

Received: 2024.05.28

Accepted: 2024.05.28

Available online: 2024.05.29

Published: 2024.06.01

# Editorial: Concerns as Highly Pathogenic Avian Influenza (HPAI) Virus of the H5N1 Subtype is Identified in Dairy Cows and Other Mammals

**Dinah V. Parums, MD PhD**

Science Editor, Medical Science Monitor, International Scientific Information, Inc., Melville, NY, USA

e-mail: [dinah.v.parums@isi-science.com](mailto:dinah.v.parums@isi-science.com)**Conflict of interest:**

None declared

**Abstract**

Highly pathogenic avian influenza (HPAI) virus subtypes have been increasingly identified in poultry and wild birds since 2021. Between 2020-2023, 26 countries have reported that the H5N1 virus had infected more than 48 mammalian species. On 1 April 2024, a public health alert was issued in Texas when the first confirmed case of human infection with the H5N1 influenza virus was reported in a dairy worker. Cases of H5N1, clade 2.3.4.4b in dairy cows have been reported in several states in the US but were unexpected, even though H5N1 was previously identified in mammalian species, including cats, dogs, bears, foxes, tigers, coyotes, goats, and seals. On 29 April 2024, almost one month after the first reported cases of H5N1 infection in dairy cows, measures were to be implemented by the US Department of Agriculture (USDA) to prevent the progression of H5N1 viral transmission. This editorial summarizes what is currently known about the epidemiology, transmission, and surveillance of the HPAI virus of the H5N1 subtype in birds, mammals, and dairy cows, and why there are concerns regarding transmission to humans.

**Keywords:** H5N1 • Avian Influenza • Zoonosis • Cows • Editorial

In just over a century, there have been five viral global pandemics; four were due to influenza, and the most recent COVID-19 pandemic was due to SARS-CoV-2 infection [1,2]. Since the beginning of the 20<sup>th</sup> century, there have been four significant influenza pandemics, which have originated in avian or mammal hosts, including the Spanish flu (1918-19), which resulted in 500 million infections and between 50-100 million human deaths, Asian flu (1957), Hong Kong flu (1968), and swine flu (2009) [3]. During the COVID-19 pandemic, reported cases of influenza were significantly reduced due to changes in social behavior [1,2]. The US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) record global and national weekly influenza infection rates in humans [2]. However, highly pathogenic avian influenza (HPAI) virus subtypes have been increasingly identified in poultry and wild birds since 2021 [4]. In October 2022, the HPAI virus of the H5N1 subtype was identified in farmed mink in the US [4]. Because influenza viruses are constantly evolving, the WHO has highlighted the importance of global viral surveillance detection and monitoring, including surveillance of epidemiological and clinical changes associated with emerging influenza viruses that may affect animal or human health, including influenza A(H5N1) avian influenza infection [5]. The first human case of H5N1 avian influenza in the US was reported in 2022 in Colorado from a patient who had direct exposure to poultry [6,7]. The patient reported fatigue, had no other symptoms, and recovered quickly [6,7].

In March 2024, Plaza and colleagues reviewed the recent available data on mammals naturally infected by the H5N1 influenza virus between 2020-2023 and retrospective data on H5N1 mammalian infection between 2003-2019 [8]. Between 2020-2023, 26 countries have reported that more than 48 mammalian species had been infected by the H5N1 virus [8]. The number of mammalian species and the global area with affected species has recently increased, with the most likely source of past and recent mammalian infection being close contact with infected birds and mammal-to-mammal transmission driven by viral mutations [8]. Because the H5N1 virus may adapt to infect mammals, it is even more important to increase continuous surveillance to reduce the risk of a global pandemic of H5N1 influenza.

