MONTHLY SCIENTIFIC REVIEW
ON AVIAN INFLUENZA A(H5N1)

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

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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 19 July 2024, **889 cases of human infection with avian influenza A(H5N1) viruses** and **463 deaths** were reported from 23 countries to the *World Health Organization (WHO)*, with the last cases detected in Cambodia on the 18th July. Individuals working in live animal markets or poultry farms, or living in close proximity to 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 autochtonous A(H5N1) infections have been reported in Cambodia, Vietnam, Australia and China following confirmed or suspected exposure with wild, captive birds or domestic poultry. Additionnally, four 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.

Two cases of human A(H5N1) in Cambodia

18 July 2024

Two human A(H5N1) infections were reported in Cambodia. A 3-year-old boy from Takeo Province was tested positive a few days following symptoms onset, and was hospitalized. A 5-year-old girl, was detected through contact tracing, despite being asymptomatic and was hospitalized for isolation and preventive oseltamivir treatment.

Source : Avian Influenza Weekly Update Number 956 | WHO Western Pacific Region. 19 July 2024.

4th cow-to-human A(H5N1) transmission in U.S.

3 July 2024

The Centers for Disease Control and Prevention (CDC) confirmed the 4th human case of A(H5N1) from infected dairy cattles in the U.S., and the first in Colorado. He reported mild conjunctivitis, received oseltamivir, and has recovered.

Source : CDC Reports Fourth Human Case of H5 Bird Flu Tied to Dairy Cow Outbreak | CDC. 3 July 2024.

3rd cow-to-human A(H5N1) transmission in U.S.

30 May 2024

A third dairy worker in the U.S., and the 2nd human case in Michigan, tested positive for A(H5N1) after exposure to infected cows. He was the first developing acute respiratory symptoms, as the two previous workers experienced only conjunctivitis, but no severe clinical outcomes were reported and he recovered.

Source : CDC Confirms Second Human H5 Bird Flu Case in Michigan; Third Case Tied to Dairy Outbreak | CDC. 30 May 2024.

2nd cow-to-human A(H5N1) transmission in U.S.

22 May 2024

A dairy worker has been diagnosed with A(H5N1) in Michigan, representing the second human case associated with an outbreak affecting dairy cows in the U.S. He experienced mild eye symptoms and has recovered.

Source : CDC Reports Second Human Case of H5 Bird Flu Tied to Dairy Cow Outbreak | CDC. 22 May 2024.

A(H5N1) imported case in a child in Australia

22 May 2024

Australia confirmed its first human case of A(H5N1) in a child returning from India. The child was hospitalized and 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 : Human case of avian influenza (bird flu) detected in returned traveller to Victoria | Department of Health, Victoria. 21 May 2024.

Detection of A(H5N1) human case in China

3 May 2024

A 33-year-old female was tested positive for avian influenza A(H5N1) virus in the Guangxi Autonomous Region, China.

Source : Avian Influenza Weekly Update Number 945 | WHO Western Pacific Region. 3 May 2024.

1st cow-to-human A(H5N1) transmission in U.S.

27 March 2024

A laboratory-confirmed human case of A(H5N1) was reported in Texas, U.S, in a 18 years old individual working at a dairy cattle farm and having a history of exposure to infected cows. This is the first known human infection with A(H5N1) acquired from an infected mammal, although human infections with other influenza subtypes have previously been acquired from mammals.

Source : Avian Influenza A(H5N1) - United States of America | WHO. 9 April 2024.

Detection of A(H5N1) human case in Vietnam

11 March 2024

A case of A(H5N1) human infection in a 21-year-old male with no underlying conditions from Khanh Hoa Province (Vietnam) developed symptoms and passed away. The case had no history of contact with dead or sick poultry nor with anyone with similar symptoms, but he was reportedly trapping wild birds.

Source : Avian Influenza Weekly Update Number 940 | WHO Western Pacific Region. 29 March 2024.

Detection of A(H5N1) human cases in Cambodia

12 February 2024

Cambodia reported the first four human A(H5N1) infections with A(H5N1), involving three children and one adult, all with recent exposure to sick or dead poultry prior to their illness. The infections were identified in late January and early February. The first two patients were epidemiologically unrelated and admitted to different hospitals. The third and fourth patients are siblings but lived in different villages ; dead poultry were brought from the household of the fourth patient and both siblings were exposed. The third patient died shortly after transfer to a pediatric hospital.

