MONTHLY SCIENTIFIC REVIEW ON AVIAN INFLUENZA A(H5N1)

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Situation at a glance

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 1 November 2024, **939 cases of human infection with avian influenza A(H5N1) viruses** and **464 deaths** (CFR of 49%) 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 most human cases.

Since the **beginning of 2024**, **13 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, **57 human cases of A(H5N1)** were recently reported in dairy farmers in **7 states of the USA** (most of them in California with 30 cases) following exposure to infected **dairy cattle (34)** or **poultry (21), 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.

Scientific articles

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

Dissecting immunological mechanisms underlying influenza viral nucleoprotein-induced mucosal immunity against diverse viral strains. Zhang W, Sloan A, Prévost J, Tamming L, Raman S, Pfeifle A, Gravel C, Chen W, Hashem AM, Wu J, Cao J, Johnston MJW, Wang L, Sauve S, Rosu-Myles M, Kobasa D, Safronetz D, Li X.

Published in Emerging Microbes & Infections on 21 November 2024.

In this study, the authors assessed the mechanistic differences between intramuscular (IM) and intranasal (IN) delivery of a recombinant adenovirus carrying NP fused with a bifunctional CD40 ligand. Despite being less effective than IM delivery in inducing systemic cellular immune responses and antibody-dependent cellular cytotoxicity (ADCC), IN immunization elicited superior antigen-specific recall humoral and cellular response in the nasal associated lymphoid tissue (NALT) of the upper respiratory tract. IN vaccination also induced significantly stronger pulmonary T cell responses in the lower respiratory tract than IM vaccination, in particular the CD8 T cells. Moreover, blocking lymphocyte circulation abrogated IM but not IN immunization induced protection, illustrating the critical role of local memory immune response upon viral infection. Notably, the CD40-targeted nasal delivery not only improved the magnitude but also the breadth of protection, including against lethal challenge with a newly isolated highly pathogenic avian H5N1 strain.

Why a teenager's bird-flu infection is ringing alarm bells for scientists. Ledford H.

Published in Nature on 20 November 2024.

A strain of avian influenza is showing signs of adaptation to human hosts, but there is no evidence that it can transmit from person to person. In a children's hospital in Vancouver, Canada, a teenager is in critical condition after being infected with an avian influenza virus. It is unclear how the teenager got infected. The teenager initially had an eye infection, which later developed into a severe lung infection. This could suggest that the virus became better able to enter airway cells after it had infected the adolescent. It's consistent with the idea that the virus might have evolved within that individual. The sequencing data suggest a mixture of viruses, all of which are similar to a lineage of H5N1 viruses that is currently infecting poultry and waterfowl in the region. It doesn't appear that there is any indication that this individual transmitted this virus on to others. Being able to bind to human cell is a prerequisite to cause a pandemic but it's often not sufficient. But this should serve as a warning: this virus has the capacity to switch very quickly into a form that can cause severe disease.

Epidemiological data of an influenza A/H5N1 outbreak in elephant seals in Argentina indicates mammal-to-mammal transmission. Uhart MM, Vanstreels RET, Nelson MI, Olivera V, Campagna J, Zavattieri V, Lemey P, Campagna C, Falabella V, Rimondi A.

Published in Nature on 11 November 2024.

H5N1 high pathogenicity avian influenza virus has killed thousands of marine mammals in South America since 2022. Our combined ecological and phylogenetic data support mammal-to-mammal transmission and occasional mammal-to-bird spillover and suggest multinational transmission of H5N1 viruses in mammals. We reflect that H5N1 viruses becoming more evolutionary flexible and adapting to mammals in new ways could have global consequences for wildlife, humans, and livestock.

Consistent H5N1 control needed for farm animals. Capua I, Fanelli A.

Published in Science on 7 November 2024.

