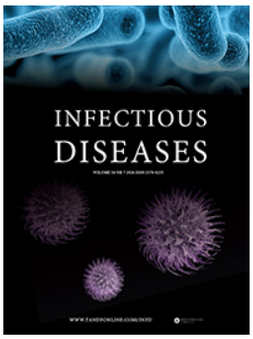

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Francesco Branda, Alessandra Ciccozzi, Chiara Romano, Marco Casu, Daria Sanna, Giancarlo Ceccarelli, Massimo Ciccozzi & Fabio Scarpa

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COMMENT

Insights into avian influenza A(H5N1) events: epidemiological patterns and genetic analysis

Influenza A viruses usually spread among animals but are also capable of infecting humans. Human infections are primarily acquired through direct contact with infected animals or contaminated environments. Based on the original host, influenza A viruses can be classified as avian influenza, swine influenza, or other types of animal influenza viruses. Human infections with avian influenza viruses can cause diseases ranging from mild upper respiratory tract infections to more severe illnesses and can be fatal. Conjunctivitis, gastrointestinal symptoms, encephalitis and encephalopathy have also been reported in previous human infections with A(H5N1) viruses. There have also been a few detections of A(H5N1) virus in asymptomatic individuals who were exposed to infected birds.

To support the understanding of the recent dynamics of human avian influenza outbreaks and accurately track the evolution of the situation in real time, despite the continuous and uncontrolled flow of news, we have developed a data dictionary [1], which serves as a comprehensive framework that systematically organizes the unstructured information found in the epidemiological bulletins of government authorities into a structured format. The data dictionary serves as a guideline for creating lists of rows, where each row represents an individual case, and each column collects specific information related to that case. Data records include biographical information (such as age and sex), symptoms, dates of disease onset and case confirmation, known exposures, contacts, laboratory test results, and other relevant details. The availability of this information in a standardized format facilitates the identification of infection clusters, the search for common sources of exposure, and the analysis of risk factors associated with infection. In addition, it makes it possible to track disease trends over time and space [2], providing a solid basis for modelling and forecasting epidemics.

Since 2022, avian influenza A(H5N1) virus belonging to the clade 2.3.4.4b. Eurasian-origin has been reported in birds in the United States. In late March 2024, Highly Pathogenic Avian Influenza (HPAI) A(H5N1) was also detected in dairy herds in Texas and Kansas [3]. In 2024, the first case has been recorded in late January in Cambodia (isolated on 23 January 2024). Indeed, a child of 3-year-old exhibited symptoms on 13 January 2024 and was hospitalized on 16 January 2024 with a high fever, cough, and runny nose [4]. The child had been exposed to backyard chickens found dead near the home. Molecular analyses indicate that the involved clade of H5N1 is the 2.3.2.1c (EPI_ISL_18823967) [5]. After his diagnosis, 14 close contacts were identified and tested, all of whom were negative for influenza. The second case involved a 69-year-old reported on 28 January 2024 from Cambodia. Initial investigations indicated the patient raised domestic poultry and fighting roosters; three chickens tested positive for influenza A(H5N1). For this patient genomic sequence of the lineage is not available. In early February the third case from Cambodia has been registered involving a 9-year-old boy who died from his infection. Also, in this case molecular investigation indicates the belonging to the clade 2.3.2.1c (EPI_ISL_18879683) [5], and as with the other cases, investigators discovered that poultry had died at the patient's residence (https://www.cidrap.umn.edu/avian-influenza-bird-flu/cambodia-reports-new-fatal-h5n1-avian-flu-case).

In March, occurred three cases in Australia, Vietnam and USA [6]. The Australian case has been reported in Victoria, and the infection occurred in a child who contracted the virus in India and fell ill in March 2024 (https://www.health.vic.gov.au/health-advisories/human-case-of-avian-influenza-bird-flu-detected-in-returned-traveller-to-victoria). Genomic sequences indicated that the infection was due to clade 2.3.2.1a (EPI_ISL_19156871) [5], which is consistent with the hypothesis of contagion

in India, considering that clade 2.3.2.1a is very common in Southeast Asia, especially in Bangladesh. On 11 March 2024, a 21-year-old male from Vietnam, developed a fever and cough and was admitted to a local hospital on 15 March due to persistent symptoms, including abdominal pain and diarrhea. On 20 March, his symptoms worsened to include severe pneumonia, severe sepsis, and acute respiratory distress syndrome, until the patient died on 23 March. The strain causing the infection was classified as belonging to clade 2.3.2.1a (EPI_ISL_19031556) [5].

