The highly pathogenic H5N1 virus found in US dairy cattle has some characteristics that could enhance infection and transmission among mammals

Published in:
Lab Animal

Publication status and date:
Published: 01/01/2024

DOI (link to publisher):
10.1038/s41684-024-01425-z

Document Version
Publisher's PDF, also known as Version of record

Infectious disease https://doi.org/10.1038/s41684-024-01425-z

The highly pathogenic H5N1 virus found in U.S. dairy cattle has some characteristics that could enhance infection and transmission among mammals

Fabien Filaire & Sander Herfst

A highly pathogenic H5N1 influenza virus is spreading in U.S. dairy cattle and has been transmitted to other species, including humans, probably through contaminated milk. Understanding how the virus spreads among cattle and its potential for mammalian adaptation and airborne transmission is crucial for effective outbreak control and public health safety.

Highly pathogenic avian influenza (HPAI) A/H5 viruses of the A/Goose/Guangdong/1/1996 (Gs/GD) lineage first emerged in Southern China, after which they have been spread to Europe and Africa. In late 2021, the virus reached the American continent and subsequently spread to Antarctica[1]. These A/H5 influenza virus outbreaks have led to major economic losses in the poultry industry, impacted food security and threatened global public health because of their zoonotic potential.

Since 1996, HPAI A/H5 viruses have not only spread across vast geographical areas, but their overall ecology has also changed. We are witnessing tremendous changes in the diversity of susceptible host species, with more frequent high-mortality outbreaks in wild birds and spillovers to terrestrial and marine mammals in direct contact with infected birds. The increasing number of susceptible species constantly impacts the bird–mammal interface, resulting in more frequent outbreaks in fur farms, such as those with foxes, minks and raccoon dogs[2].

In March 2024, the United States authorities reported the first outbreak of HPAI A/H5N1 in dairy cattle in Texas due to the introduction of the new clade 2.3.4.4b B3.13 genotype. This strain is a combination of a Eurasian HPAI virus ancestor and a North American low pathogenicity avian influenza virus, which has been circulating in wild birds and mammals across North America since January 2024[3]. The cattle presented unexplained symptoms such as loss of appetite, abnormal milk consistency, a drop in milk production and mild respiratory distress. This event, marking the beginning of a still ongoing epizootic, is unprecedented as cattle were not previously reported to be susceptible to HPAI viruses. As of August 1, 2024, 175 outbreaks in dairy cattle have been reported in 13 states.

This new spillover to a mammalian species, especially in farming animals, is highly concerning as it may be a step toward persistent mammal-to-mammal transmission, increasing the risk to global public health[1,4]. Published reports have confirmed the efficient transmission of HPAI from infected cattle to wild animals (e.g., raccoons, skunks), domestic cats and humans, making cattle a focal point of a multi-species transmission scheme[3]. On 19 July 2024, the US Centers for Diseases Control and Prevention (US CDC) reported a total of ten human cases of mild infection with HPAI A/H5 since April 24, mostly conjunctivitis. Four of these cases were associated with exposure to sick dairy cows and six were associated with exposure to HPAI A/H5-infected poultry[5].

Given that mammal-to-mammal transmission of avian-origin influenza viruses are rare and rely on genetic and phenotypic adaptation to the new mammalian host, rapid understanding and characterization of transmission routes in this new context are critical. Only with this understanding can diagnostic methods be efficiently optimized and adapted, and surveillance and control strategies be deployed to limit the spread of the virus and the risk of enhanced pathogenicity and zoonotic transmission abilities. The use of experimental models to assess the pandemic risk of emerging zoonotic influenza viruses provides crucial information to support public-health efforts.

In *Nature*, Eisfeld and colleagues investigated the pathogenicity and transmission routes of an A/H5N1 clade 2.3.4.4b virus isolated from milk in a 2024 dairy cattle outbreak in New Mexico (A/dairy cattle/New Mexico/A240920343-93/2024)[6]. In mice, the authors investigated the pathogenicity of this Cow-H5N1 virus following different exposure routes. It was shown that oral ingestion of infected milk led to rapid virus dissemination in both non-respiratory and respiratory organs. Vertical transmission from lactating infected mice to their pups was also established. These results not only confirm the possible vertical transmission from lactating cows to calves, but also raise concerns about farm and dairy workers' exposure to contaminated milk, implying the need for adapted biosafety and biosecurity protocols.