The article highlights the challenges of controlling the H5N1 avian influenza virus, which has caused mass deaths in birds, mammals, and farm animals, with recent spillovers into cattle in the U.S. Current U.S. policies are inconsistent, with strict control measures for poultry, including culling and trade restrictions, but more lenient rules for infected cattle. Unlike poultry, cattle are not culled, and there is no mandatory destruction of infected milk, even though raw milk remains available in some states. Vaccination is restricted for poultry but under development for cattle. The authors advocate for unified, effective control strategies across all species, emphasizing vaccination availability and reconsidering trade restrictions to mitigate the zoonotic and pandemic potential of H5N1.

[Preprint] Emergence of a Novel Reassortant Clade 2.3.2.1c Avian Influenza A/H5N1 Virus Associated with Human Cases in Cambodia. Jurre Y. Siegers, Ruopeng Xie, Alexander M.P. Byrne, Kimberly M. Edwards, Shu Hu, Sokhoun Yann, Sarath Sin, Songha Tok, Kimlay Chea, Sreyviseth Horm, Chenthearath Rith, Seangmai Keo, Leakhena Pum, Veasna Duong, Heidi Auerswald, Yisuong Phou, Sonita Kol, Andre Spiegel, Ruth Harvey, Sothyra Tum, San Sorn, Bunnary Seng, Yi Sengdoeurn, Chau Darapheak, Chin Savuth, Makara Hak, Vanra Ieng, Sarika Patel, Han Di, Charles Todd Davis, Alyssa Finlay, Borann Sar, Peter Thielen, Filip F. Claes, Nicola S. Lewis, Ly Sovann, Vijaykrishna Dhanasekaran, Erik A. Karlsson.

Published in MedRxiv on 5 November 2024.

After nearly a decade without reported human A/H5N1 infections, Cambodia faced a sudden resurgence with 16 cases between February 2023 and August 2024, all caused by A/H5 clade 2.3.2.1c viruses. Fourteen cases involved a novel reassortant A/H5N1 virus with gene segments from both clade 2.3.2.1c and clade 2.3.4.4b viruses. The emergence of this novel genotype underscores the persistent and ongoing threat of avian influenza in Southeast Asia. This study details the timeline and genomic epidemiology of these infections and related poultry outbreaks in Cambodia.

Genetic characterization and receptor binding analysis of a novel H5N1 HPAI virus with a H6Nx-derived PA gene in Guangdong, China. He J, Liu J, Yan Z, Chen G, Liu R, Yang Y, Yan Y, Yuan S, Guo J, Li Y, Yu H, Liang Z, Ren T, Huang S, Wen F.

Published in Emerging Microbes & Infections on 4 November 2024.

This short report presents the identification, genetic characterization, and receptor binding analysis of a novel HPAIV of the H5N1 subtype, designated A/Goose/GuangDong/1189/2023 (H5N1) (GD1189). Notably, GD1189 possesses a PA gene derived from an H6 subtype circulating in southern China. This unique genetic makeup, particularly the emergence of the PA gene in late 2023, highlights the crucial need for continuous genomic surveillance to track the evolution of novel reassortant viruses and inform the development of effective control measures. These findings are particularly relevant in the context of the current HPAIV situation in the China poultry market. The emergence of reassortant viruses, such as GD1189, emphasizes the dynamic nature of HPAIV evolution and the need for ongoing monitoring to identify potential threats to poultry production and public health.

Transmission of a human isolate of clade 2.3.4.4b A(H5N1) virus in ferrets. Jurre Pulit-Penaloza JA, Belser JA, Brock N, Kieran TJ, Sun X, Pappas C, Zeng H, Carney P, Chang J, Bradley-Ferrell B, Stevens J, De La Cruz JA, Hatta Y, Di H, Davis CT, Tumpey TM, Maines TR.

Published in Nature on 28 October 2024.

