

Highly Pathogenic Avian Influenza A (H5N1) in North America

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Background

On 1 April 2024, the United States (US) reported a laboratory-confirmed human case of highly pathogenic avian influenza (HPAI) A (H5N1) in Texas¹. HPAI A (H5N1) is part of the influenza A viruses. There are four influenza viruses (A, B, C, and D) belonging to the *Orthomyxoviridae* viral family²⁻⁴. Only influenza A is believed to be capable of causing a global pandemic and has caused four pandemics since 1900 (**Figure 1**)^{2,5-9}. Influenza A pandemics occur when a new virus emerges that can infect humans and sustain human-to-human transmission^{2,9}. There are over 130 subtypes of influenza A viruses categorised according to numerous haemagglutinin (H) and neuraminidase (N) antigens^{3,10}. Some subtypes such as H1N1 and H3N2 routinely circulate among humans however, others such as H5N1 predominantly affect animals with only sporadic human cases^{3,11}.

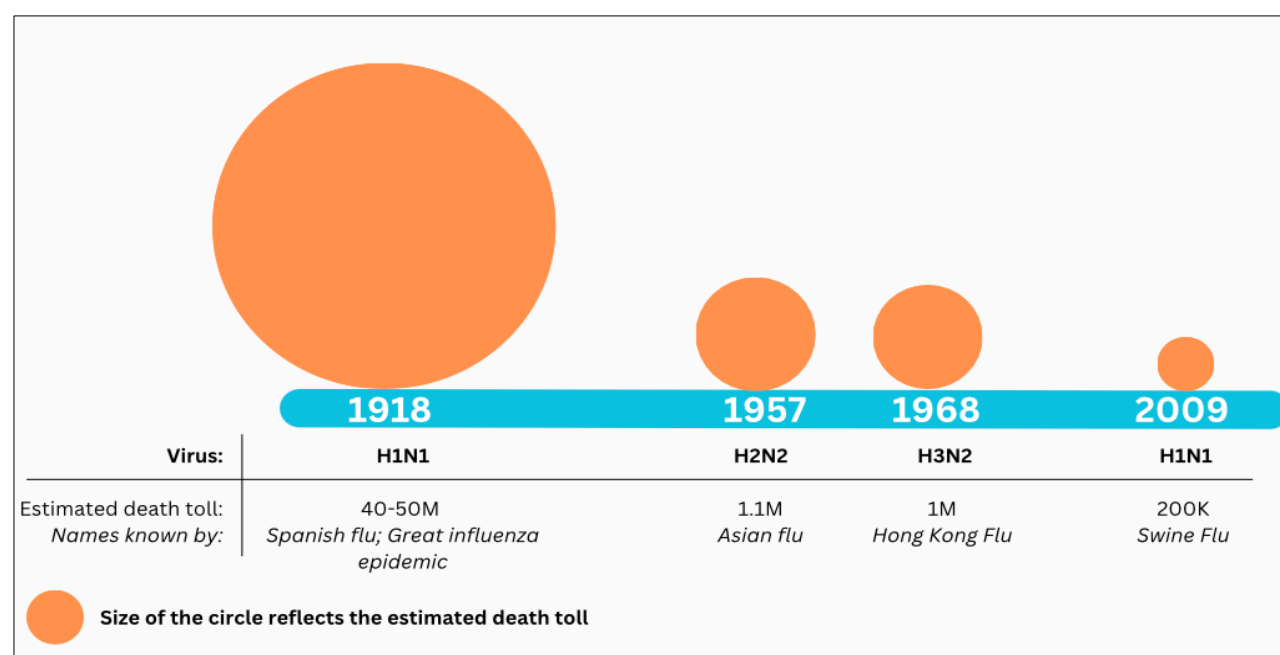


Figure 1: Pandemics caused by influenza A since 1900

Data used: LePan N. (2020). Visualizing the History of Pandemics. Visual Capitalist. Healthcare. Available from: <https://www.visualcapitalist.com/history-of-pandemics-deadliest/>

Many animals are infected with influenza A viruses, and these do not easily transmit to humans². Animal influenza viruses are named according to the infected host species, for example, avian, swine, or equine influenza (**Figure 2**)². Avian influenzas (also known as bird flu viruses) infect birds globally and can be categorised according to disease severity: low pathogenicity avian influenza (LPAI) and high pathogenicity avian influenza (HPAI)¹². Some HPAI strains can infect humans such as HPAI A (H5N1).

