

WEEKLY SCIENTIFIC REVIEW ON AVIAN INFLUENZA A(H5N1)

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<https://anrs.fr/fr/Cellules-Emergence/cellule-emergence-influenza-aviaire-a-h5n1/>

General informations

This section presents a detailed timeline of the outbreak, with significant events related to its progression, current status and case reports.

The content of this document is subject to change as the health situation evolves. All informations comes from a valid and credible source.

Since 2024

Human A(H5N1) infection with exposure to dairy cows in U.S.

Other human infections with A(H5N1) worldwide

On **30 May 2024**, a 3rd U.S. dairy worker tested positive for bird flu after exposure to infected cows and was the first to suffer respiratory problems.

The infection was the 2nd human case in Michigan, which has confirmed more cases of bird flu in dairy cattle than any other state. It also expands the symptoms for human cases, after the 2 workers who previously tested positive experienced only conjunctivitis, or pink eye, and recovered.

Source: [Reuters](#). 30 May 2024.

On **22 May 2024**, a Michigan dairy worker has been diagnosed with bird flu, the second human case associated with an outbreak in US dairy cows.

The male worker had been in contact with cows at a farm with infected animals. He experienced mild eye symptoms and has recovered.

Source: [APnews](#). 23 May 2024

On **22 May 2024**, the first human case of A(H5N1) highly pathogenic avian influenza (bird flu) has been confirmed in Australia, in a child recently returned from India.

The child who became unwell whilst in India was hospitalized upon return to Australia in March 2024. Influenza A was detected by PCR during admission, and the child was treated with oseltamivir during a prolonged stay in intensive care with severe lower respiratory tract infection and hypoxia with respiratory failure. The child has since been discharged home and has made a complete recovery.

Source: [Victoria Health government](#). 21 May 2024.

May

March

On **28 March 2024**, a case of human infection with avian influenza A(H5N1) virus was reported in China. The reported case was a 33-year-old female tested positive for H5N1 in the Guangxi Autonomous Region, China.

Source: [WHO](#). 3 May 2024.

On **27 March 2024**, a laboratory-confirmed human case of avian influenza A(H5N1) has been detected in the state of Texas.

The case is aged over 18 years, working at a commercial dairy cattle farm and had a history of exposure to dairy cattle (cows). It appears to be the first human infection with A(H5N1) acquired from contact with an infected mammal, although human infections with other influenza subtypes have previously been acquired from mammals.

Source: [WHO](#). 9 April 2024.

On **11 March 2024**, a case of human infection with an influenza A(H5N1) virus in a 21-year-old male with no underlying conditions from Viet Nam developed symptoms. Exposure to birds was ascertained to have taken place in the third week of February.

This is the first human infection with an avian influenza A (H5N1) virus reported in Viet Nam since 2022.

Source: [WHO](#). 2 April 2024

February

On **12 February 2024**, Cambodia has reported four recent human infections with highly pathogenic avian influenza (HPAI) A(H5N1) (bird flu) virus. These are the first human infections with HPAI A(H5N1) virus identified in Cambodia in 2024.

The four infections occurred in three children, one of whom died, and an adult, all of which were identified in late January and early February. All patients reportedly had a history of recent exposure to sick or dead poultry prior to their illness.

Source: [CDC](#). 12 February 2024

From **1 January 2003 to 21 December 2023**, a total of 248 cases of human infection with avian influenza A(H5N1) virus were reported from four countries within the Western Pacific Region (Table 1). Of these cases, 139 were fatal.

Source: [WHO](#).

Scientific articles

This section presents relevant articles published on peer-reviewed scientific journals or pre-print platforms. The content of this document is subject to change as the health situation evolves. All informations comes from a valid and credible source.

Does pasteurization inactivate bird flu virus in milk?. Cui P, Zhuang Y, Zhang Y, Chen L, Chen P, Li J, Feng L, Chen Q, Meng F, Yang H, Jiang Y, Deng G, Shi J, Chen H, Kong H.

Published in *Emerging Microbes & Infections* on 16 June 2024.
<https://doi.org/10.1080/22221751.2024.2364732>

An outbreak of highly pathogenic avian influenza A (H5N1) was recently reported in dairy cows in the United States. Currently, little data is available regarding the efficacy of pasteurization against H5N1 virus in raw milk. In this study, authors provide direct evidence that pasteurization is sufficient to inactivate all tested influenza A viruses in raw milk collected from healthy dairy cattles, addressing a common concern among milk consumers and those with food safety concerns.

