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Travel Medicine and Infectious Disease

Emerging threats: Is highly pathogenic avian influenza A(H5N1) in dairy herds a prelude to a new pandemic?

Dear Editor,

The recent confirmation by the United States Department of Agriculture (USDA) of the detection of Highly Pathogenic Avian Influenza (HPAI) A(H5N1) strain in dairy cattle herds across several states, including Texas, Kansas, Michigan, New Mexico, and Idaho (https://www.science.org/content/article/us-dairy-farm-worker-infected-as-bird-flu-spreads-to-cows-in-five-states), has ignited significant concern and raised pertinent questions regarding the implications of this unprecedented occurrence. This divergence from the typical avian host raises alarms, as avian influenza rarely infects cattle. The USDA's confirmation of HPAI A(H5N1) presence in multiple herds, particularly in states not historically associated with avian influenza outbreaks, underscores the gravity of the situation.

The identified strain, belonging to the Eurasian lineage of H5N1 goose/Guangdong virus clade 2.3.4.4b, is suspected to have been introduced by wild migratory birds. Symptoms exhibited by infected cows, including decreased milk production, altered milk consistency, and diminished appetite, further accentuate the severity of the situation. Furthermore, the emergence of the virus in a human case in Texas, although with low risk of transmission, accentuates the need for heightened vigilance and response measures. While the risk to public health remains categorized as low by the CDC (https://www.cdc.gov/flu/avianflu/spotlights/2023-2024/h5n1-analysis-texas.htm#print), individuals with close contact with infected animals or contaminated environments are at increased risk. Authorities are swiftly responding to contain the spread, with the National Veterinary Services Laboratory (NVSL) conducting confirmatory testing and genomic analysis to understand the extent of the outbreak. Implementing restrictions on cattle movement to curb transmission poses logistical challenges, particularly considering the seasonal transport of herds. Nevertheless, such measures are deemed necessary to prevent further dissemination of the virus. The USDA and the U.S. Food and Drug Administration (FDA) are working in tandem to ensure the safety of the commercial supply of pasteurized milk, as pasteurization effectively inactivates viruses such as influenza and is mandatory for milk marketed in the United States. Milk from symptomatic or exposed cows is diverted or destroyed, and the FDA recommends stringent measures to prevent the marketing of raw milk or unpasteurized cheeses from infected or exposed animals (https://www.fda.gov/food/milk-guidance-documents-regulatory-information/questions-and-answers-regarding-milk-safety-during-highly-pathogenic-avian-influenza-hpai-outbreaks). Farms are advised to closely monitor animals for signs of disease and consult state veterinary authorities for diagnostic testing if necessary. Strict biosecurity measures, including the prompt isolation of sick animals and safe disposal of their milk, are imperative. In addition, the evaluation of possible vaccines for cattle, adapted from existing ones for pigs, is underway.

To verify the occurrence of a genetic signature of a spillover event, all available genomes isolated in avian, mammals, and human hosts in 2024 have been compared for the genes HA and NA. The FUBAR method (Fast, Unconstrained Bayesian AppRoximation) [1], implemented in the Datamonkey platform [2], has been applied individually to each dataset to identify sites under selection. The test indicates that for the gene HA, sites under positive pressure are present only in the avian dataset, specifically at site 154 (nt position 460-2), while no sites under positive selection have been detected in mammal and human datasets. Conversely, many sites under negative selection have been detected in all datasets. The presence of a site under positive selective pressure in the HA gene of birds indicates potential adaptive evolution (albeit light, considering that there is only one site) to resist environmental pressures or enhance infectivity in avian hosts. Additionally, the presence of numerous sites under negative selective pressure implies ongoing genetic variation in avian influenza virus, possibly to adapt to environmental changes or evade the immune response of bird hosts. Conversely, the datasets on mammals (general) and humans, with only sites under negative selective pressure, suggest that the avian influenza virus in these mammalian hosts is undergoing genetic changes that do not confer an obvious selective advantage. This could indicate greater genetic stability of the virus in mammalian populations compared to birds. However, the presence of sites under negative selective pressure still suggests ongoing genetic variations over time, which potentially could impact the virus's pathogenicity, transmissibility, or ability to evade host immune responses.