Source : First Human Influenza A(H5N1) (Bird Flu) Virus Infections in Cambodia Reported for 2024 | CDC. 12 February 2024.

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

Human A(H5N1) infections with exposure to wild and domestic birds

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.

Spillover of highly pathogenic avian influenza H5N1 virus to dairy cattle. Caserta, L.C., Frye, E.A., Butt, S.L. et al.

Published in *Nature* on 25 July 2024.
https://doi.org/10.1038/s41586-024-07849-4

This article investigates HPAI H5N1 clade 2.3.4.4b outbreaks affecting dairy cattle, identifying an epidemiological link between the herds in Texas. The viral sequences from these farms belong to the novel reassortant B3.13 genotype, which is also linked with mortality events in wildlife occuring around affected farms at the same time sick cows were reported. The affected farms are all large with open-air pens, which ould facilitate indirect contact between cattle and wild birds and mediate spillovers infections. Additional evidence suggests that healthy lactating cattle may have spread the virus between farms, with resident animals developing clinical signs shortly after. These results, supported by phylogenetic analysis revleaing closely related viral strains, indicates efficient cattle-to-cattle transmission and long-range viral dispersal. The main transmission route is unclear, but high viral loads in mammary glands and milk suggest mechanical transmission through milking equipment. These findings underscore the need for robust biosecurity and enhanced surveillance to control the virus spread among dairy farms.

Cytomegalovirus vaccine vector-induced effector memory CD4 + T cells protect cynomolgus macaques from lethal aerosolized heterologous avian influenza challenge. Malouli, D., Tiwary, M., Gilbride, R.M. et al.

Published in *Nat Commun* on 19 July 2024.
https://doi.org/10.1038/s41467-024-50345-6

This study explores to determine whether lung-resident effector memory T cells induced by cytomegalovirus (CMV)-vectored vaccines expressing conserved internal influenza antigens could protect against lethal influenza challenge. Mauritian cynomolgus macaques (MCM) were immunized with cynomolgus CMV (CyCMV) vaccines expressing H1N1 1918 influenza M1, NP, and PB1 antigens (CyCMV/Flu), and challenged with heterologous, aerosolized avian H5N1 influenza. All six unvaccinated MCM died by seven days post infection with acute respiratory distress, while 54.5% (6/11) CyCMV/Flu-vaccinated MCM survived. Survival correlates with the magnitude of lung-resident influenza-specific CD4 + T cells prior to challenge. These data demonstrate that CD4 + T cells targeting conserved internal influenza proteins can protect against highly pathogenic heterologous influenza challenge and support further exploration of effector memory T cell-based vaccines for universal influenza vaccine development.

Licensed H5N1 vaccines generate cross-neutralizing antibodies against highly pathogenic H5N1 clade 2.3.4.4b influenza virus. Khurana, S., King, L.R., Manischewitz, J. et al.

Published in *Nat Med* on 16 July 2024.
https://doi.org/10.1038/s41591-024-03189-y

In this study, authors evaluated the binding, hemagglutination inhibition and neutralizing antibody response against the HPAI clade 2.3.4.4b generated after vaccination of adults with the three licensed vaccines in the US. These vaccines are derived from earlier strains of HPAI H5N1 (A/Vietnam, clade 1, and A/Indonesia, clade 2.1) virus, with (MF59 or AS03) or without adjuvants. Individuals vaccinated with the two adjuvanted licensed H5N1 vaccines generated cross-reactive binding and cross-neutralizing antibodies against the HPAI clade 2.3.4.4b A/Astrakhan/3212/2020 virus. Seroconversion rates of 60–95% against H5 clade 2.3.4.4b were observed after two doses of AS03-adjuvanted-A/Indonesia or three doses of MF59-adjuvanted-A/Vietnam vaccine. These findings suggest that the stockpiled US-licensed adjuvanted H5N1 vaccines generate cross-neutralizing antibodies against circulating HPAI H5N1 clade 2.3.4.4b in humans and may be useful as bridging vaccines until updated H5N1 vaccines become available.