Antiviral Susceptibility of Highly Pathogenic Avian Influenza A(H5N1) Viruses Circulating Globally in 2022-2023. Andreev K, Jones JC, Seiler P, Kandeil A, Turner JCM, Barman S, Rubrum AM, Webby RJ, Govorkova EA.

Published in *The Journal of Infectious Diseases* on 15 June 2024.
<https://doi.org/10.1093/infdis/jiad418>

In this study, the antiviral susceptibility of currently circulating (2022–2023) highly pathogenic avian influenza (HPAI) A(H5N1) viruses was assessed by genotypic and phenotypic approaches. The frequency was low for neuraminidase (NA) and polymerase acidic (PA) substitutions associated with reduced inhibition by NA inhibitors (21/2698, 0.78%) or the PA inhibitor baloxavir (14/2600, 0.54%). Phenotypic testing of 22 clade 2.3.2.1a and 2.3.4.4b viruses revealed broad susceptibility to NA inhibitors and baloxavir. Authors therefore concluded that most contemporary HPAI A(H5N1) viruses retain susceptibility to antiviral drugs. Novel NA-K432E and NA-T438I substitutions (N2 numbering) were identified at elevated frequencies in samples (104/2698, 3.85%) and caused reduced zanamivir and peramivir inhibition.

Sialic Acid Receptor Specificity in Mammary Gland of Dairy Cattle Infected with Highly Pathogenic Avian Influenza A(H5N1) Virus. Nelli RK, Harm TA, Siepker C, Groeltz-Thrush JM, Jones B, Twu NC, Nenninger AS, Magstadt DR, Burrough ER, Piñeyro PE, Mainenti M, Carnaccini S, Plummer PJ, Bell TM.

Published in *Emerging Infectious Diseases* on 11 June 2024.
<https://doi.org/10.3201/eid3007.240689>

In March 2024, highly pathogenic avian influenza (HPAI) A(H5N1) virus was detected for the first time in dairy cattle in the United States. This discovery has triggered public health alerts and raised concerns about HPAI H5N1 spread. A key factor of a virus-host range is receptor availability ; however, little is known about the distribution of Influenza A viruses (IAVs) receptors, sialic acids (SA), in dairy cattle, particularly in mammary glands. This study explored the presence and distribution of cellular and receptor factors that enable HPAI H5N1 virus infection in Holstein dairy cattle.

Cow's Milk Containing Avian Influenza A(H5N1) Virus - Heat Inactivation and Infectivity in Mice. Guan L, Eisfeld AJ, Pattinson D, Gu C, Biswas A, Maemura T, Trifkovic S, Babujee L, Presler R Jr, Dahn R, Halfmann PJ, Barnhardt T, Neumann G, Thompson A, Swinford AK, Dimitrov KM, Poulsen K, Kawaoka Y.

Published in *Emerging Infectious Diseases* on 11 June 2024.
<https://doi.org/10.1056/nejmc2405495>

Highly pathogenic avian influenza virus (HPAI) of the H5N1 subtype was recently detected in nasal swabs and milk of dairy cows, increasing concern that HPAI A(H5N1) viruses may enter the human food chain. In this study, the authors assessed temperature stability and infectivity in mice of HPAI A(H5N1) virus-positive milk samples. Results showed that heat treatment reduced virus titers but did not completely inactivate the virus. At 4°C, HPAI A(H5N1) virus remained infectious for several weeks in raw milk. In addition, high virus titers were detected in the respiratory organs and moderate virus titers in several other organs of mice upon oral inoculation. Collectively, these data indicate that HPAI A(H5N1) virus in untreated milk can infect susceptible animals that consume it.

Avian Influenza A(H5N1) Virus among Dairy Cattle, Texas, USA. Oguzie JU, Marushchak LV, Shittu I, Lednicky JA, Miller AL, Hao H, Nelson MI, Gray GC.

Published in *Emerging Infectious Diseases* on 7 June 2024.
<https://doi.org/10.3201/eid3007.240717>

During March and April 2024, this study was conducted on dairy cattle specimens from a farm in Texas, revealing that highly pathogenic avian influenza (HPAI) A(H5N1) virus strains were the sole cause of an epizootic. Since the arrival of the H5N1 clade 2.3.4.4b in North America in 2021, there have been frequent mammalian spillover events across various species, including one human infection, though cattle had not been affected until this incident. Samples from 30 cows (24 sick and 6 healthy) were collected and analyzed using molecular screening, cell culture, and metagenomics techniques. The results confirmed the presence of the H5 avian influenza A virus, specifically HPAI H5N1, without other viral co-infections. The virus was more prevalent in nasal swabs than rectal swabs, suggesting respiratory transmission among cattle.

