

MONTHLY SCIENTIFIC REVIEW ON AVIAN INFLUENZA A(H5N1)

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General informations

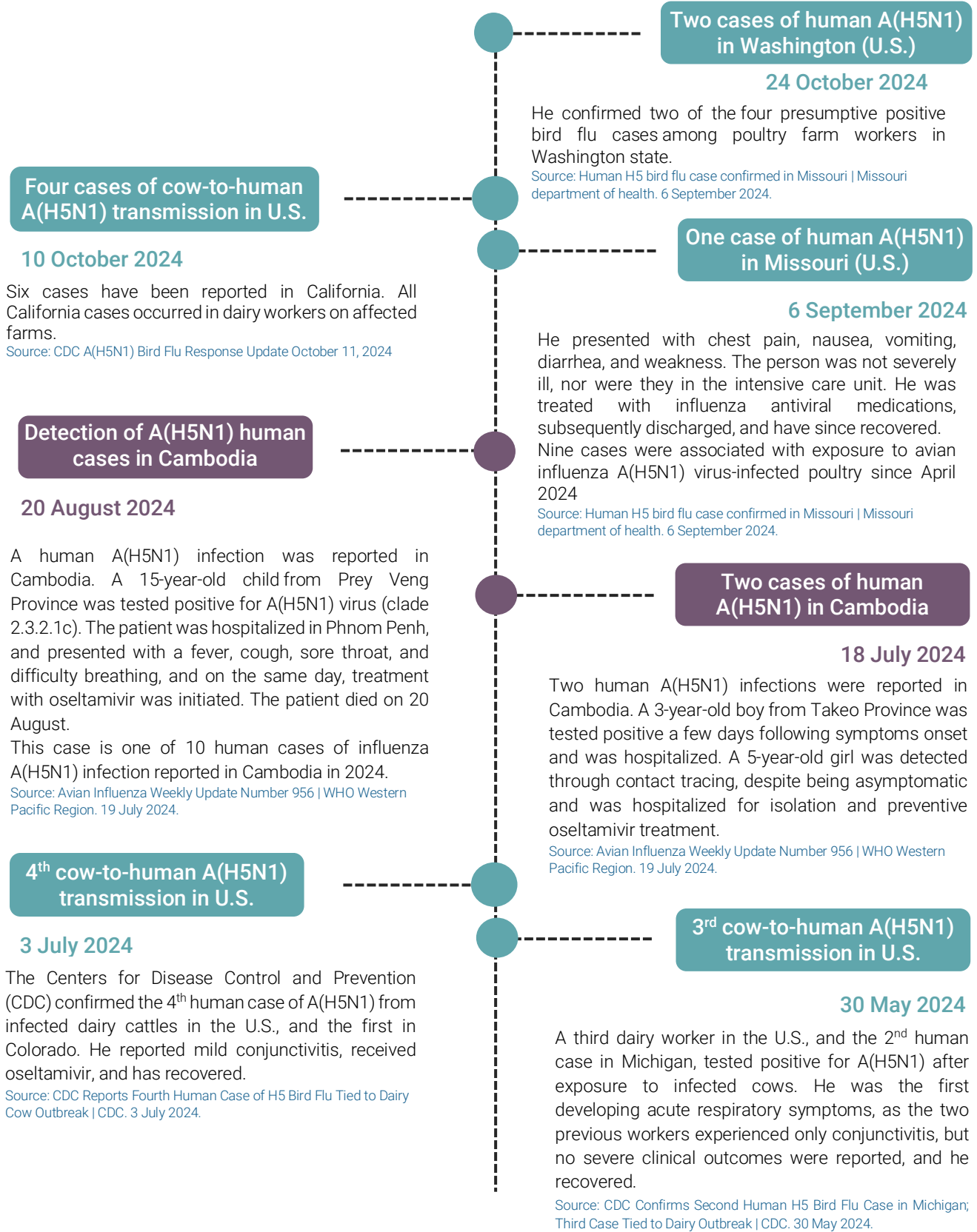
This section details the history and latest developments of the outbreak, with significant events and updates on its current status.

