibility of developing other intermediate hosts. This could lead to the virus circulating among domestic pets, which might then spill over to humans and potentially result in a pandemic.

In 2024, A(H5N1) virus has been detected in several mammals in the United States including,[19] mountain lion (Montana), skunks (Washington, Idaho, California), bobcats (Washington, Vermont, New York), domestic cats (Texas, New Mexico, Ohio, Michigan, Montana, South Dakota), American mink (Kentucky), raccoons (New York, Colorado), red fox (Missouri, New York, Michigan), Virginia opossum (Michigan), farmed goats (Minnesota) and dolphins (Florida). In addition, in New York city, Canada geese, red-tailed hawk, peregrine falcon and a chicken, have been reported to be infected with A(H5N1) virus clade 2.3.4.4b[20] (Figure 1); A(H5N1) has also been reported in thousands of poultry and birds in 2024, as well as, in Alpacas in a farm in Idaho. In February 2024, A(H5N1) virus was detected in mainland Antarctica for the first time. It was first detected in two brown skua seabirds, on the western side of Antarctica, close to South America.[21] Subsequently, H5N1 was detected in 12 Antarctic skua seabird carcasses on Beak Island, with further cases in Hope Bay and Devil and Paulet islands of Antarctica.[22,23] In March 2024, nine Adelie penguins and one Antarctic cormorant tested positive for H5N1, posing a significant threat to the local wildlife. So far, Australia and New Zealand have not reported any cases of A(H5N1) in animals.

The infection of several US cattle herds with A(H5N1) virus has raised alarms about its potential spread to humans. Previously circulating primarily in birds, the virus now infects mammals that regularly interact with humans. The development of a vaccine against A(H5N1) virus is essential for control measures.[24] As such, H5N1 adjuvanted cell-based monovalent vaccine, AUDENZ™, was approved by the FDA in September 2020 to help protect people over the age of 6 months against A(H5N1) infection in the event of a pandemic.[25] This is important for pandemic preparedness and the company Sequiris, a subsidiary of CSL Limited in Australia, has stockpile of the vaccine. GlaxoSmithKline and Sanofi have seasonal influenza production capacity and would be able to scale up production of H5N1 vaccines including AUDENZ, if needed. Previously, egg-based H5N1 vaccines were approved for Sanofi Pasteur's vaccine in April 2007 in the United States, GlaxoSmithKline's Prepandrix vaccine was approved by the EU in May 2008, and CSL Limited Panvax vaccine was approved in Australia in June 2008. Further, efforts should be made to expand use of poultry A(H5N1) viral vaccines despite challenges such as inter-flock deployment and restrictions on selling vaccinated poultry products abroad.[26] Cows are vaccinated against several diseases, but there are currently no approved H5N1 avian influenza vaccines for cattle, and companies have started to work on a A(H5N1) vaccine for cows. The current situation in the United States with the two infected humans from milk cows suggests the dynamic nature of zoonotic viruses and their potential to disrupt scientific and economic systems.[27] The detection of HPAI A(H5N1) in four dairy farm workers is a crucial alert for the global health community, urging a reassessment of our understanding of viral spread and human infection. This case not only enhances our knowledge of A(H5N1) viral transmission but also influences our strategy for emerging infectious diseases. Immediate action is essential to improve surveillance, refine diagnostics and strengthen public health infrastructure. Strengthening these areas will better protect frontline food system workers and the general public from the persistent threat of emerging zoonoses.

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Consent for publication

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Author contributions

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