Next-generation sequencing (NGS) of a complete genome from a sick cow's nasal swab indicated high similarity to H5N1 strains from dead birds, other cattle, and a cattle worker in Texas, suggesting a single interconnected multispecies outbreak. A significant mutation (PB2-M631L) in the virus enhances its replication in human cells.

Despite limitations, such as the lack of milk samples, environmental specimens, and a comprehensive farm investigation, this study highlights the necessity of interdisciplinary cooperation under a One Health framework to address complex epizootics. Ensuring that epidemiological investigations do not harm farm owners' businesses is crucial for effective outbreak management.

COBRA HA and NA vaccination elicits long-live protective immune responses against pre-pandemic H2, H5, and H7 influenza virus subtypes. Ge P, Ross TM.

Published in *Virology* on 1 June 2024.
<https://doi.org/10.1016/j.virol.2024.110119>

In this study, a multivalent pre-pandemic influenza vaccine was evaluated in both naïve and pre-immune mice to mimic immunity in humans. Mice were vaccinated with COBRA H2, H5, and H7 hemagglutinin (HA) and two neuraminidase (NA) proteins, N1 and N2. Vaccinated mice were fully protected against lethal challenge with H5N6 influenza virus. Sera collected after vaccination showed cross-reactive IgG antibodies against a panel of wild-type H2, H5, and H7 HA proteins, and N1 and N2 NA proteins. Mice with pre-existing immunity to H1N1 and H3N2 influenza viruses that were subsequently vaccinated with COBRA HA/NA vaccines had enhanced anti-HA stem antibodies compared to vaccinated mice without pre-existing immunity. Little to no lung injury was observed in the lungs of COBRA HA/NA vaccinated mice following influenza virus challenge. In addition, sera collected after vaccination had hemagglutinin inhibitory activity against a panel of H2Nx, H5Nx, and H7Nx influenza viruses. These protective antibodies were maintained up for up to 4 months after vaccination.

Development of a nucleoside-modified mRNA vaccine against clade 2.3.4.4b H5 highly pathogenic avian influenza virus. Furey C, Scher G, Ye N, Kercher L, DeBeauchamp J, Crumpton JC, Jeevan T, Patton C, Franks J, Rubrum A, Alameh MG, Fan SHY, Phan AT, Hunter CA, Webby RJ, Weissman D, Hensley SE.

Published in *Nature Communications* on 23 May 2024.
<https://doi.org/10.1038/s41467-024-48555-z>

In this study, an mRNA lipid nanoparticle (LNP) vaccine encoding the hemagglutinin (HA) glycoprotein from a clade 2.3.4.4b H5 isolate was generated. The H5 mRNA-LNP vaccine elicits strong T cell and antibody responses in female mice, including neutralizing antibodies and broadly-reactive anti-HA stalk antibodies. The H5 mRNA-LNP vaccine elicits antibodies at similar levels compared to whole inactivated vaccines in female mice with and without prior H1N1 exposures. Finally, the H5 mRNA-LNP vaccine was immunogenic in male ferrets and prevents morbidity and mortality of animals following 2.3.4.4b H5N1 challenge. Together, our data demonstrate that a monovalent mRNA-LNP vaccine expressing 2.3.4.4b H5 is immunogenic and protective in pre-clinical animal models.

Structures of H5N1 influenza polymerase with ANP32B reveal mechanisms of genome replication and host adaptation. Staller E, Carrique L, Swann OC, Fan H, Keown JR, Sheppard CM, Barclay WS, Grimes JM, Fodor E.

Published in *Nature Communications* on 15 May 2024.
<https://doi.org/10.1038/s41467-024-48470-3>

Genome replication of avian influenza A viruses (IAVs) in mammalian cells is dependent on host acidic nuclear phosphoprotein 32 (ANP32) proteins and IAV RNA polymerase (FluPol) oligomerisation. This study reveals cryo-electron microscopy structures of monomeric and dimeric avian H5N1 FluPolA with human ANP32B. It provides insight into the molecular mechanisms governing IAV genome replication, while enhancing our understanding of the molecular processes underpinning mammalian adaptations in avian-origin FluPolA.