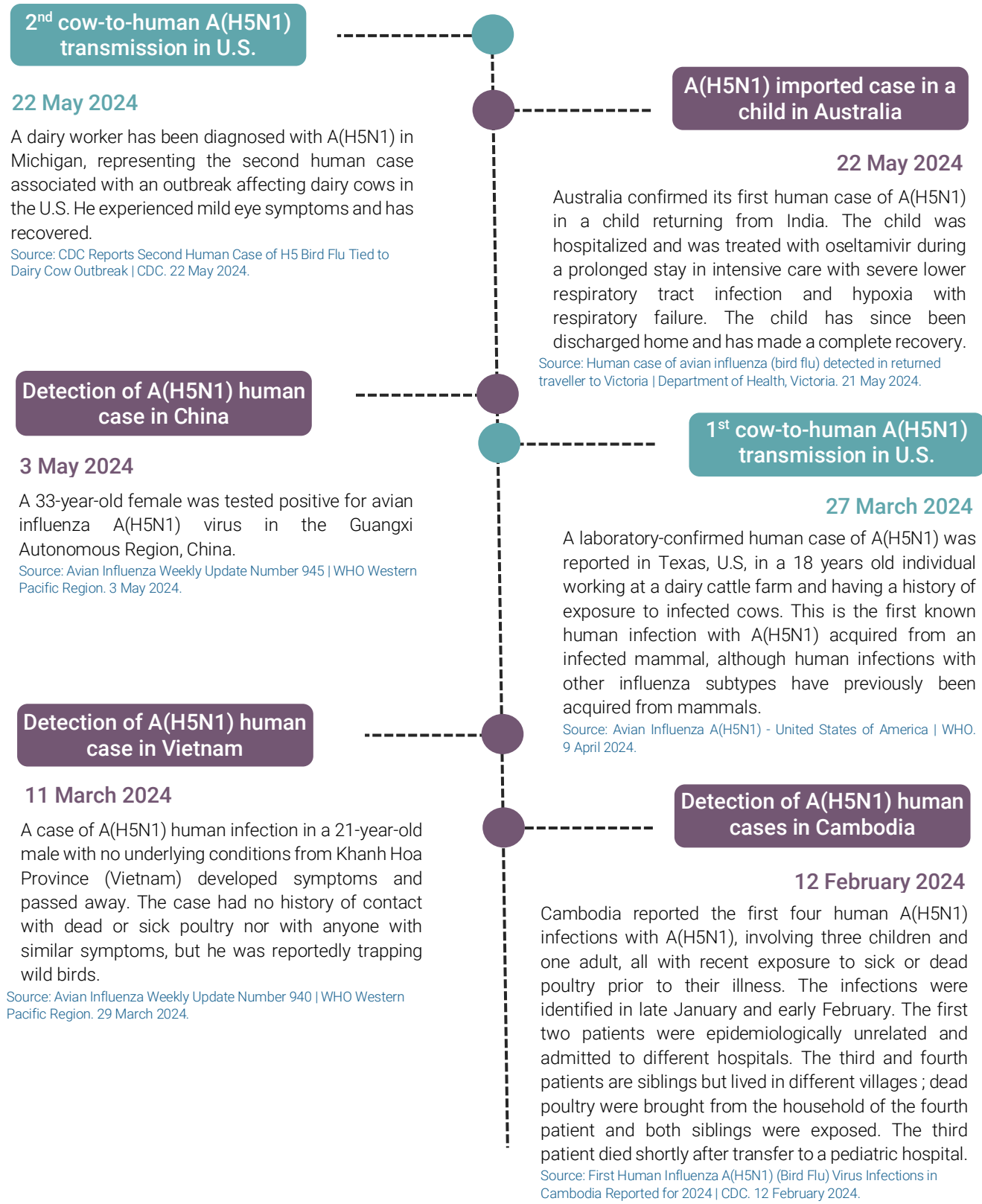
From 1 January 2003 to 27 September 2024, **904 cases of human infection with avian influenza A(H5N1) viruses** and **464 deaths** were reported from 24 countries to the *World Health Organization (WHO)*, with the last cases detected in Cambodia on the 20th August 2024. Individuals working in live animal markets or poultry farms or living near wild and domestic birds, are particularly exposed to this risk and account for the majority of human cases.

Since the beginning of 2024, nine human cases of imported or autochthonous A(H5N1) infections have been reported in Cambodia, Vietnam, Australia and China following confirmed or suspected exposure with wild, captive birds or domestic poultry. Additionally, 24 human cases of A(H5N1) were recently reported in dairy farmers in three states of the United States (Texas, Michigan, Colorado) following exposure to infected dairy cattle, **marking the first documentation of zoonotic transmissions of the A(H5N1) virus from a mammal**, although human infections with other influenza subtypes have previously been acquired from mammals. These individuals reported conjunctivitis, one of them developed acute respiratory symptoms without severe complications, after contact with infected cows, received oseltamivir treatment and have recovered. Contact tracing activities conducted by health authorities declared no associated secondary cases.