Genomic characterization of highly pathogenic avian influenza A H5N1 virus newly emerged in dairy cattle. Hu, X., Saxena, A., Magstadt, D. R., Gauger, P. C., Burrough, E. R., Zhang, J., … Li, G.

Published in *Nat Med* on 16 July 2024.
https://doi.org/10.1080/22221751.2024.2380421

In this study the authors genetically characterize HPAI viruses from dairy cattle, two cats, six wild birds, and one skunk. They share nearly identical genome sequences, forming a new genotype B3.13 within the 2.3.4.4b clade. B3.13 viruses underwent two reassortment events since 2023 and exhibit critical mutations in HA, M1, and NS genes but lack critical mutations in PB2 and PB1 genes, which enhance virulence or adaptation to mammals. The PB2 E627 K mutation in a human case associated with cattle underscores the potential for rapid evolution post infection, highlighting the dynamic nature of influenza viruses and the importance of continued surveillance and vigilance in monitoring potential threats to human health.

H5N1 avian influenza: tracking outbreaks with real-time epidemiological data. Branda F., Ciccozzi M., and Scarpa F.

Published in *The Lancet Infectious Diseases* on 9 July 2024.
https://doi.org/10.1016/S1473-3099(24)00414-6

To contribute to the surveillance of human avian influenza, which has spread worldwide since 1996, the authors propose to create a centralized publicly available database. Considering the sporadic cases of avian influenza in humans with various strains, the Italian team propose to collect data from various public sources to compile a detailed list of cases including: Disease Outbreak News (DON), which is the official online reporting system operated by WHO ; reliable news websites specializing in public health and infectious disease and peer-reviewed scientific papers published in high-impact journals . Information will be evaluated in terms of credibility, accuracy and relevance. The team is composed of epidemiologists, statisticians, bioinformatics geneticists and experts in data analysis.

Genotypic and phenotypic susceptibility of emerging avian influenza A viruses to neuraminidase and cap-dependent endonuclease inhibitors. Andreev K., Jones J. C., Seiler P., Kandeil A., Webby R. J., and Govorkova E. A.

Published in *Antiviral Research* on 8 July 2024.
https://doi.org/10.1016/j.antiviral.2024.105959

In this study, the authors screened >20,000 neuraminidase (NA) or polymerase acidic (PA) protein sequences of potentially pandemic A(H5Nx), A(H7Nx), and A(H9N2) viruses that circulated globally in 2010–2023. The frequencies of NA or PA substitutions associated with reduced inhibition (RI) or highly reduced inhibition (HRI) by NA inhibitors (NAIs) (oseltamivir, zanamivir) or a cap-dependent endonuclease inhibitor (baloxavir) were low: 0.60% (137/22,713) and 0.62% (126/20,347), respectively. All tested subtypes were susceptible to NAIs and baloxavir at sub-nanomolar concentrations. A(H9N2) viruses were the most susceptible to oseltamivir. NA-I222M conferred RI of A(H5N1) viruses by oseltamivir (with a 26-fold IC50 increase), but NA-S246N did not reduce inhibition. This data indicate antiviral susceptibility is high among avian influenza A viruses with pandemic potential and present novel markers of resistance to existing antiviral interventions.

Pathogenicity and transmissibility of bovine H5N1 influenza virus. Eisfeld, A.J., Biswas, A., Guan, L. et al.

Published in *Nature* on 8 July 2024.
https://doi.org/10.1038/s41586-024-07766-6

Highly pathogenic H5N1 avian influenza (HPAI H5N1) viruses occasionally infect, but typically do not transmit, in mammals. In the Spring of 2024, an unprecedented outbreak of HPAI H5N1 in bovine herds occurred in the US, with virus spread within and between herds and spillover into humans. In this study, the authors characterized an HPAI H5N1 virus isolated from infected cow milk in mice and ferrets. Like other HPAI H5N1 viruses, the bovine H5N1 virus spread systemically, including to the mammary glands of both species. Importantly, bovine HPAI H5N1 virus bound to sialic acids expressed in human upper airways and inefficiently transmitted to exposed ferrets (one of four exposed ferrets seroconverted without virus detection). Bovine HPAI H5N1 virus thus possesses features that may facilitate infection and transmission in mammals.