On 1 April 2024, a public health alert was issued in Texas when the first confirmed case of human infection with the H5N1 influenza virus was reported in a dairy worker who developed conjunctivitis and mild symptoms [9-11]. Although cows can be infected with influenza D, the cases of H5N1, clade 2.3.4.4b in dairy cows were unexpected, even though it was previously identified in mammalian species, including cats, dogs, bears, foxes, tigers, coyotes, goats, and seals, [12]. Currently, there are no H5N1 vaccines for cattle, and although poultry vaccines exist, they have limited efficacy [12]. H5N1 influenza vaccines for humans are available, and vaccines developed for related viruses are available for vaccine manufacturing should studies show they protect against the 2.3.4.4b clade [6,7].

Burrough and colleagues reported cases of pathogenic avian influenza A(H5N1) virus in dairy cows and cats in Texas and Kansas, identified as derived from clade 2.3.4.4b viruses that entered the US in late 2021 [13]. Infection to new herds in Michigan, Idaho, and Ohio supported viral transmission between cows, which showed mild symptoms [13]. However, cats given raw milk from infected cows developed fatal systemic influenza [13]. As of 22 May 2024, the US Food and Drug Administration (FDA) has indicated that the commercial milk supply remains safe [14]. However, the potential cross-species transmission of the H5N1 influenza virus in unpasteurized bovine milk has become a public health concern in the US [13,15]. Therefore, the CDC recommends that continued surveillance of highly pathogenic avian influenza viruses in animals providing milk and meat for human consumption is needed to prevent mammal-to-mammal and cross-species transmission of H5N1 [6,7].

On 29 April 2024, almost one month after the first reported cases of H5N1 infection in dairy cows, measures were to be implemented by the US Department of Agriculture (USDA) to prevent the progression of infection [16,17]. The USDA has banned cattle transportation, but H5N1 was already infecting farms in at least nine US states before these recommendations were made [17]. Some scientists have criticized the lack of widespread testing for the clade 2.3.4.4b of the H5N1 influenza virus [17-19]. The US outbreak of H5N1 in cows may have begun as early as October 2023, with initial transmission from wild birds [17]. Analysis of samples from wastewater plants is another approach to public health surveillance of the presence of H5N1, particularly in agricultural areas [17]. There are concerns that the US outbreak could put other countries at risk, as US dairy cows are transported by road across the border to Mexico and Canada and flown to different countries [17].

On 17 May 2024, the CDC reported that 51 dairy cow herds in nine US states had confirmed cases of H5N1 influenza virus infections [6]. The CDC supports states that monitor people exposed to infected birds and mammals, including cattle [6]. The CDC has embarked on a comprehensive process of conducting a pandemic risk assessment of human influenza virus infection from Texas (A/Texas/37/2024) using the Influenza Risk Assessment Tool (IRAT), which includes ten risk elements to measure the potential of an emerging influenza virus to cause a pandemic and the potential public health impact of the pandemic [7]. Infection surveillance data for H5N1 viruses in dairy cows or other animals has begun to investigate trends in infection [7]. The collection of wastewater surveillance data commenced in the last week of May 2024 [7]. For the most recent week of data, the CDC influenza surveillance systems show no indicators of unusual influenza activity in humans, including for avian influenza A(H5N1) viruses [6,7].

There are now concerns that H5N1 could enter the food chain and be transmitted to humans by drinking milk from infected dairy cows. A recent study by Guan and colleagues at the Texas A&M Veterinary Medical Diagnostic Laboratory studied cows' milk samples from affected dairy cows in the US state of New Mexico [15]. They identified eight HPAI A(H5N1) viruses that formed a single clade consisting of many smaller clades of viruses isolated from wild birds, chickens, cats, and raccoons [15]. During the bovine foot-and-mouth disease epidemics during the 1990s, heat inactivation of virus-positive samples of milk required higher temperature and longer incubation times, so Guan and colleagues found that heat treatment at 72°C for 15 or 20 seconds reduced virus titers but did not completely inactivate the virus [15]. However, these laboratory conditions are not replicated in commercial dairies and suppliers [15]. Also, the stability of the H5N1 virus in raw cows' milk stored at 4°C showed that although viral titers reduced with time, milk remained infectious for several weeks [15]. To evaluate the possible threat of transmission of H5N1-positive milk to animals and humans, BALB/c mice were infected with the H5N1 influenza virus, which was identified in several organs, including the mammary glands [15].