Human cases descriptions

This section presents a detailed timeline of human A(H5N1) case reports and contact tracing since the start of 2024.





Human A(H5N1) infections with exposure to dairy

Human A(H5N1) infections with exposure to wild and

Fact sheets

This section provides a short overview of of the epidemiology, virology, clinical features and risk assessment related with the disease.

Influenza A viruses are segmented, negative-sense single-stranded RNA viruses, members of the *Orthomyxoviridae* family. The antigenic diversity of these viruses arises from two surface glycoproteins: **hemagglutinin (HA)** and **neuraminidase (NA)**. Combinations of these proteins create numerous influenza subtypes, with currently 18 HA and 11 NA subtypes recognized in the environment. The segmented nature of influenza viral genomes enables genetic reassortment, which can lead to an interchange of RNA segments during co-infection events of the same host by two distinctive parental viruses. When HA and NA segments are exchanged, it can result in a substantial antigenic shift and generate new influenza subtypes with a highly different genetic backbone compared to currently circulating strains. These frequent reassortments and antigenic changes has pertained complex classification, requiring a universal system and a standardized nomenclature for classifying influenza viruses, implemented by the WHO in 1980. Influenza A viruses are grouped into « clades » according to the sequence proximity patterns of HA encoding gene.

Since its first observation in China in 1996, highly pathogenic influenza (HPAI) epidemics of A(H5N1) viruses regularly ravage wild bird colonies and poultry farms around the world, resulting in dramatic consequences for avian biodiversity and the health of living ecosystems. The increase in the number of epidemic outbreaks are largely attributed to the implementation, spread and persistence of **influenza A(H5N1) 2.3.4.4b clade** among avian fauna in recent years, which has demonstrated a remarkable ability for geographic propagation and global dissemination through bird migratory routes. There is no longer seasonal patterns as observed in previous avian flu seasons, which usually begin in October and end in March, due to the abnormally high prevalence and circulation of HPAI viruses among seabird colonies during the summer months, a family of birds historically considered to play a minor role in the epidemiology of HPAI lineages. The ability to infect a greater range of bird species contributed largely to the abnormal epidemiological patterns and demographic changes observed in past and ongoing avian flu seasons. To date, viruses related to clade 2.3.4.4b have become endemic in almost all regions of the world, with the exception of Oceania, representing a major risk to animal and human health.

Although avian influenza viruses spread mainly among waterfowl, particularly Anseriformes and Charadriiformes, as well as in other susceptible bird species such as Galliformes, widely represented among domestic poultry, they can occasionally infect humans and mammals. These sporadic infections occur mainly through environmental contamination or exposure to infected birds. Unlike most other avian influenza viruses, A(H5N1) 2.3.4.4b has infected more than 200 mammal species, and there has been an increasing number of deadly reports. Mammals can contract A(H5N1) avian influenza by consuming infected birds, poultry, or other animals, or by exposure to contaminated environments. While mammal-to-mammal transmission of H5N1 is rare, it is possible. The virus can also infect humans, but no sustained human-to-human transmission has been identified. The most commonly identified risk factor for A(H5N1) virus infection is contact with infected birds or contaminated environments.

The incubation period for A(H5N1) infection is typically two to five days after the last known exposure. A(H5N1) influenza virus infection can cause a range of diseases in humans, from mild to severe, and in some cases, it can even be fatal. Symptoms are primarily respiratory, including fever, malaise, cough, sore throat, and muscle aches. Other early symptoms may include conjunctivitis and other non-respiratory symptoms. The infection can quickly progress to severe respiratory illness and neurological changes. A(H5N1) virus has also been detected in asymptomatic individuals.

Diagnosis and care

This section offers a short overview of currently available countermeasures and recommendations for diagnosis, prevention and care.

People presenting with severe respiratory or influenza-like infection and a history of exposure to poultry or wild birds require careful investigation, management, and infection control. Appropriate samples for influenza tests should be rapidly taken and processed from patients with a relevant exposure history within ten days preceding symptom onset. If positive specimens cannot be subtyped, they should be shared with the national reference laboratory. A(H5N1) viruses have been detected in raw milk from infected dairy cows in some locations. Due to potential health risks, the consumption of raw milk should be avoided. The WHO advises consuming pasteurized milk.