In this study, the authors assessed in a ferret model, the viral pathogenicity and transmissibility of the A/Texas/37/2024 (TX/37) A(H5N1) virus isolated from a dairy farm worker in Texas. They show that the virus has a remarkable ability for robust systemic infection in ferrets, leading to high levels of virus shedding and spread to naïve contacts. Ferrets inoculated with TX/37 rapidly exhibited a severe and fatal infection, characterized by viremia and extrapulmonary spread. The virus efficiently transmitted in a direct contact setting and was capable of indirect transmission via fomites. Airborne transmission was corroborated by the detection of infectious virus shed into the air by infected animals, albeit at lower levels compared to the highly transmissible human seasonal and swine-origin H1 subtype strains.

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

Gu C, Maemura T, Guan L, Eisfeld AJ, Biswas A, Kiso M, Uraki R, Ito M, Trifkovic S, Wang T, Babujee L, Presler R Jr, Dahn R, Suzuki Y, Halfmann PJ, Yamayoshi S, Neumann G, Kawaoka Y.

Published in Nature on 28 October 2024.

Since 2020, there has been unprecedented global spread of highly pathogenic avian influenza A(H5N1) in wild bird populations with spillover into a variety of mammalian species and sporadically humans. In this study, the authors employed the ferret model, a well-characterized species that permits concurrent investigation of viral pathogenicity and transmissibility in the evaluation of A/Texas/37/2024 (TX/37) A(H5N1) virus isolated from a dairy farm worker in Texas. They show that the virus has a remarkable ability for robust systemic infection in ferrets, leading to high levels of virus shedding and spread to naïve contacts. Airborne transmission was corroborated by the detection of infectious virus shed into the air by infected animals, albeit at lower levels compared to the highly transmissible human seasonal and swine-origin H1 subtype strains. These results show that despite maintaining an avian-like receptor binding specificity, TX/37 displays heightened virulence, transmissibility, and airborne shedding relative to other clade 2.3.4.4b virus isolated prior to the 2024 cattle outbreaks, underscoring the need for continued public health vigilance.

Effectiveness of pasteurization for the inactivation of H5N1 influenza virus in raw whole milk.

Alkie TN, Nasheri N, Romero-Barrios P, Catford A, Krishnan J, Pama L, Hooper-McGrevy K, Nfon C, Cutts T, Berhane Y.

Published in Food Microbiology on 28 October 2024.

This study examined whether pasteurization could effectively inactivate HPAI clade 2.3.4.4b H5N1 spiked into raw whole milk. Authors heated 1 mL of non-homogenized cow milk samples to attain an internal temperature of 63°C or 72°C and spiked with 6.3 log10 EID50 of clade 2.3.4.4b H5N1 virus. Complete inactivation was achieved after incubation of the H5N1 spiked raw milk at 63°C for 30 min. In addition, viral inactivation was observed in seven of eight experimental replicates when treated at 72°C for 15s. In one of the replicates, a 4.44 log10 virus reduction was achieved, which is about 1 log higher than the average viral quantities detected in bulk milk in affected areas. Therefore, the study concludes that pasteurization of milk is an effective strategy for mitigation of the risk of human exposure to milk contaminated with H5N1 virus.

Highly pathogenic avian influenza management policy in domestic poultry: from reacting to preventing.

Vergne T, Paul MC, Guinat C, Delpont M, Hayes BH, Lambert S, Vaillancourt JP, Guérin JL.

Published in Eurosurveillance on 17 October 2024.

The article discusses the challenges and solutions for managing highly pathogenic avian influenza (HPAI) in poultry, particularly following the emergence of clade 2.3.4.4b H5N1 in 2021. Traditional strategies like culling and biosecurity have proven insufficient against year-round outbreaks and increased transmission to mammals. France has implemented nationwide poultry vaccination, targeting ducks, to curb outbreaks, demonstrating significant success. However, vaccination faces challenges, including logistical costs and trade implications. The authors advocate for regional biosecurity, emphasizing reduced farm density and spatial redistribution to limit virus spread. These combined approaches aim to enhance poultry sector resilience against HPAI.

Serological analysis in humans in Malaysian Borneo suggests prior exposure to H5 avian influenza near migratory shorebird habitats.