Pathogenicity and transmissibility of bovine H5N1 influenza virus. Jelinek, T., Schwarz, T.F., Reisinger, E., Malfertheiner, P., Versage, E., Van Twuijver, E., Hohenboken, M.

Published in *Vaccines* on 30 April 2024.
https://doi.org/10.3390/vaccines12050481

In this Phase III, stratified, randomized, controlled, blinded, multicenter study, the authors evaluate the safety and immunogenicity of the aH5N1 vaccine in four distinct groups of adults: healthy adults aged 18-60 years or with high-risk pathologies, and older adults ≥61 years of age in good health or with high-risk pathologies. Subjects were randomly assigned to aH5N1 vaccine or to the comparator, adjuvanted trivalent seasonal influenza vaccine (aTIV). Antibody responses to the aH5N1 virus increased in all four subgroups and, in each age stratum, were largely consistent between healthy and problematic subjects, healthy and those with health problems. Pain at the injection site was reported by 66% to 73% of young subjects and 36% to 42% of older aH5N1 subjects, and fatigue and myalgia were reported by 22% to 41% of subjects in all age and health status subgroups. No serious adverse events or deaths were considered to be related to the study vaccine. To conclude, the aH5N1 vaccine increased antibody responses irrespective of age or health status, and demonstrated clinically acceptable safety and tolerability.

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® / Afllunox ®, Preprandix® / Pumarix®, and Foclivia® / Adjupanrix®. 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 antigenes** 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® / Adjupanrix® (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 Adjupanrix® (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® / Afllunox ® (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	Developped 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.

New initiative launched to advance mRNA vaccine development against human avian influenza (H5N1).

Published by WHO on 29 July 2024.
https://www.who.int/news/item/29-07-2024-new-initiative-launched-to-advance-mrna-vaccine-development-against-human-avian-influenza-(h5n1)

The WHO and the Medicines Patent Pool (MPP) have launched a new initiative to accelerate the development and accessibility of H5N1 avian influenza mRNA vaccines in low- and middle-income countries. Argentine manufacturer Sinergium Biotech will lead this initiative, leveraging the mRNA Technology Transfer Programme established by WHO and MPP in July 2021. Sinergium Biotech aims to develop H5N1 vaccine candidates and, upon successful preclinical testing, share the technology and expertise with other manufacturers to boost vaccine development and pandemic preparedness. This project aligns with the vision of the mRNA Technology Transfer Programme: to enhance research and production capabilities in LMICs for a more equitable global response to future pandemics. This effort builds on previous successes of the mRNA programme, which has already been demonstrated with COVID-19 vaccine development.

Avian influenza overview March–June 2024.

Published in *EFSA Journal* on 19 July 2024.
https://doi.org/10.2903/j.efsa.2024.8930

Between 16 March and 14 June 2024, 42 highly pathogenic avian influenza (HPAI) A(H5) virus detections were reported in domestic (15) and wild (27) birds across 13 countries in Europe. Although the overall number of detections in Europe has not been this low since the 2019–2020 epidemiological year, HPAI viruses continue to circulate at a very low level. Most detections in poultry were due to indirect contact with wild birds, but there was also secondary spread. Outside Europe, the HPAI situation intensified particularly in the USA, where a new A(H5N1) virus genotype (B3.13) has been identified in >130 dairy herds in 12 states. Infection in cattle appears to be centred on the udder, with milk from infected animals showing high viral loads and representing a new vehicle of transmission.

Study suggests earlier US-licensed H5N1 vaccines prompt antibodies to current strain.

Published in *WHO* on 17 July 2024.
https://www.cidrap.umn.edu/avian-influenza-bird-flu/study-suggests-earlier-us-licensed-h5n1-vaccines-prompt-antibodies-current

In conducting the study, the team used blood samples from 68 adults who had participated in earlier H5N1 vaccine trials. The hemagglutinin (HA) sequence of the 2.3.4.4b H5N1 clade has several mutations compared to the HA of the three H5N1 viruses targeted by the earlier vaccines. The researchers found that the two adjuvanted licensed H5N1 vaccines generated cross-reactive binding antibodies and cross-neutralization titers against the 2.3.4.4b clade. These findings suggest that the stockpiled U.S. licensed adjuvanted H5N1 vaccines generate cross-neutralizing antibodies against circulating HPAI H5N1 clade 2.3.4.4b in humans and may be useful as bridging vaccines until updated H5N1 vaccines become available.