Influenza patients should be managed properly to prevent severe illness and death. Patients with laboratory-confirmed influenza virus infection with progressive, complicated, or severe illness, or those with asymptomatic or mild disease but who are at increased risk of severe disease, should be treated with antiviral medicines like oseltamivir as soon as possible.

Scientific articles

This section presents relevant articles published on peer-reviewed scientific journals or pre-print platforms.

H5N1 clade 2.3.4.4b dynamics in experimentally infected calves and cows. Halwe NJ, Cool K, Breithaupt A, Schön J, Trujillo JD, Nooruzzaman M, Kwon T, Ahrens AK, Britzke T, McDowell CD, Piesche R, Singh G, Pinho Dos Reis V, Kafle S, Pohlmann A, Gaudreault NN, Corleis B, Ferreyra FM, Carossino M, Balasuriya UBR, Hensley L, Morozov I, Covaleta LM, Diel D, Ulrich L, Hoffmann D, Beer M, Richt JA.

Published in *Nature* on 25 September 2024.
<https://doi.org/10.1038/s41586-024-08063-y>

In March 2024, highly pathogenic avian influenza virus (HPAIV) clade 2.3.4.4b H5N1 infections in dairy cows were first reported from Texas, USA. The authors provide results of 2 independent clade 2.3.4.4b experimental infection studies evaluating (i) oronasal susceptibility and transmission in calves to a US H5N1 bovine isolate genotype B3.13 (H5N1 B3.13) and (ii) susceptibility of lactating cows following direct mammary gland inoculation of either H5N1 B3.13 or a current EU H5N1 wild bird isolate genotype. Inoculation of the calves resulted in moderate nasal replication and shedding with no severe clinical sign or transmission to sentinel calves. In dairy cows, infection resulted in no nasal shedding, but severe acute mammary gland infection with necrotizing mastitis and high fever was observed for both H5N1 isolates. This data suggests that in addition to H5N1 B3.13, other HPAIV H5N1 strains have the potential to replicate in the udder of cows and that milk and milking procedures, rather than respiratory spread, are likely the primary routes of H5N1 transmission between cattle.

The global H5N1 influenza panzootic in mammals. Peacock T, Moncla L, Dudas G, VanInsberghe D, Sukhova K, Lloyd-Smith JO, Worobey M, Lowen AC, Nelson MI.

Published in *Nature* on 24 September 2024.
<https://doi.org/10.1038/s41586-024-08054-z>

In this review, the authors examine the molecular and ecological factors driving the recent expansion of H5N1's host range and evaluate the likelihood of various zoonotic pathways that could lead to an H5N1 pandemic. Going forward we know more about H5N1's global distribution, non-human host range, and genetic diversity than virtually any other zoonotic pathogen. One major concern is the potential for undetected transmission chains silently spreading within farm worker housing, swine facilities, or in resource-limited regions, evolving out of sight due to narrow testing criteria, fear of authorities, or insufficient resources. The severity of a future H5N1 pandemic remains uncertain. Recent human cases of infection with H5N1 2.3.4.4b viruses have shown a significantly lower case fatality rate compared to previous H5N1 outbreaks.

Bovine Highly Pathogenic Avian Influenza Virus Stability and Inactivation in the Milk Byproduct Lactose. Kwon T, Gebhardt JT, Lyoo EL, Nooruzzaman M, Gaudreault NN, Morozov I, Diel DG, Richt JA.

Published in *Viruses* on 12 September 2024.
<https://doi.org/10.3390/v16091451>

In this brief report, the authors assessed the stability of a bovine highly pathogenic avian influenza H5N1 virus isolate in the milk byproduct lactose and evaluated two inactivation methods using industrial procedures. The bovine isolate of the highly pathogenic avian influenza H5N1 virus was stable for 14 days in a concentrated lactose solution under refrigerated conditions. Heat or citric acid treatments successfully inactivated the virus in lactose. This is the first study to investigate the inactivation of a bovine HPAI H5N1 virus in the milk coproduct, concentrated lactose, which is frequently used as a feed ingredient for agricultural animals including pigs as well as for other purposes. This study provides insights on the persistence of bovine HPAIV in dairy byproducts and effective inactivation strategies under industrial standards.