The fifth human case in 2024 occurred in late March in Texas (USA), representing the first case in USA [7]. Indeed, on April 1, 2024, Texas reported a human case of H5N1 bird flu, confirmed by the CDC. This marks the first instance of this virus being detected in a cow and the second human H5N1 bird flu case in the United States. The first case occurred in 2022 in Colorado, involving a poultry worker. The new case is linked to a multi-state veterinary outbreak of H5N1 bird flu in U.S. dairy cows. It comes amid ongoing H5N1 bird flu outbreaks in U.S. poultry, sporadic infections across an increasing number of animal species, and widespread circulation of the virus in wild birds worldwide.

The man in Texas with H5N1 bird flu, who was exposed to likely infected cows, exhibited conjunctivitis as their only symptom and is recovering. They were advised to stay isolated at home and received antiviral flu treatment [7]. Human H5N1 infections are rare but typically occur after unprotected exposure to infected birds, where the virus enters through the eyes, nose, or mouth, or is inhaled, or when a person touches a contaminated surface and then their face. This Texas case is the first known instance of human infection from a cow. The exact transmission method in this case remains unclear. Human bird flu symptoms can range from mild, such as eye infections and respiratory symptoms, to severe, including pneumonia, multi-organ failure, and death. The strain causing the infection was classified as belonging to clade 2.3.4.4b (EPI_ISL_19027114) [5]. The sixth and seventh human cases in 2024 occurred in Michigan in mid and late May, respectively [8]. Also for these cases the isolated strain belongs to the clade 2.3.4.4b (EPI_ISL_19162802; EPI_ISL_19177746) [5]. Like the previous one in Texas, these cases occurred in a dairy farm worker who was exposed to infected cows, suggesting another probable instance of cow-to-person transmission. This marks the first human case of H5 in the United States exhibiting typical symptoms of acute respiratory illness commonly associated with influenza viruses, including A(H5N1). These sudden and sometimes unexpected cases have drawn attention to the risk of viruses jumping from animals to humans.

Anyhow, it should be noted that spill-over is an event that can be clearly identified at a genetic level once it has occurred. Figure 1 represents the phylogeny of every recognized clade of avian flu based on the HA gene for the H5 subtype. The tree illustrates the absence of clades composed solely of strains that infected humans, as would be expected if there had been a species jump or an accumulation of mutations making the virus more akin to the human host. Of course, some mutations may have occurred that make the virus more

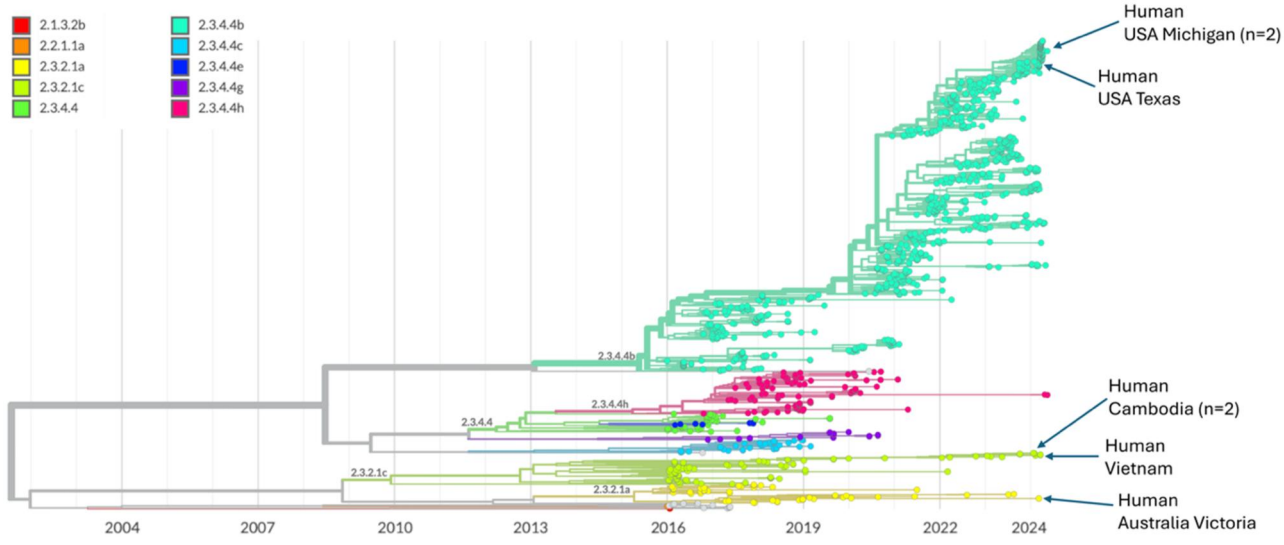

Figure 1. Phylogenetic time-calibrated tree of a representative global subsample of 1184 sequence of H5Nx virus sampled between January 2016 and May 2024 reconstructed by using nextstrain/influenza. Figure has been edited by using the software GIMP 2.8 (https://www.gimp.org/downloads/oldstable/).