Ferrets are considered the 'gold standard' animal model for influenza A virus (IAV) research. They are naturally susceptible to IAV infection and share key respiratory anatomical and physiological features with humans, making them ideal for studying transmission via the air[7]. IAV uses its hemagglutinin (HA) protein to bind to receptors on the cell surface to initiate infection. Ferrets and humans have an identical receptor distribution across the respiratory tract with human-type α-2.6- and avian-type α-2.3-linked sialic acids in the upper and lower respiratory tract, respectively. As a result, human IAV can be efficiently transmitted through the air via respiratory droplets, while transmission of avian IAV is absent or limited.

To assess whether the Cow-H5N1 can transmit among mammals via respiratory droplets, Eisfeld and colleagues used a conventional ferret transmission set-up, where intranasally inoculated donor ferrets were housed in individual cages, and contact ferrets were placed in adjacent separate cages one day later[6]. Whereas a human A/H1N1 control virus was efficiently transmitted in four out of four donor–contact pairs, none of the

four Cow-H5N1 contact ferrets tested positive for virus in nasal swabs or presented clinical signs. However, a single contact ferret seroconverted, but no Cow-H5N1 RNA or virus could be isolated from the swabs.

The *Nature* publication's findings on the absence of efficient airborne transmission align with a report from the US CDC, which observed inefficient respiratory droplet transmission between ferrets (in only 1 out of 3 donor–contact pairs) of an HPAI A/H5N1 virus (A/Texas/37/2024) isolated from a human case who had been exposed to infected dairy cattle in Texas[8]. This still low transmission efficiency is not surprising, as several phenotypic changes are required for avian A/H5N1 influenza viruses to be transmissible via the air between mammals. These changes include a shift in HA-binding specificity from α-2.3 to α-2.6-linked sialic acid receptors, increased HA acid stability and enhanced virus replication in mammalian cells[9]. Over the years, several such mammalian adaptation markers have been described, including the E627K mutation in the PB2 subunit of the influenza virus polymerase complex which is involved in replication of the viral genome. This mutation is present in the human Texas virus but absent in the Cow-H5N1 virus used by Eisfeld and colleagues. The presence of this mutation can partially explain the moderate increase in airborne transmission efficiency observed by the US CDC.

However, Eisfeld and colleagues report dual binding specificity for α-2,3 and α-2,6-linked sialic acid receptors, which they hypothesize to be a specific feature of A/H5N1 viruses isolated from cattle. This finding suggests that one of the traits required for mammal-to-mammal transmission via the air is already present in Cow-H5N1. However, the α-2,6-linked sialic acid-binding specificity must be further investigated in detail, as others have reported different observations[10].

Overall, the introduction of HPAI A/H5 viruses into dairy cattle and their spillover to other (mammalian) hosts constitutes an alarming signal and raises concerns regarding the evolution of an A/H5N1 virus that is adapted to replication and transmission in mammals and, ultimately, humans. Genotypic and phenotypic analyses, along with initial airborne transmission studies in ferrets, have revealed inefficient transmission via respiratory droplets. Furthermore, studies in mice have confirmed that exposure to contaminated milk constitutes a new, alternative route for spillover infections. Monitoring the genotype and phenotype of HPAI clade 2.3.4.4b virus in dairy cattle and derived viruses is of utmost importance. This close investigation is necessary to develop and implement effective prevention strategies. The urgency of this situation cannot be overstated.

Fabien Filaire[1] & Sander Herfst[1,2] ✉
[1]Department of Viroscience, Erasmus University Medical Center, Rotterdam, the Netherlands. [2]Pandemic and Disaster Preparedness Center, Delft, Rotterdam, the Netherlands.
✉e-mail: s.herfst@erasmusmc.nl

Published online: 14 August 2024

References

1. Lewis, N. & Beer, M. *Science* **385**, 123–123 (2024).
2. Lindh, E. et al. *Euro Surveill.* **28**, 2300400 (2023).
3. Caserta, L. C. et al. *Nature* https://doi.org/10.1038/s41586-024-07849-4 (2024).
4. Abdelwhab, E. M. & Beer, M. *npj Viruses* **2**, 22 (2024).
5. cdc.gov. https://www.cdc.gov/bird-flu/spotlights/h5n1-response-07192024.html#:~:text=Since%20April%202024%2C%2010%20human,reported%20in%20the%20United%20States
6. Eisfeld, A. J. et al. *Nature* https://doi.org/10.1038/s41586-024-07766-6 (2024).
7. Belser, J. A. et al. *mBio* **13**, e0117422 (2022).
8. cdc.gov. https://www.cdc.gov/bird-flu/spotlights/ferret-study-results.html
9. Linster, M. et al. *Cell* **157**, 329–339 (2014).
10. Good, M. R. et al. *bioRvix* https://doi.org/10.1101/2024.06.22.600211 (2024).

Competing interests

The authors declare no competing interests.