Comparison of Extraction Methods for the Detection of Avian Influenza Virus RNA in Cattle Milk.

Snoeck CJ, Sausy A, Bourg M, Hübschen JM.

Published in *Viruses* on 10 September 2024.
<https://doi.org/10.3390/v16091442>

Influenza viral RNA concentrations in milk make it an ideal matrix for surveillance purposes. This study aims at optimizing detection methods. Raw bulk tank milk and mastitis milk samples were artificially contaminated with an avian influenza strain and subjected to five extraction methods. HCoV-229E and synthetic RNA were included as exogenous internal process controls. Given the high viral load usually observed in individual raw milk samples, four out of five tested methods would enable influenza detection in milk with normal texture, over a time window of at least 2 weeks post-onset of clinical signs. Sample dilution 1:3 in molecular transport medium prior to RNA extraction provided the best results for dilution of inhibitory substances and a good recovery rate of influenza RNA, that reached $12.5 \pm 1.2\%$ and $10.4 \pm 3.8\%$ in two independent experiments in bulk milk and $11.2 \pm 3.6\%$ and $10.0 \pm 2.9\%$ on two cohorts of mastitis milk samples. Authors have also shown compatibility of an influenza RT-qPCR system with synthetic RNA detection for simultaneous validation of the RNA extraction and RT-qPCR processes.

Detection and Monitoring of Highly Pathogenic Influenza A Virus 2.3.4.4b Outbreak in Dairy Cattle in the United States.

Giménez-Lirola LG, Cauwels B, Mora-Díaz JC, Magtoto R, Hernández J, Cordero-Ortiz M, Nelli RK, Gorden PJ, Magstadt DR, Baum DH.

Published in *Viruses* on 29 August 2024.
<https://doi.org/10.3390/v16091376>

This study investigates the presence of anti-nucleoprotein (NP) antibodies in serum and milk and viral RNA in milk on dairy farms affected by H5N1 outbreaks in Texas, Kansas, and Michigan using a multi-species influenza virus A (IAV) ELISA and RT-qPCR. The analysis of ELISA results from a Michigan dairy farm outbreak demonstrated a positive correlation between paired serum and milk sample results, confirming the reliability of both specimen types. Findings also revealed high diagnostic performance during the convalescent phase (up to 96%), further improving sensitivity through serial sampling. Additionally, the evaluation of diagnostic specificity using serum and milk samples from IAV-free farms showed an excellent performance (99.6%). This study underscores the efficacy of the IAV NP-blocking ELISA for detecting and monitoring H5N1-IAV 2.3.4.4b circulation in dairy farms for surveillance purposes.

This section provides a digested list of a more extensive content accessible in Excel format [here](#).

Vaccine development

This section provides a review of influenza vaccine production platforms and existing licensed and candidate vaccines.

Vaccine candidates for seasonal and zoonotic influenza viruses are developed using a range of various production platforms. The **inactivated influenza vaccine (IIV) platform** - in split and whole virus formats - is the most advanced and primarily used for stockpiling influenza vaccines. Wild-type strains are generated and inactivated using reverse genetics to remove the multibasic cleavage site of haemagglutinin, rendering the vaccine strains safer and production possible. Other platforms, such as cell-culture derived IIVs (relying on mammalian or insect cells), offer potential advantages like faster production and higher yields since they do not depend on embryonated egg supplies. Live-attenuated influenza vaccines (LAIVs), which are authorized for the development of seasonal influenza vaccine, may induce broader and stronger immune responses. However, they pose safety concerns for very young children and immunocompromised individuals and are currently under clinical evaluation.

Zoonotic influenza vaccine formulations and regimens must pass **haemagglutination inhibition (HI) tests**, the gold standard for assessing vaccine-elicited protection. This assay measures the ability of haemagglutinin-specific antibodies to inhibit virus-induced haemagglutination, a recognized correlate of protection for both avian and seasonal influenza viruses. High dosages or the complementary use of adjuvants might be necessary to achieve reliable HI titers above 1:40, which correlates with a 50% protection rate in adults. This threshold is required for regulatory approval by U.S. and European authorities. Due to the low immunogenicity of IIVs, these vaccines are **strain-specific and are not recommended for different subtypes or anti genically-distant haemagglutinins**. Therefore, the continued development and updating of vaccines for zoonotic influenza viruses currently circulating are crucial for pandemic preparedness. Since 1952, the WHO Global Influenza Surveillance and Response System (GISRS) has been conducting global influenza surveillance, and based on the monitoring results, recommends influenza virus vaccine compositions, including seasonal formulations for northern (February) and southern (September) hemispheres.