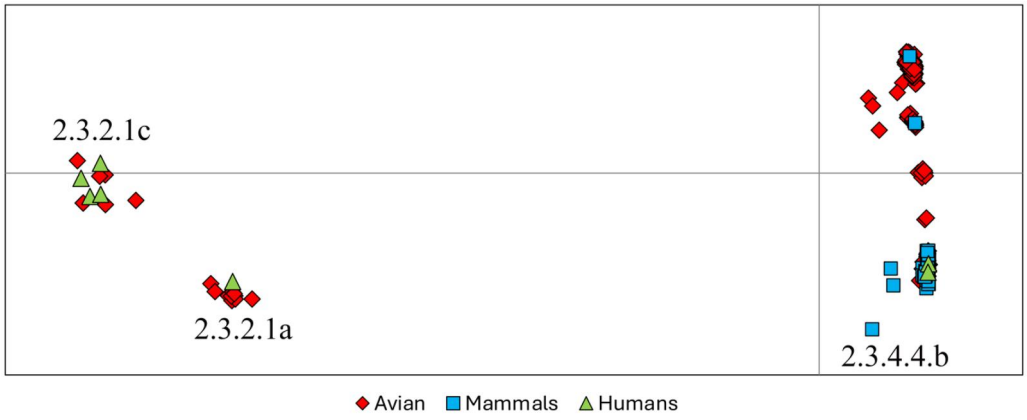

Figure 2. PCoA Reconstruction based on sequences of HA gene for H5N1 clades 2.3.2.1a, 2.3.2.1c and 2.3.4.4.b. PCoA in HA and NA produced the same structuring. Figure has been edited by using the software GIMP 2.8 (https://www.gimp.org/downloads/oldstable/).

akin to the human host, but this does not describe a species jump but rather simple genetic drift, which causes some strains to exhibit a greater affinity for incidental hosts. In fact, the tree shows that the different human cases were infected by different strains that were spread heterogeneously, without demonstrating a greater affinity for one strain over another. This indicates that infections occurred based on exposure to certain infected animals and/or the region of origin.

These results were also confirmed by the PCoA (Figure 2) based on Hamming distances between the nucleotide sequences, which shows a marked structuring among the isolates. However, this structuring is not host-based but is clade-based. In fact, the PCoA graph denotes a separation among the three clades included in the analysis, forming three groups, with all hosts clustering within all groups. This confirms that the virus has not yet specialized toward the human host, which is present in all three groups.

Further confirmation is given by the genetic distances that indicates that for HA, the difference between strains isolated in humans and their animal counterparts ranges from 0.002 to 0.008, while for NA, it ranges from 0.002 to 0.007. Also, in this case, it is interesting to point out that in case of spill-over the difference is significantly higher and spans a different order of magnitude. For instance, the average distance between 2.3.2.1(ac) and 2.3.4.4b is 0.147, despite the potential for both to infect the same hosts.

All genetic analyses here presented indicate that these viruses remain primarily avian and are not well adapted to humans. Of course, these results do not imply that it can never happen, but it has not yet occurred. Indeed, spill-over occurs when a pathogen, highly prevalent within a specific population (reservoir), encounters individuals of different species, leading to the pathogen's transmission between species. This transmission is initiated by the reservoir population and spreads within the new susceptible host population. The genetic characteristics of a spill-over event differ significantly from those observed in reported cases. Genetic drift, which induces nucleotide substitutions, represents the potential for substantial changes. In influenza viruses, such changes are driven by antigenic drift, involving minor mutations in the HA and NA genes, thereby altering these surface proteins. These alterations occur gradually over time as influenza viruses replicate, producing strains that are distinct yet closely related. This variation allows for the occurrence of limited human cases. Conversely, the shift that can result in a spill-over event is abrupt and caused by antigenic shift, where reassortment events lead to the emergence of new HA and NA proteins, thus enabling infection in humans or other species. This shift may introduce a new subtype that infects humans for the first time. An example of such a shift occurred in the spring of 2009, when an H1N1 virus, incorporating genes from North American swine, Eurasian swine, humans, and birds, emerged, causing a pandemic. As of now, Influenza A H5N1 lacks these characteristics, and the genetic signature of a spill-over event remains absent. However, this does not preclude the possibility of future relapses. Although HPAI H5N1 can induce severe disease in humans, no cases of human-to-human transmission have been identified, but this should not be interpreted as a reason to become complacent.

