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 20 August 2024, **903 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 18th July. 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, 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.

nine were associated with exposure to avian influenza A(H5N1) virus-infected poultry

Human cases descriptions

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

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.

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.

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.

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.

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.

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.

Intranasal administration of octavalent next-generation influenza vaccine elicits protective immune responses against seasonal and pre-pandemic viruses. Uno N, Ebensen T, Guzman CA, Ross TM.

Published in *J Virol* on 17 September 2024.
https://doi.org/10.1128/jvi.00354-24

In this study, authors used computationally optimized broadly reactive antigen (COBRA) methodology to generate broadly reactive immunogens for individual influenza subtypes, which elicit protective immune responses against a broad range of strains over numerous seasons. Octavalent mixtures of COBRA hemagglutinin (HA) (H1, H2, H3, H5, H7, and influenza B virus) plus neuraminidase (NA) (N1 and N2) recombinant proteins mixed with c-di-AMP adjuvant were administered intranasally to naive or pre-immune ferrets in prime-boost fashion. Four weeks after final vaccination, collected sera were analyzed for breadth of antibody response, and the animals were challenged with seasonal or pre-pandemic strains. The octavalent COBRA vaccine elicited antibodies that recognized a broad panel of strains representing different subtypes, and these vaccinated animals were protected against influenza virus challenges. Overall, this study showed that the mixture of eight COBRA HA/NA proteins mixed with an intranasal adjuvant is a promising candidate for a universal influenza vaccine.

Personal Protective Equipment Guidance for Highly Pathogenic Avian Influenza H5N1 Should Be Adapted to Meet the Needs of Dairy Farm Workers. Bagdasarian N, Wineland N, Callo SL..

Published in *Journal of Medical Virology* on 16 September 2024.
https://doi.org/10.1093/infdis/jiae380

The article addresses the outbreak of highly pathogenic avian influenza H5N1, which spread to dairy cows in the U.S. in 2024, with cases reported in several states. Human cases have also been recorded, primarily due to direct contact with infected cattle or their secretions. Current PPE guidance, adapted from poultry outbreaks, is deemed inadequate for dairy farm workers who require ongoing interaction with ill cows. The study emphasizes the need to modify PPE recommendations to suit the practical realities of farm work, focusing on simplicity and comfort to encourage adherence. It suggests using protective gear like surgical masks with face shields and emphasizes proper hygiene practices to reduce transmission risks.

An Update on Highly Pathogenic Avian Influenza A(H5N1) Virus, Clade 2.3.4.4b. Webby RJ, Uyeki TM.

Published in *Journal of Medical Virology* on 15 September 2024.
https://doi.org/10.1093/infdis/jiae379

The resurgence of highly pathogenic avian influenza (HPAI) A(H5N1), clade 2.3.4.4b, since 2021 has led to global spread in birds, poultry, and mammals. Outbreaks in poultry, wild birds, and mammals have raised public health concerns, particularly with human cases ranging from mild to severe illness, including fatal pneumonia. The virus has shown increased fitness and ability to infect mammals, with mammal-to-mammal transmission observed in some cases, notably in dairy cattle in the U.S. Effective global surveillance, virus characterization, and rapid data sharing are crucial for monitoring evolving risks to public health. While antiviral treatments are recommended, no vaccines for clade 2.3.4.4b are currently available.

Sequencing-Based Detection of Avian Influenza A(H5N1) Virus in Wastewater in Ten Cities. Webby RJ, Uyeki TM.

Published in *Journal of Medical Virology* on 15 September 2024.
https://doi.org/10.1093/infdis/jiae379

Since May 2022, the Texas Epidemic Public Health Institute has been using hybrid-capture sequencing to analyze weekly wastewater samples from urban areas across Texas, detecting over 400 human and animal viruses, including SARS-CoV-2, influenza, and mpox, which align with clinical case data. Between March 4 and July 15, 2024, H5N1 was found in 10 cities, 22 of 23 sites, and 100 of 399 samples. However, H5N1 sequences did not correlate with influenza-related hospitalizations, which declined in Texas during that period. The sequences matched bird and mammal H5N1 genomes from the 2.3.4.4b clade, indicating limited adaptation to humans. While the exact source remains unclear, genomic data and the lack of clinical cases suggest multiple animal origins. Wastewater monitoring could serve as an early detection tool for viral evolution. Expanding sequencing efforts to include wastewater, livestock, exposed workers, and migratory birds is recommended to track sources and prevent future flu pandemics.

