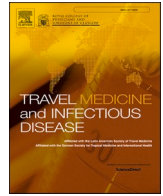




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Is it safe to travel? The H5N1 avian flu and the Aesop novel

The fairy tale “*to the wolf, to the wolf*” by Aesop tells the story of a little shepherd boy who guarded his father’s flock during the night. Often overcome by boredom, he decided to play a joke on everyone and in the night, he began to scream: Wolf, wolf! The moral is, if you lie too much you end up not being believed, even when you tell the truth. Highly pathogenic avian influenza (HPAI) viruses pose a significant threat to wild birds and poultry worldwide. Of particular concern at present is the A(H5N1) strain because of its frequent spread in mammalian species. In February 2024, veterinarians observed a syndrome occurring in lactating dairy cattle in Texas. One month after similar clinical cases were reported in dairy cattle in Kansas and New Mexico; deaths of wild birds and domestic cats were observed within affected sites in the Texas.

After specific research and analysis, milk and tissue samples from cattle and from the cats tested positive for HPAI H5N1 virus [1]. Recently a human case of avian influenza A(H5N1) infection has been reported in the state of Victoria, Australia. The State Health Department announced this in a statement, explaining that it is the first human case of avian influenza H5N1 in Australia. The infection occurred in a child who travel to India where contracted the virus and became ill in March 2024. Avian influenza was detected through further testing of positive influenza samples conducted to identify novel or concerning flu virus strains as part of Victoria’s enhanced surveillance system. Contact tracing has not identified any additional cases of avian influenza connected to this one (<https://www.health.vic.gov.au/health-advisories/human-case-of-avian-influenza-bird-flu-detected-in-returned-traveller-to-victoria>). From this moment on, debates began all over the world on the concern of a possible spillover and passage to humans with certainly not pleasant consequences. The questions we must ask ourselves are: is this the prelude to a new pandemic? What can we do to avoid it? [2].

A recent article published in The Lancet Infectious Diseases [3] described two human cases of HPAI A(H5N1) virus. One case in Viet Nam occurred following exposure to infected birds and resulted in death. The other case occurred in Texas, USA, where a worker on a commercial dairy farm experienced mild illness related to HPAI A(H5N1) virus infection detected in cattle and dead birds from the same farm. Subsequently, a third confirmed human case of avian influenza contracted from a cow was reported in the USA. This man presented respiratory symptoms, marking the first instance of such symptoms in the USA, indicating a potentially higher danger of exposure to the virus compared to previous cases that only involved eye infections. While attempting to prevent alarmism and reiterating that the risk for people contracting the H5N1 virus remains low, scientists are beginning to express concerns about the ability to contain the spread of infections, given the emergence of respiratory symptoms in the third man infected on a cattle farm [4].

The HPAI A(H5N1) is not an unknown virus, it was discovered in domestic waterfowl in China in 1996 causing human infections with high mortality rate (50 %). Over time, through random mutations and genetic reassortment with other avian influenza viruses, HPAI A(H5N1) has evolved into various clades and subclades. Despite this, the resulting viruses have only sporadically infected humans, suggesting no human adaptation, up to now. To verify the occurrence of a genetic signature of a spillover event a recent study compared the genomes isolated in avian, mammals, and human hosts in 2024 for the genes HA and NA [2]. The authors indicated how for the gene HA, sites under positive pressure are present only in the avian dataset indicating a potential adaptive evolution to resist environmental pressures or enhance infectivity in avian hosts. Conversely, the datasets on mammals and humans, with only sites under negative selective pressure, suggest that the avian influenza virus in these mammalian hosts do not confer a selective advantage. This could indicate greater genetic stability of the virus in mammalian populations compared to birds but of concern 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. In the NA gene was observed that the only site under positive selective pressure was found in mammals. This could indicate a specific adaptive evolution of the avian influenza virus in mammalian hosts regarding the NA gene. This could imply a probable increase in transmissibility, virulence, or the ability to evade the immune response in mammalian hosts.

An overview of the spread of the cases by the European Food Safety Authority (EFSA) (<https://www.efsa.europa.eu/>) showed how between December 2023 and March 2024, in Europe the reported cases were 227 in domestic birds whether 414 in wild birds across 26 different countries, significantly lower, possibly due to some level of flock immunity in previously affected wild bird species, resulting in reduced contamination of the environment, and a different composition of circulating A(H5N1) genotypes. Looking these last reports, human infections with avian influenza remain rare and no sustained human-to-human infection has been observed. The risk of infection with H5 avian influenza virus (clade 2.3.4.4b) currently circulating in Europe remains low for the general EU/EEA population, while it remains low to moderate for those who work with or are otherwise exposed to infected animals.

This avian virus, which had previously been found in mammals such as mink and sea lions, had never been detected in cows, and this is the important news, but without excessive alarmism, without frightening the population, but trying to take preventive and monitoring measures, trying to make people understand the importance of sharing data [5] and information that can make us ready for any serious emergency. Careful monitoring must be done by veterinarians in intensive farms to prevent the spread of the virus and avoid possible mutations that could make the situation worse. With cases identified in several countries, the

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importance of timely antiviral intervention to reduce mortality rates is critical. For example, Adisasmito et al. [6] emphasize the need for early diagnostic and therapeutic measures, particularly with treatment with oseltamivir, which showed a significant reduction in mortality rates when started within 6–8 days of symptom onset.

The recent outbreaks underscore 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. The only tool that allows us to have clear insights and an up-to-date perspective on the real situation is the constant genetic monitoring. In fact, only through this way it is possible to trace the origin of each contagion without necessarily fearing that a species jump has occurred.

In conclusion we are obliged to return to the reading of Aesop's fable, trying not to cry "wolf" when there is no need, otherwise when a mutation or reassortment of the virus occurs, which can lead to human-to-human transmission, no one will believe it anymore.

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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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