In light of the lessons learned from the COVID-19 pandemic, the scientific community recognises that continuous One Health surveillance, incorporating ongoing genome-based monitoring, is the most effective tool for

enhanced comprehension. Surveillance efforts must remain uninterrupted to detect any genetic signatures within the viral genome, indicating the occurrence of a genuine spill-over event. Through our work, we aim to ensure that the data collected are complete, accurate and up-to-date, for the following objectives: (i) identify and assess risk factors associated with avian influenza infection, thereby contributing to a better understanding of transmission dynamics and prevention; (ii) communicate relevant information on the avian influenza situation to the public and professionals in a clear and timely manner, promoting greater awareness and adherence to prevention and control measures; (iii) actively collaborating with health authorities and international bodies to share relevant data and information on avian influenza, thereby facilitating a coordinated and comprehensive response; (iv) developing and evaluating new avian influenza control strategies, using innovative evidence-based approaches to minimise the incidence and impact of the disease.

Author contributions

Conception and design: F.B., M.C., F.S.; Investigations: F.B., M.C., F.S.; Validation: M.C.; Supervision: M.C.; Writing – Original: F.B., M.C., F.S.; Writing – Revision: F.B., A.C., C.R., M.CA., D.S., G.C., M.CI., F.S.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

[1] Branda F, Mazzoli S. The importance of rapid and robust availability of epidemiological data for real-time mapping of the risk of avian influenza a (H5N1) spread. Pathog Glob Health. 2023;117(6):521–524. doi: 10.1080/20477724.2023.2228055.

[2] Branda F, Mazzoli S, Pierini M, et al. Trends and spatiotemporal patterns of avian influenza outbreaks in Italy: a data-driven approach. Infect Dis Rep. 2023;16(1):1–12. doi: 10.3390/idr16010001.

[3] Centers for Disease Control and Prevention. Highly Pathogenic Avian Influenza A (H5N1) Virus Infection Reported in a Person in the U.S. Atlanta CDC-US: 2024. Available from: https://www.cdc.gov/media/releases/2024/p0401-avian-flu.html.

[4] World Health Organization. Disease Outbreak News; Avian Influenza A (H5N1) - Cambodia; 2024. (8 February). Available from: http://www.who.int/emergencies/disease-outbreak-news/item/2024-DON501.

[5] GISAID portal. Available from: https://gisaid.org/.

[6] World Health Organization. Disease Outbreak News; Avian Influenza A (H5N1) (2 April 2024). - Vietnam. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON511.

[7] Centers for Disease Control and Prevention. Highly Pathogenic Avian Influenza A (H5N1) VirusInfection Reported in a Person in the U.S. Atlanta CDC-US; 2024; Available from: https://www.cdc.gov/media/releases/2024/p0401-avian-flu.html.

[8] Centers for Disease Control and Prevention. Technical Report: highly Pathogenic AvianInfluenza A(H5N1) Viruses. Available from: https://www.cdc.gov/flu/avianflu/spotlights/2023-2024/h5n1-technical-report-06052024.htm.

Francesco Branda
Unit of Medical Statistics and Molecular Epidemiology, Università Campus Bio-Medico di Roma, Rome, Italy
f.branda@unicampus.it

Alessandra Ciccozzi
Department of Biomedical Sciences, University of Sassari, Sassari, Italy

Chiara Romano
Unit of Medical Statistics and Molecular Epidemiology, Università Campus Bio-Medico di Roma, Rome, Italy

Marco Casu
Department of Veterinary Medicine, University of Sassari, Sassari, Italy

Daria Sanna
Department of Biomedical Sciences, University of Sassari, Sassari, Italy

Giancarlo Ceccarelli
Department of Public Health and Infectious Diseases, University Hospital Policlinico Umberto I, Sapienza University of Rome, Rome, Italy

Massimo Ciccozzi
Unit of Medical Statistics and Molecular Epidemiology, Università Campus Bio-Medico di Roma, Rome, Italy

Fabio Scarpa
Department of Biomedical Sciences, University of Sassari, Sassari, Italy

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