Susceptibilities and viral shedding of peridomestic wildlife infected with clade 2.3.4.4b highly pathogenic avian influenza virus (H5N1). Root JJ, Porter SM, Lenoch JB, Ellis JW, Bosco-Lauth AM.

Published in *Virology* on 5 September 2024.
https://doi.org/10.1016/j.virol.2024.110231

In this study, the authors tested the ability of six peridomestic wildlife species to replicate a highly pathogenic (HP) clade 2.3.4.4b AIV (H5N1) isolated in the U.S. during 2022. All six peridomestic wildlife species that were tested replicated and shed virus. The mammal species tested shed higher viral titers than the bird species tested. HP AIV infection appeared to be lethal to some but not all species or individuals tested. Overall, the results of this study indicate that certain peridomestic species could pose a biosecurity threat to poultry operations in some situations. In addition, this study and field reports indicate that the HP AIVs circulating in the U.S. during 2022–2024 may have an extremely broad range of species that can be impacted by and/or replicate and shed these viruses.

Acute and persistent responses after H5N1 vaccination in humans. Apps R, Biancotto A, Candia J, Kotliarov Y, Perl S, Cheung F, Farmer R, Mulè MP, Rachmaninoff N, Chen J, Martins AJ, Shi R, Zhou H, Bansal N, Schum P, Olnes MJ, Milanez-Almeida P, Han KL, Sellers B, Cortese M, Hagan T, Rouphael N, Pulendran B, King L, Manischewitz J, Khurana S, Golding H, van der Most RG, Dickler HB, Germain RN, Schwartzberg PL, Tsang JS.

Published in *Cell reports* on 4 September 2024.
https://doi.org/10.1016/j.celrep.2024.114706

In this study, authors use systems immunology to study human H5N1 influenza vaccination with or without the adjuvant AS03, longitudinally assessing 14 time points including multiple time points within the first day after prime and boost. An unsupervised computational framework is developed to discover high-dimensional response patterns, which uncover adjuvant- and immunogenicity-associated early response dynamics, including some that differ post prime versus boost. With or without adjuvant, some vaccine-induced transcriptional patterns persist to at least 100 days after initial vaccination. Single-cell profiling of surface proteins, transcriptomes, and chromatin accessibility implicates transcription factors in the erythroblast-transformation-specific (ETS) family as shaping these long-lasting signatures, primarily in classical monocytes but also in CD8+ naive-like T cells. These cell-type-specific signatures are elevated at baseline in high-antibody responders in an independent vaccination cohort, suggesting that antigen-agnostic baseline immune states can be modulated by vaccine antigens alone to enhance future responses.

Detection and spread of high pathogenicity avian influenza virus H5N1 in the Antarctic Region.

Banyard AC, Bennison A, Byrne AMP, Reid SM, Lynton-Jenkins JG, Mollett B, De Silva D, Peers-Dent J, Finlayson K, Hall R, Blockley F, Blyth M, Falchieri M, Fowler Z, Fitzcharles EM, Brown IH, James J.

Published in *Nat Commun* on 3 September 2024.
https://doi.org/10.1038/s41467-024-51490-8

Until recently, Antarctica was the only major region where highly pathogenic avian influenza virus (HPAIV) had not been detected.. Researchers have now identified clade 2.3.4.4b H5N1 HPAIV in the Antarctic and sub-Antarctic regions, specifically in South Georgia and the Falkland Islands (situated approximately 1500 km to South Georgia). All samples were collected from carcasses found dead on the islands. The first detection occurred in October 2023 from samples taken from brown skuas on Bird Island, South Georgia. Subsequent deaths in various bird and mammal species were reported across both regions. These islands are key habitats for avian biodiversity, and the virus poses a significant threat to the susceptible bird populations. Genetic analysis showed no increased risk to humans and antiviral resistance.