Klim H, William T, Mellors J, Brady C, Rajahram GS, Chua TH, Brazal Monzó H, John JL, da Costa K, Jeffree MS, Temperton NJ, Tipton T, Thompson CP, Ahmed K, Drakeley CJ, Carroll MW, Fornace KM.

Published in Nature on 17 October 2024.

In this study, the authors perform a serological survey of human influenza exposure in Sabah, Malaysian Borneo, to examine the immunological footprint of H5N1 in the region. They additionally present a method for minimising the impact of IAV hemagglutinin (HA) subtype cross-reactivity on serological results. In addition, they define species distributions of domesticated poultry and migratory wild shorebirds and demonstrate that environmental covariates can be used as a proxy to model wild shorebird contact. They additionally identify shared spatial distributions and environmental risk factors between the presence of migratory shorebirds and clade-specific H5N1 seroprevalence using a Bayesian framework. This study highlights the need to increase surveillance for rare zoonotic diseases at migratory sites and presents an approach for modelling the distributions of serological results and reservoir species.

Dairy cows inoculated with highly pathogenic avian influenza virus H5N1.

Baker AL, Arruda B, Palmer MV, Boggiatto P, Sarlo Davila K, Buckley A, Ciacci Zanella G, Snyder CA, Anderson TK, Hutter CR, Nguyen TQ, Markin A, Lantz K, Posey EA, Kim Torchetti M, Robbe-Austerman S, Magstadt DR, Gorden PJ.

Published in Nature on 15 October 2024.

Highly pathogenic avian influenza (HPAI) H5N1 haemagglutinin clade 2.3.4.4b was detected in the USA in 2021. These HPAI viruses caused mortality events in poultry, wild birds and wild mammals. In this study, the authors sought to experimentally reproduce infection with genotype B3.13 in Holstein yearling heifers and lactating cows. Heifers were inoculated by an aerosol respiratory route and cows by an intramammary route. Clinical disease was mild in heifers, but infection was confirmed by virus detection, lesions and seroconversion. Clinical disease in lactating cows included decreased rumen motility, changes to milk appearance and production losses. Infection was confirmed by high levels of viral RNA detected in milk, virus isolation, lesions in mammary tissue and seroconversion. According to the authors, this study provides the foundation to investigate additional routes of infection, pathogenesis, transmission and intervention strategies.

Wastewater monitoring of human and avian influenza A viruses in Northern Ireland: a genomic surveillance study.

Lee AJ, Carson S, Reyne MI, Marshall A, Moody D, Allen DM, Allingham P, Levickas A, Fitzgerald A, Bell SH, Lock J, Coey JD, McSparron C, Nejad BF, Troendle EP, Simpson DA, Courtney DG, Einarsson GG, McKenna JP, Fairley DJ, Curran T, McKinley JM, Gilpin DF, Lemon K, McGrath JW, Bamford CGG.

Published in Lancet Microbe on 9 October 2024.

The aim of the study was to assess whether whole-genome sequencing (WGS) of Influenza A viruses (IAVs) from wastewater is possible and can be used to discriminate between circulating strains of human and any non-human IAVs, such as those of avian origin. Detection tool was a pan-IAV RT-quantitative PCR assay, used to screen six wastewater treatment works (WWTWs) across Northern Ireland from Aug 1 to Dec 5, 2022. A nanopore WGS approach was used to sequence RT-qPCR-positive samples and phylogenetic analysis followed. Authors detected a dynamic IAV signal in wastewater from Sept 5, 2022, onwards across Northern Ireland, which did not show a clear positive relationship with the clinical data obtained for the region. Meta (mixed strain) whole-genome sequences were generated from wastewater samples displaying homology to only human and avian IAV strains. The relative proportion of IAV reads of human versus avian origin differed across time and sample site. A diversity in subtypes and lineages was detected (eg, H1N1, H3N2, and several avian). Avian segment 8 related to those found in recent H5N1 clade 2.3.4.4b was identified. Therefore, WBE affords a means to monitor circulating human and avian IAV strains and provide crucial genetic information. However, optimisation of WBE protocols are necessary to ensure observed wastewater signals not only correlate with clinical case data, but yield information on the wider environmental pan-influenzome.