The US Department of Agriculture (USDA) has initiated detection programs to evaluate the presence of the H5N1 influenza virus in dairy cows to contain the spread of the disease [16]. On 10 May 2024, the USDA announced financial initiatives and support for farmers with affected herds [16]. On 23 May 2023, the USDA announced further measures to prevent the spread of H5N1, including biosecurity measures for individuals who move between herds, reimbursement of costs for sample collection for H5N1 testing, covering veterinarian fees for veterinarians to collect samples for testing by the National Animal Health Laboratory Network, and compensation for financial loss of milk production from infected herds [16]. A combined approach now involves the USDA, the US government, and the FDA, which is primarily responsible for the safety of milk and dairy products [16]. Milk pasteurization testing has begun at USDA laboratories [16]. Collaboration with the CDC, which is responsible for public health, aims to assess the level of risk to human health and encourage cooperation between dairy farmers, industry, and public health officials to improve infection surveillance and assess the risk level to human health [16].

Since 2020, H5 influenza viruses have spread worldwide among wild birds, with outbreaks in poultry resulting in food safety and security concerns [20,21]. The recent spread of the HPAI virus of the H5N1 subtype (clade 2.3.4.4b) has rapidly spread to mammals, with increasing diversity of infected species [21]. The mode of viral transmission to most mammals is likely due to the preying on or eating infected birds, which is thought to be the main source of mammalian infection [20,21]. However, the mode of transmission of H5N1 to animals such

as cows is poorly understood [22]. There is a need for global concern due to the ongoing re-assortment of pathogenic avian influenza viruses, the diversification of the H5N1 influenza viruses, and the late start to initiate infection surveillance programs, which could mean that cases are increasing but remain undetected [23].

## Conclusions

There is concern that the first known outbreak of H5N1 avian influenza in cows continues, mainly in the US. Transmission from birds to cows and cows to birds is possible, as is transmission from cows and birds to humans. There is the possibility that animals, including mammals, could become a permanent reservoir for HPAI virus subtypes, including H5N1, with the risk of mutations that may increase viral virulence in birds, mammals, and humans.