Novel Genotypes of Highly Pathogenic Avian Influenza H5N1 Clade 2.3.4.4b Viruses, Germany, November 2023. Ahrens AK, Pohlmann A, Grund C, Harder T, Beer M.

Published in *Emerg Infect Dis* on 30 Auguste 2024.
https://doi.org/10.3201/eid3008.240103

In this article, the authors analyzed the genotypes of highly pathogenic avian influenza (HPAI) and low pathogenicity avian influenza LPAI viruses by using full-genome sequencing. They analyzed 244 sequences from 33 viruses collected from late May to late November 2023, of which 22 originated from wild birds, 5 from poultry, and 6 from captive birds. They found various LPAIVs and 16 HPAIVs of H5N1 subtype in the resulting sequences. This study shows a high number of emerging new HPAIV H5 clade 2.3.4.4b genotypes in November 2023 and identified related LPAIVs circulating at the same time in the same area, which may have served as reassortment partners. These findings highlight the continued promiscuity of currently circulating HPAI H5 strains of clade 2.3.4.4b and the need for genotypic surveillance of both HPAIVs and LPAIVs.

Multiplex Dual-Target Reverse Transcription PCR for Subtyping Avian Influenza A(H5) Virus. Sahoo MK, Morante IEA, Huang C, Solis D, Yamamoto F, Ohiri UC, Romero D, Pinsky BA.

Published in *Emerg Infect Dis* on 30 Auguste 2024.
https://doi.org/10.3201/eid3008.240785

In this study, authors adapted to recent H5 clade 2.3.4.4b diversity a previously published primer-probe sets for an internally controlled dual-target H5 subtyping qRT-PCR test. Very low to no mismatch when aligning to available sequences (GISAID or sequences from infections in US) was confirmed. The 95% lower limit of detection was 2.5 copies/µL (95% CI 1.8–5.3 copies/µL) for the clade 1 ssDNA mix and <0.5 copies/µL for the clade 2.3.4.4b ssDNA mix. Subsequently, 0.97 reaction efficiency for the H5 target was validated on H5N3 isolates. Specificity of the tool was tested on cultured human and avian virus isolates encoding non-H5 HA genes, and on upper respiratory swab samples (including co-infection samples), with good performance. Overall, this dual-target H5 qRT-PCR test demonstrated high analytical performance and could be used to directly test samples from patients with suspected HPAI A(H5) virus infection or as a secondary test to subtype known influenza A–positive samples after routine respiratory virus testing, while reducing dales negative.

A broad-spectrum vaccine candidate against H5 viruses bearing different sub-clade 2.3.4.4 HA genes. Zhang Y, Cui P, Shi J, Zeng X, Jiang Y, Chen Y, Zhang J, Wang C, Wang Y, Tian G, Chen H, Kong H, Deng G.

Published in *NPJ Vaccines* on 19 August 2024.
https://doi.org/10.1038/s41541-024-00947-4

In this study, authors examined the antigenic sites that determine the antigenic differences between two H5 vaccine strains, H5-Re8 (clade 2.3.4.4g) and H5-Re11 (clade 2.3.4.4h). Epitope mapping data revealed that all eight identified antigenic sites were located within two classical antigenic regions, with five sites in region A (positions 115, 120, 124, 126, and 140) and three in region B (positions 151, 156, and 185). Through antigenic cartography analysis of mutants with varying numbers of substitutions, it was confirmed that a combination of mutations in these eight sites reverses the antigenicity of H5-Re11 to that of H5-Re8, and vice versa. These analyses also identified H5-Re11_Q115L/R120S/A156T (H5-Re11 + 3) as a promising candidate for a broad-spectrum vaccine, positioned centrally in the antigenic map, and offering potential universal protection against all variants within the clade 2.3.4.4. H5-Re11 + 3 serum has better cross-reactivity than sera generated with other 2.3.4.4 vaccines, and H5-Re11 + 3 vaccine provided 100% protection of chickens against antigenically drifted H5 viruses from various 2.3.4.4 antigenic groups. These findings suggest that antigenic regions A and B are immunodominant in H5 viruses, and that antigenic cartography-guided vaccine design is a promising strategy for selecting a broad-spectrum vaccine.