Highly Pathogenic Avian Influenza A(H5N1) Virus Infection in a Dairy Farm Worker. Uyeki TM, Milton S, Abdul Hamid C, Reinoso Webb C, Presley SM, Shetty V, Rollo SN, Martinez DL, Rai S, Gonzales ER, Kniss KL, Jang Y, Frederick JC, De La Cruz JA, Liddell J, Di H, Kirby MK, Barnes JR, Davis CT.

Published in *The New England Journal of Medicine* on 3 May 2024.
<https://doi.org/10.1056/nejmc2405371>

Conjunctivitis with H5N1 virus in a dairy farm worker in Texas, 03/2024 - close contact with sick cows - H5N1 virus regional cattle epidemic - recovery with oseltamivir - clade 2.3.4.4b (genotype B3.13) identification - PB2 E627K mutation associated with viral adaptation to mammalian hosts - probable sensitivity to two existing clade 2.3.4.4b A(H5N1) candidate vaccine viruses.

The avian and human influenza A virus receptors sialic acid (SA)- α 2,3 and SA- α 2,6 are widely expressed in the bovine mammary gland. Kristensen C, Jensen H, Trebbien R, Webby R, Larsen L.

Published in *BioRxiv* on 01 May 2024.
<https://doi.org/10.1101/2024.05.03.592326>

Cattle were considered almost resistant to IAV infection until recently, when an outbreak of H5N1 highly pathogenic influenza A virus (HPIAV) was detected in dairy cows in the United States. The main aim of this study was to investigate the in situ expression of IAV receptors in the bovine respiratory tract, cerebrum, and mammary glands by lectin histochemistry. The authors demonstrated that duck and human IAV receptors were widely expressed in the bovine mammary gland, whereas chicken receptor dominated the respiratory tract. Only a low expression of IAV receptors was observed in the neurons of the cerebrum. These results provide a mechanistic rationale for the high levels of H5N1 virus reported in infected bovine milk and show that cattle have the potential to act as a mixing vessel for novel IAV generation.

Highly Pathogenic Avian Influenza A(H5N1) Clade 2.3.4.4b Virus Infection in Domestic Dairy Cattle and Cats, United States, 2024. Burrough ER, Magstadt DR, Petersen B, Timmermans SJ, Gauger PC, Zhang J, Siepker C, Mainenti M, Li G, Thompson AC, Gorden PJ, Plummer PJ, Main R.

Published in *Emerging Infectious Diseases* on 29 April 2024.
<https://doi.org/10.3201/eid3007.240508>

This article discusses an outbreak of highly pathogenic avian influenza A virus (H5N1) among dairy cows and cats in the United States. It explores the virus's spread and interspecies transmission. Dairy cows showed decreased milk production, nonspecific illness, and sudden drops in milk yield. Cats fed raw milk from infected cows died. The virus was detected in milk samples, marking the first reported transmission of IAV from livestock to cats through milk consumption. The authors recommend further research into interspecies transmission. Dairy cattle are susceptible to infection with HPAI H5N1 virus and can shed the virus in milk, potentially transmitting infection to other mammals via unpasteurized milk. Clinical signs in affected cows often include reduced milk production and vague systemic illness, while affected domestic cats may rapidly develop neurological signs and death. Veterinarians should consider HPAI virus infection in dairy cattle experiencing unexpected drops in feed intake and milk production, and in cats showing sudden onset of neurological signs and blindness. The recurring global outbreaks of HPAI H5N1 and detection of spillover events in various hosts are concerning, indicating increasing virus adaptation in mammals.

Relevant news

This section presents official reports from health agencies, manufacturers and press releases with reliable sources.

Avian Influenza Weekly Update Number 952

Published in WHO on 21 June 2024.

https://cdn.who.int/media/docs/default-source/wpro--documents/emergency/surveillance/avian-influenza/ai_20240621.pdf?sfvrsn=78c8c282_5

On 22 May 2024, the World Health Organization (WHO) was notified of a laboratory-confirmed case of human infection with avian influenza A(H5N1) virus (clade 2.3.2.1a) by the International Health Regulations (IHR) National Focal Point (NFP) of Australia. This is the first confirmed human infection caused by avian influenza A(H5N1) virus detected and reported by Australia. Although the source of exposure to the virus in this case is currently unknown, the exposure likely occurred in India, where the case had travelled, and where this clade of A(H5N1) viruses has been detected in birds in the past. According to the IHR (2005), a human infection caused by a novel influenza A virus subtype is an event that has the potential for high public health impact and must be notified to the WHO. Based on available information, WHO assesses the current risk to the general population posed by this virus as low.