## References:

1. Olsen SJ, Winn AK, Budd AP, et al. Changes in influenza and other respiratory virus activity during the COVID-19 pandemic – United States, 2020-2021. *MMWR Morb Mortal Wkly Rep.* 2021;70(29):1013-19
2. Parums DV. Editorial: A decline in influenza during the COVID-19 pandemic and the emergence of potential epidemic and pandemic influenza viruses. *Med Sci Monit.* 2021;27:e934949
3. Liang Y. Pathogenicity and virulence of influenza. *Virulence.* 2023;14(1):2223057
4. Parums DV. Editorial: Global surveillance of highly pathogenic avian influenza viruses in poultry, wild birds, and mammals to prevent a human influenza pandemic. *Med Sci Monit.* 2023;29:e939968
5. World Health Organization (WHO). Cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO. Geneva: WHO; 2024. Available from: [https://www.who.int/publications/m/item/cumulative-number-of-confirmed-human-cases-for-avian-influenza-a\(h5n1\)-reported-to-who--2003-2024-26-february-2024](https://www.who.int/publications/m/item/cumulative-number-of-confirmed-human-cases-for-avian-influenza-a(h5n1)-reported-to-who--2003-2024-26-february-2024)
6. Centers for Disease Control and Prevention (CDC). Avian Influenza (Flu). May 17, 2024. Available from: [https://www.cdc.gov/flu/avianflu/spotlights/2023-2024/bird-flu-update\\_05172024.html](https://www.cdc.gov/flu/avianflu/spotlights/2023-2024/bird-flu-update_05172024.html)
7. Centers for Disease Control and Prevention (CDC). Current H5N1 Bird Flu Situation in Dairy Cows. May 24, 2024. Available from: <https://www.cdc.gov/flu/avianflu/mammals.htm>
8. Plaza PI, Gamarra-Toledo V, Euguí JR, Lambertucci SA. Recent changes in patterns of mammal infection with highly pathogenic avian influenza A(H5N1) virus worldwide. *Emerg Infect Dis.* 2024;30(3):444-52
9. Abbasi J. Bird flu outbreak in dairy cows is widespread, raising public health concerns. *JAMA.* 2024 May 8. doi: 10.1001/jama.2024.8886. Epub ahead of print
10. Harris E. CDC: H5N1 bird flu confirmed in person exposed to cattle. *JAMA.* 2024;331(19):1615
11. Uyeki TM, Milton S, Abdul Hamid C, et al. Highly pathogenic avian influenza A(H5N1) virus infection in a dairy farm worker. *N Engl J Med.* 2024 May 3. doi: 10.1056/NEJMc2405371. Epub ahead of print
12. Cohen J. Worries about bird flu in U.S. cattle intensify. *Science.* 2024;384(6691):12-13
13. Burrough ER, Magstadt DR, Petersen B, et al. Highly pathogenic avian influenza A(H5N1) clade 2.3.4.4b virus infection in domestic dairy cattle and cats, United States, 2024. *Emerg Infect Dis.* 2024 Apr 29;30(7). doi: 10.3201/eid3007.240508. Epub ahead of print
14. Food and Drug Administration (FDA). Updates on highly pathogenic avian influenza (HPAI). May 22, 2024. Available from: <https://www.fda.gov/food/alerts-advisories-safety-information/updates-highly-pathogenic-avian-influenza-hpai>
15. Guan L, Eisfeld AJ, Pattinson D, et al. Cow's milk containing avian influenza A (H5N1) virus – heat inactivation and infectivity in mice. *N Engl J Med.* 2024 May 24. doi: 10.1056/NEJMc2405495. Epub ahead of print
16. US Department of Agriculture (USDA) Expands support for producers to stop the spread of H5N1 in dairy cattle. May 23, 2024. Available from: <https://www.usda.gov/media/press-releases/2024/05/23/usda-expands-support-producers-stop-spread-h5n1-dairy-cattle>
17. Cohen J, Enserink M. Bird flu appears entrenched in U.S. dairy herds. *Science.* 2024;384(6695):493-94
18. Mallapaty S. Could bird flu in cows lead to a human outbreak? Slow response worries scientists. *Nature.* 2024 May 17. doi: 10.1038/d41586-024-01416-7. Epub ahead of print
19. Kozlov M, Mallapaty S. Bird flu outbreak in US cows: Why scientists are concerned. *Nature.* 2024; 628(8008):484-85
20. Kojima N, Adlhoch C, Mitja O, et al. Building global preparedness for avian influenza. *Lancet.* 2024 May 9: S0140-6736(24)00934-6. doi: 10.1016/S0140-6736(24)00934-6. Epub ahead of print
21. Kojima N, Blumberg A, Radcliffe R, et al. US public health preparedness and response to highly pathogenic avian influenza A (H5N1) viruses. *JAMA.* 2024 May 21. doi: 10.1001/jama.2024.10116. Epub ahead of print
22. Ly H. Highly pathogenic avian influenza H5N1 virus infections of dairy cattle and livestock handlers in the United States of America. *Virulence.* 2024;15(1):2343931
23. Graziosi G, Lupini C, Catelli E, Carnaccini S. Highly pathogenic avian influenza (HPAI) H5 clade 2.3.4.4b virus infection in birds and mammals. *Animals (Basel).* 2024;14(9):1372