For what the NA gene is concerned, it was observed that the only site under positive selective pressure was found in mammals, specifically at site 369 (nt position 1105-7) while many sites under negative selection were detected in all datasets also in this case. This could indicate a specific adaptive evolution of the avian influenza virus in mammalian hosts regarding the NA gene. Positive selective pressure at this site might suggest that the virus has developed a mutation conferring a selective advantage in binding and replication within the mammalian context. This could imply an increase in transmissibility, virulence, or the ability to evade the immune response in mammalian hosts. The absence of sites under positive selective pressure in birds and humans could indicate that the NA gene of the avian influenza virus is generally more conserved in these host populations compared to mammals. However, also in this case the presence of sites under negative selective pressure may still suggest that the virus is undergoing genetic variations over time, although not necessarily with obvious adaptive consequences as in the case of positive selective pressure.

It is interesting to note that the genetic distance between groups is very small (0.002–0.144) for both genes, especially considering that Influenza A, along with other RNA viruses, reproduces with minimal

accuracy [3]. This condition suggests that the strains affecting different hosts are similar and no spillover events have occurred yet. Indeed, the strain infecting humans is very closely related to those present in birds. A similar phenomenon occurred in Cambodia in recent years when two individuals, a father and daughter, were affected. While the father showed no symptoms, the daughter tragically passed away in a nearby hospital [4]. After a genetic evaluation emerged that the most likely scenario is that these two individuals were infected by the same reservior species [5]. Similarly, in this case, the comparison between the genetic makeup of humans, mammals, and avian species did not reflect the signature of a genetic spillover, but this does not mean that it can never happen.

Indeed, a constant monitoring and real-time mapping of the spread of avian influenza A(H5N1) are crucial to understanding and containing this rapidly evolving threat [6,7]. A coordinated "One Health" approach that integrates animal, human, and environmental health is essential for effective monitoring. Transparent sharing of epidemiological data among governments, researchers, and health authorities can facilitate in-depth scientific analysis, informed policies, and rapid response to this dynamic threat. Although this HPAI outbreak in dairy cattle poses a new challenge, at present, the risk to public health remains low. Authorities continue to monitor the situation closely, conducting further testing, genomic analysis, and research to assess the disease and possible interventions. Producers are encouraged to promptly report livestock diseases and take strict biosecurity measures.

In conclusion, the emergence of HPAI A(H5N1) in dairy herds across several states presents a significant cause for concern. This unexpected occurrence challenges conventional understanding of avian influenza transmission and prompts urgent action to mitigate potential risks to public health, animal welfare, and economic stability within the dairy industry. While the current risk to public health is assessed as low, proactive measures are essential to contain the outbreak and prevent further spread. Indeed, according to selective pressure on the HA gene, birds remain the primary host, but the virus is also accumulating genetic variability in other hosts through genetic drift phenomena. This accumulation enhances the virus's potential hazard and increases the likelihood of antigenic drift, characterized by minor mutations in the HA and NA genes, which can alter the structure of these surface proteins. We need to be vigilant as uncontrolled circulation among mammals increases the likelihood of transmission to a new host, driven by heightened variability due to unchecked circulation. Currently, there is no genetic signature certifying that it has already occurred, but the probabilities increase over time, and, the presence of a site under positive selective pressure in the NA gene in mammals suggests a specific adaptation to this host population. Swift implementation of robust surveillance, rapid response mechanisms, and stringent biosecurity protocols is crucial to safeguard both human and animal well-being and maintain the resilience of the dairy sector. In essence, this outbreak underscores the necessity of a unified approach that integrates animal, human, and environmental health to effectively monitor, mitigate, and manage emerging infectious threats. By fostering collaboration and vigilance, we can confront this challenge and strengthen our preparedness for future outbreaks.

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CRediT authorship contribution statement

Francesco Branda: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing. **Chiara Romano:** Writing – original draft, Writing – review & editing. **Marta Giovanetti:** Writing – original draft, Writing – review & editing. **Alessandra Ciccozzi:** Writing – original draft, Writing – review & editing. **Massimo Ciccozzi:** Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing. **Fabio Scarpa:** Data curation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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