Bird flu could become a human pandemic. How are countries preparing?

Published in *Nature* on 12 July 2024.
https://www.nature.com/articles/d41586-024-02237-4

Wealthy nations are purchasing vaccines against H5N1 influenza and boosting surveillance, but there are concerns that low-income countries will be left behind.

Stop H5N1 influenza in US cattle now.

Published in *Science* on 12 July 2024.
https://doi.org/10.1126/science.adr5866

The relentless march of a highly pathogenic avian influenza virus (HPAIV) strain, known as H5N1, to become an unprecedented panzootic continues unchecked. The leap of H5N1 clade 2.3.4.4b from Eurasia and Africa to North America in 2021 and its further spread to South America and the Antarctic have exposed new avian and mammalian populations to the virus and led to outbreaks on an unrivaled scale. The virus has infected wild birds across vast geographic regions and caused wildlife deaths in some of the world's most biodiverse ecosystems. Hundreds of millions of poultry have died or been culled, affecting global food security in some of the world's poorest regions. Numerous mammalian species, including sea lions and fur animals, have been infected. Outbreaks in dairy cows in the United States have been occurring for months, seemingly unchecked in most affected states. Why is there not a greater sense of urgency to control these infections?

Is 'cow flu' here to stay? Three months after it emerged, fears are growing.

Published in *Science* on 2 July 2024.
https://www.science.org/content/article/cow-flu-here-stay-three-months-after-it-emerged-fears-are-growing

More than 3 months after the first reported H5N1 avian influenza outbreak at a U.S. dairy farm, some researchers are starting to wonder whether the virus is here to stay.

Fatal Infection in Ferrets after Ocular Inoculation with Highly Pathogenic Avian Influenza A(H5N1) Virus.

Published in *Emerging Infectious Disease* on July 2024.
https://doi.org/10.3201%2Feid3007.240520

Ocular inoculation of a clade 2.3.4.4b highly pathogenic avian influenza A(H5N1) virus caused severe and fatal infection in ferrets. Virus was transmitted to ferrets in direct contact. The results highlight the potential capacity of these viruses to cause human disease after either respiratory or ocular exposure.

Highly Pathogenic Avian Influenza Virus A(H5N1) Clade 2.3.4.4b Infection in Free-Ranging Polar Bear, Alaska, USA

Published in *Emerging Infectious Diseases* on 28 June 2024.
https://doi.org/10.3201/eid3008.240481

We report a natural infection with a Eurasian highly pathogenic avian influenza A(H5N1) clade 2.3.4.4b virus in a free-ranging juvenile polar bear (Ursus maritimus) found dead in North Slope Borough, Alaska, USA. Continued community and hunter-based participation in wildlife health surveillance is key to detecting emerging pathogens in the Arctic.

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.

Commission secures access for Member States to 665,000 doses of zoonotic influenza vaccines to prevent avian flu

Published in *European Commission* on 11 June 2024.
https://ec.europa.eu/commission/presscorner/detail/en/ip_24_3168

The Commission's Health Emergency Preparedness and Response Authority (HERA) as part of its mandate on preparedness, has signed on behalf of participating Member States, a joint procurement framework contract for the supply of up to 665,000 pre-pandemic vaccine doses of the up-to-date Zoonotic Influenza Vaccine Seqirus, as well as an option for a further 40 million doses over the duration of the contract.

Bird flu: Australia records first human case of H5N1

Published in *BMJ* on 10 June 2024.
https://doi.org/10.1136/bmj.q1281

Australia has notified the World Health Organization (WHO) of its first human case of H5N1 influenza (clade 2.3.2.1a), in a 2 year old child who was probably exposed in India. The child has no underlying conditions and had travelled to Kolkata, India, in February before returning to Australia on 1 March. The Victoria Department of Health reported that the child had started to feel unwell in India, with symptoms including loss of appetite, irritability, fever, and vomiting. After two and a half weeks in hospital, she was discharged and is now reported to be “clinically well,”.

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(H5N5) 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 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.

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)