Vaccine development and stockpiling against A(H5N1) began during the earlier HPAI H5N1 outbreaks in Vietnam and Indonesia in 2003-2005, leading to the **licensure of three H5N1 vaccines - clade 1 and 2.1** - by the Food Drug and Administration (FDA) and European Medical Agency (EMA) under the trade name Audenz® / Aflunox ®, Preprandix® / Pumarix®, and Foclivia® / Adjupanix®. Current studies are assessing the potency of these vaccines to elicit cross-reactive binding antibodies and cross-neutralization against the predominant 2.3.4.4b strains, including those detected in dairy farmers. The WHO GISRS vaccine pipeline has registered **43 candidate zoonotic vaccines A(H5)** for emergency use, including 33 A(H5N1) and 10 non-A(H5N1). **Four candidate vaccines have been developed specifically against A(H5) 2.3.4.4b antigens** and successfully passed relevant safety and potency testing. One of these candidates, developed against an avian influenza A(H5N8) clade 2.3.4.4b isolated from a poultry worker in Southern Russia and sharing antigenic similarities with the A(H5N1) 2.3.4.4b strains found in dairy farmers, has received approval by EMA on the 9th October 2023 under the trademark Seqirus®. Several clinical studies evaluating this vaccine in adult populations are expected to be completed by the end of 2024.

A(H5N1) human infections have been sporadic, and mass or ring vaccination campaigns using available zoonotic influenza vaccines are not currently implemented. These vaccines should only be used once a flu pandemic has been officially declared by the WHO.

Source:

[Summary of status of development and availability of A\(H5N1\) candidate vaccine viruses and potency testing reagents. 23 May 2024.](#)

[Summary of status of development and availability of A\(H5\) non-A\(H5N1\) candidate vaccine viruses and potency testing reagents. 23 May 2024.](#)

Technological landscape

This section outlines the current pipeline of drug development, clinical trials and technologies aimed at preventing and treating the disease.

VACCINE	IDCDC-RG71A (Seqirus®) (A/Astrakhan/3212/2020)	A(H5N8) antigenic prototype 2.3.4.4b Split-inactivated virion, adjuvanted	Restricted use	Developed by CDC, U.S and referenced on WHO GISRS pandemic candidate vaccine pipeline. Successfully passed relevant safety and potency HI testing. Approved by EMA for emergency use in EU/EEA countries since 9 October 2023. Pre-clinical studies have demonstrated that antisera produced against this vaccine is cross-reactive against the currently circulation H5N1 2.3.4.4b from a Texas dairy farm worker. Two phase I/II clinical studies are currently under evaluation in adults, expected to be completed end of 2024 (NCT05874713 and NCT05975840).
	A/Fujian-Sanyuan/21099/2017-like	A(H5N6) antigenic prototype 2.3.4.4b	Restricted use	Developed by CCDC, China and referenced on WHO GISRS pandemic candidate vaccine pipeline. Successfully passed relevant safety and potency HI testing.
	IDCDC-RG78A (A/American wigeon/South Carolina/22-000345-001/2021-like)	A(H5N1) antigenic prototype 2.3.4.4b	Restricted use	Developed by CDC, U.S and referenced on WHO GISRS pandemic candidate vaccine pipeline. Successfully passed relevant safety and potency HI testing.
	NIID-002 (A/Ezo red fox/Hokkaido/1/2022)	A(H5N1) antigenic prototype 2.3.4.4b	Restricted use	Developed by NIID, Japan and referenced on WHO GISRS pandemic candidate vaccine pipeline. Successfully passed relevant safety and potency haemagglutination inhibition testing.
	A/chicken/Ghana/AVL-76321VIR7050-39/2021-like	A(H5N1) antigenic prototype 2.3.4.4b	In development	In development by CDC, U.S. Currently passing relevant safety and potency testing.
	A/chicken/Ghana/20/2015-like	A(H5N1) antigenic prototype 2.3.2.1f	In development	In development by CDC, U.S. Currently passing relevant safety and potency testing.
	Preprandix® / Pumarix® (A/Indonesia/05/2005)	A(H5N1) clade 2.1 Split-inactivated virion, adjuvanted	Restricted use	Contain reactive AS03 adjuvant. Approved by EMA for emergency use in EA/EEA countries since March 2011. Licensed by the FDA in 2013 and is currently in the U.S. National stockpile for pre-pandemic preparedness. Usable in persons six months of age and older. Generates cross-reactive binding antibodies cross-neutralization titers against H5 clade 2.3.4.4b A/Astrakhan/3212/2020 strain (Khurana et al., 2024).
	Foclivia® / Adjupanix® (A/VietNam/1194/2004)	A(H5N1) clade 1 Split-inactivated virion, adjuvanted	Restricted use	Developed by Sanofi Pasteur (unadjuvanted), Seqirus (adjuvanted with MF59) or GSK (adjuvanted with AS03) and approved by FDA since September 2016. Vaccines are stored in the U.S. National stockpile for pre-pandemic preparedness. Foclivia® (adjuvanted with MF59) and Adjupanix® (adjuvanted with AS03) formulation are approved for emergency use in EA/EEA countries in October 2009. Generates cross-reactive binding antibodies cross-neutralization titers against H5 clade 2.3.4.4b A/Astrakhan/3212/2020 strain (Khurana et al., 2024).
	Audenz® / Aflunox® (A/turkey/Turkey/1/2005)	A(H5N1) 2.2.1 inactivated, monovalent vaccine, adjuvanted	Restricted use	Approved for emergency use in EA/EEA countries in November 2010. Approved by FDA since January 2020 for use in persons six months of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine. The license has been renewed in the U.S. on 24 April 2024.
	Panvax®	A(H5N1) Inactivated vaccine, adjuvanted	Restricted use	Developed by CSL Limited and approved by Australia since 2008. The vaccine, given in two doses, was found to be safe and well tolerated among adults aged 18 to 64 and adults older than 64.
Influenza Virus Vaccine, H5N1 (A/Vietnam/1203/2004)	A(H5N1) clade 1 Inactivated, monovalent vaccine	Restricted use	Developed by Sanofi Pasteur and approved by FDA for emergency use in U.S since 2007. This vaccine is stored in the U.S. National stockpile for pre-pandemic preparedness. Indicated for active immunization of persons 18 through 64 years of age at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.	