This section provides a digested list of a more extensive content accessible in Excel format here.

Relevant news

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

Current H5N1 Bird Flu Situation in Dairy Cows.

Published by CDC on 2 December 2024.

Since 2022, USDA APHIS has reported HPAI A(H5N1) virus detections in more than 200 mammals.

How CDC is monitoring influenza data among people to better understand the current avian influenza A (H5N1) situation.

Published by CDC on 23 November 2024.

CDC influenza (flu) surveillance systems show no indicators of unusual influenza activity in people, including avian influenza A(H5N1).

H5N1 and Safety of U.S. Meat Supply.

Published by USDA on 18 November 2024.

USDA is confident that the meat supply is safe. USDA has a rigorous meat inspection process, which includes Food Safety and Inspection Service (FSIS) veterinarians who are present at all Federal livestock slaughter facilities. FSIS personnel inspect each animal before slaughter, and all cattle carcasses must pass a second inspection after slaughter and be determined to be fit to enter the human food supply.

Information for Workers Exposed to H5N1 Bird Flu.

Published by CDC on 8 November 2024.

H5N1 bird flu is a virus that has been found in cows. It can also be found in poultry and other animals. People who work with infected animals or their byproducts (for example, raw milk), such as dairy and poultry workers, might get sick from the virus.

Serologic Evidence of Recent Infection with Highly Pathogenic Avian Influenza A(H5) Virus Among Dairy Workers — Michigan and Colorado, June–August 2024.

Published by CDC on 7 November 2024.

Health officials conducted surveys and serologic testing to identify recent HPAI A(H5) infections among dairy workers in two states. Serologic testing indicated that 7% of participating dairy workers had evidence of recent infection with HPAI A(H5) virus.

Latest Events

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

Detection of the first A(H5N1) human cases in Canada

13 November 2024

This is the first domestically acquired human case of H5N1 avian influenza.

Source : Public Health Agency of Canada

Three cases of human A(H5N1) in Washington (U.S.)

24 October 2024

Confirmed three of the four presumptive positive bird flu cases among poultry farm workers in Washington state.

Source: Human H5 bird flu case confirmed in Missouri | Missouri department of health. 6 September 2024.

Four cases of cow-to-human A(H5N1) transmission in U.S.

10 October 2024

Six cases have been reported in California. All California cases occurred in dairy workers on affected farms.

Source: CDC A(H5N1) Bird Flu Response Update October 11, 2024

One case of human A(H5N1) in Missouri (U.S.)

6 September 2024

He presented with chest pain, nausea, vomiting, diarrhea, and weakness. The person was not severely ill, nor were they in the intensive care unit. He was treated with influenza antiviral medications, subsequently discharged, and have since recovered.
Nine cases were associated with exposure to avian influenza A(H5N1) virus-infected poultry since April 2024

Source: Human H5 bird flu case confirmed in Missouri | Missouri department of health. 6 September 2024.

Detection of A(H5N1) human cases in Cambodia

20 August 2024

A human A(H5N1) infection was reported in Cambodia. A 15-year-old child from Prey Veng Province was tested positive for A(H5N1) virus (clade 2.3.2.1c). The patient was hospitalized in Phnom Penh, and presented with a fever, cough, sore throat, and difficulty breathing, and on the same day, treatment with oseltamivir was initiated. The patient died on 20 August.
This case is one of 10 human cases of influenza A(H5N1) infection reported in Cambodia in 2024.

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

Human A(H5N1) infections with exposure to wild and

Factsheet

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 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.

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® / 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.

Guidelines and practical information

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

12 November 2024	Interim Guidance for Employers to Reduce Exposure to Novel Influenza A (Such as H5N1 Bird Flu) for People Working with or Exposed to Animals
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)