Multiple transatlantic incursions of highly pathogenic avian influenza clade 2.3.4.4b A(H5N5) virus into North America and spillover to mammals. Erdelyan CNG, Kandeil A, Signore AV, Jones MEB, Vogel P, Andreev K, Bøe CA, Gjerset B, Alkie TN, Yason C, Hisanaga T, Sullivan D, Lung O, Bourque L, Ayilara I, Pama L, Jeevan T, Franks J, Jones JC, Seiler JP, Miller L, Mubareka S, Webby RJ, Berhane Y.

Published in *Cell Rep* on 23 July 2024.
https://doi.org/10.1016/j.celrep.2024.114479

In the present study, the authors describe the incursion of a fully Eurasian (EA) clade 2.3.4.4b A(H5N5) virus into North America, most likely through the movement of seabirds across the Atlantic Flyway. They also present cases of A(H5N5) in multiple species of mesocarnivores-small mammals, like raccoons, skunks, and foxes. They examine viral evolutionary relationships, possible transatlantic routes of incursion from Eurasia to North America, possible intermediate hosts, in vitro antiviral susceptibility, and the virulence exhibited by A(H5N5) in a ferret model. A(H5N5) viruses demonstrated rapid 100% mortality and some transmission

in ferrets.

Characterization of highly pathogenic avian influenza virus in retail dairy products in the US.

Spackman E, Jones DR, McCoig AM, Colonius TJ, Goraichuk IV, Suarez DL.

Published in *J Virol* on 23 July 2024.
https://doi.org/10.1128/jvi.00881-24

In this study, the authors characterize whether the virus could be detected by quantitative real-time RT-PCR (qrRT-PCR) in pasteurized retail dairy products and, if detected, to determine whether the virus was viable. Pasteurized dairy products (23 product types) were collected from 17 states in April 2024. Viral RNA was detected in 60 samples (20.2%), with qrRT-PCR-based quantity estimates (non-infectious) of up to 5.4 log 10 50% egg infectious doses per mL, with a mean and median of 3.0 log10/mL and 2.9 log10/mL, respectively. Samples that were positive for type A influenza by qrRT-PCR were confirmed to be clade 2.3.4.4 H5 HPAIV by qrRT-PCR. No infectious virus was detected in any of the qrRT-PCR-positive samples in embryonating chicken eggs.

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.

CDC A(H5N1) Bird Flu Response Update September 27, 2024

Published by *CDC* on 27 September 2024.
https://www.cdc.gov/bird-flu/spotlights/h5n1-response-09272024.html

CDC provides an update on its response activities related to the multistate outbreak of avian influenza A(H5N1) virus, or "H5N1 bird flu," in dairy cows and other animals in the United States.

Updates on Highly Pathogenic Avian Influenza (HPAI)

Published by *FDA* on 26 September 2024.
https://www.fda.gov/food/alerts-advisories-safety-information/updates-highly-pathogenic-avian-influenza-hpai

The FDA is providing an update about ongoing research efforts it is undertaking to help ensure the safety of dairy products during the outbreak of Highly Pathogenic Avian Influenza A (H5N1) virus in dairy cattle and to work towards reducing the threat of H5N1 to human and animal health.

H5 Influenza Vaccines—Moving Forward Against Pandemic Threats

Published by *JAMA* on 4 September 2024.
https://jamanetwork.com/journals/jama/article-abstract/2823004

North America is increasingly impacted by H5N1 influenza infections among poultry, cows, wild birds, and marine and terrestrial mammals, including at least 13 human infections related to animal contact,[1] with genetic clade 2.3.4.4b viruses responsible for most recent cases. Although human illness has been mild so far, previous H5N1 viruses caused substantial mortality. Additionally, human-to-human transmission has not been reported in this outbreak and was uncommon with prior H5N1 strains, but surveillance is limited. The current extent of mammalian infection appears unprecedented, and a 2024 study suggested the virus may have acquired enhanced ability to bind mammalian airway receptors

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.

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)