Relevant news

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

A human isolate of bovine H5N1 is transmissible and lethal in animal models

Published by Nature on 28 October 2024.
<https://www.nature.com/articles/s41586-024-08254-7>

Researchers found that an isolate from a sick dairy worker may be capable of replicating in human airway cells, is pathogenic in mice and ferrets, and can transmit among ferrets by respiratory droplets.

The current situation with H5N1 avian influenza and the risk to humans

Published by Internal Medicine Journal on 25 October 2024.
<https://onlineibrary.wiley.com/doi/10.1111/imj.16550>

Overall, HPAI H5N1 is a complex problem, affecting wildlife, ecosystems, domestic animals, companion animals and humans, and therefore requires a OneHealth response and solution but, fortunately, the risk of this virus progressing to be the cause of the next human pandemic following COVID-19 is currently low.

The practical longevity of stockpiled A(H5N1) influenza vaccine

Published by Nature on 26 September 2024.
<https://www.nature.com/articles/s41591-024-03256-4>

Stockpiled A(H5N1) influenza vaccines made using viruses from the mid-2000s stimulate antibodies that cross-react with current strains, despite being separated by 20 years of viral evolution – supporting investment in vaccine stockpiling for pandemic preparedness.

Guidelines and practical information

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

28 August 2024	Practical interim guidance to reduce the risk of infection in people exposed to avian influenza viruses
20 June 2024	Highly Pathogenic Avian Influenza A(H5N1) Virus in Animals: Interim Recommendations for Prevention, Monitoring, and Public Health Investigations (CDC)
14 June 2024	Prevention and Antiviral Treatment of Avian Influenza A Viruses in People (CDC)
24 May 2024	Avis du COVARS du 24 mai 2024 - Point sur la situation liée au virus influenza H5N1 (MESRI)
20 December 2023	Considerations for emergency vaccination of wild birds against high pathogenicity avian influenza in specific situations (WOAH)
26 June 2023	Enhanced surveillance of severe avian influenza virus infections in hospital settings in the EU/EEA (ECDC)
1 January 2022	Guidelines for the clinical management of severe illness from influenza virus infections (WHO)
10 December 2021	Avis relatif à la prévention de la transmission à l'homme des virus influenza porcins et aviaires (HCSP)