Enhanced influenza surveillance to detect avian influenza virus infections in the EU/EEA during the inter-seasonal period

Published in ECDC on 20 June 2024.

<https://www.ecdc.europa.eu/en/publications-data/enhanced-influenza-surveillance-detect-avian-influenza-virus-infections-eueea>

Highly pathogenic avian influenza A(H5N1) viruses continue to be widespread in wild bird populations across the European Union/European Economic Area (EU/EEA). Viruses circulating in wild birds have spilled over to both wild and domestic/farmed animals, leading to outbreaks in poultry and other animal farms. ECDC encourages national public health authorities to provide messaging to the general public to avoid close contact with or touching of sick or dead birds (especially seabirds and wildfowl) and dead wild mammals.

Technical Report: June 2024 Highly Pathogenic Avian Influenza A(H5N1) Viruses.

Published in CDC on 26 April 2024.

<https://www.cdc.gov/bird-flu/php/technical-report/h5n1-06052024.html>

This report provides an update to the April 26, 2024, report to include three additional sporadic human cases (1 in Australia and 2 in the United States) and recent activity in wild birds, poultry, and other animals, including the multi-state outbreak in U.S. dairy cattle, and updated information on monitoring for human infections with highly pathogenic avian influenza A(H5N1) virus infections in the United States. CDC continues to believe that the overall risk to human health associated with the ongoing outbreaks of highly pathogenic avian influenza A(H5N1) viruses has not changed and remains low to the U.S. general public at this time.

Avian influenza overview December 2023–March 2024

Published in European Centre for Disease Prevention and Control on 23 March 2024.

<https://www.ecdc.europa.eu/en/publications-data/avian-influenza-overview-december-2023-march-2024>

Compared to previous years, although still widespread, the overall number of HPAI virus detections in birds was significantly lower, among other reasons, 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. Most HPAI outbreaks reported in poultry were primary outbreaks following the introduction of the virus by wild birds. Outside Europe, the majority of outbreaks in poultry were still clustered in North America, while the spread of A(H5) to more naïve wild bird populations on mainland Antarctica is of particular concern. For mammals, A(H5N1) was reported for the first time in Europe, while goat kids in the United States of America represented the first natural A(H5N1) infection in ruminants. Since the last report and as of 12 March 2024, five human avian influenza A(H5N1) infections, including one death, three of which were clade 2.3.2.1c viruses, have been reported by Cambodia. China has reported two human infections, including one fatal case, with avian influenza A(H5N6), four human infections with avian influenza A(H9N2) and one fatal case with co-infection of seasonal influenza

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A(H3N2) and avian influenza A(H10N5). The latter case was the first documented human infection with avian influenza A(H10N5). Human infections with avian influenza remain rare and no sustained human-to-human infection has been observed. The risk of infection with currently circulating avian H5 influenza viruses of clade 2.3.4.4b in Europe remains low for the general population in the EU/EEA. The risk of infection remains low to moderate for those occupationally or otherwise exposed to infected animals.

Guidelines and practical information

This section lists official manuals of recommendations for clinical practice or public health policy published by leading health organizations.

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April 2024	Highly Pathogenic Avian Influenza A(H5N1) Virus: Identification of Human Infection and Recommendations for Investigations and Response (CDC)
June 2024	Prevention and Antiviral Treatment of Avian Influenza A Viruses in People (CDC)
June 2024	Détection des génomes du virus de la grippe A et B et du SARS-CoV-2 par RT-PCR dans un contexte d'exposition à risque à un virus influenza zoonotique (HAS)
May 2024	Avis du COVARS - Point sur la situation liée au virus influenza H5N1 (COVARS)
December 2023	Considerations for emergency vaccination of wild birds against high pathogenicity avian influenza in specific situations (WOAH)
June 2023	Enhanced surveillance of severe avian influenza virus infections in hospital settings in the EU/EEA (ECDC)
2022	Guidelines for the clinical management of severe illness from influenza virus infections (WHO)
December 2021	Avis relatif à la prévention de la transmission à l'homme des virus influenza porcins et aviaires (HCSP)
April 2014	Risk assessment guidelines for infectious diseases transmitted on aircraft (ECDC)