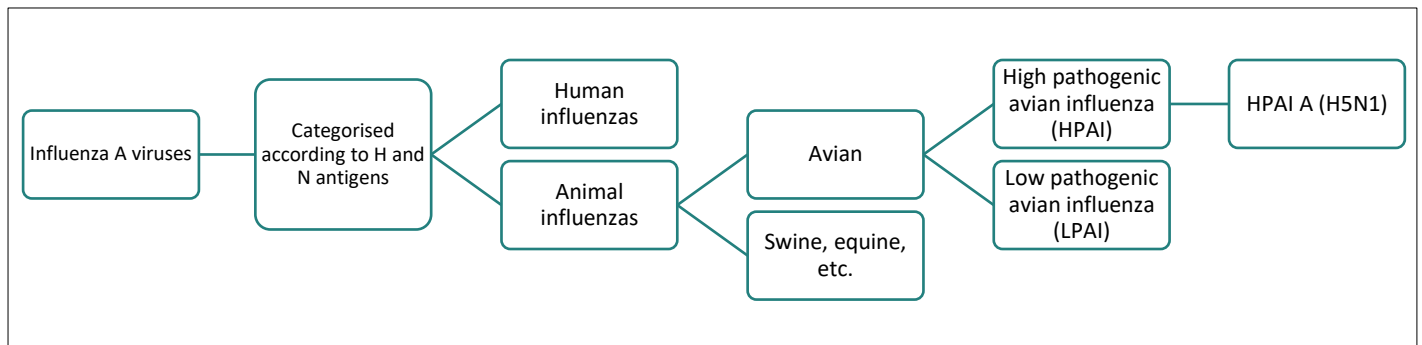


Figure 2: Categorisation of influenza A avian viruses to illustrate the category HPAI A (H5N1) falls under

Transmission, Clinical Presentation, Diagnosis, and Treatment of HPAI A (H5N1)

HPAI A (H5N1) can spread to humans when they come into direct contact with infected poultry or their contaminated environments¹³. Spread from direct contact with infected mammals such as cattle has also been reported however, this is rare¹³. There has been no known sustained human-to-human transmission of the virus yet¹⁴. Humans infected with HPAI A (H5N1) may be asymptomatic or present with mild symptoms of fever, cough, malaise, and a sore throat¹³. In some cases, the disease can become severe and lead to conjunctivitis, respiratory illness, or neurological complications such as seizures^{13,15}. Cases can be treated with antivirals such as oseltamivir and there are four antivirals recommended for use in the US^{13,16}. Vaccination with seasonal flu vaccines does not protect against H5N1¹³.

HPAI A (H5N1) 2024 outbreak in the United States

Infected animals

Since December 2021, poultry, wild birds, and mammals infected with H5N1 have been detected throughout North America¹⁷. Birds are more affected than mammals, and wild aquatic birds are considered to be the reservoir host for avian influenza A viruses^{17,18}. Between January 2022 and 13 November 2024, at least 100 million poultry, 10,000 wild birds, 600 dairy cattle, and one pig have been infected with HPAI A(H5) viruses across almost all 50 states in the US^{19–21}. Genetic sequencing of poultry, where available, confirms infection with H5N1 clade 2.3.4.4²². Infected dairy cattle have only been detected in the US since March 2024, and there is concern that the spread of H5N1 to dairy cattle indicates virus adaptation and the possibility that the virus may become easier to spread to humans^{20,23}.

The first infected cattle in the US were reported on 25 March and involved cattle in two dairy farms in Kansas and one in Texas²⁴. Since then, infected cattle have been reported from 16/50 states and 22/50 states have implemented restrictions on the importation of dairy cattle^{20,25}. California has the highest number of affected dairy cattle with 685 confirmed cases as of 26 December 2024²⁰. Colorado is the second most affected state with 64 herds affected as of 13 August²⁰. Since 1 December 2024, only California, Texas, and Nevada have reported new cases of infected cattle²⁰. Infected cattle develop a low appetite, reduced milk production, and produce thickened, discoloured milk²⁵. Genetic sequencing so far has confirmed infection with 2.3.4.4b (Eurasian lineage goose/Guangdong clade)²⁵. The virus has spread between cattle in the same herd, but mortality rates have been recorded as low as 2%²⁵. This is less than the high mortality associated with infected birds²⁵. Infected cats have been reported from areas with

infected dairy cattle and their illness has been more severe²⁵. Since 2022, sporadic infections have occurred in various animals and while the virus has been transmitted from mammal to mammal in 2024, testing so far has not found evidence that there have been changes in the virus that could make it more transmissible^{25,26}.

On 29 October, H5N1 was reported in a pig on a non-commercial farm in Oregon. This is the first time that H5N1 has been confirmed in a pig in the US²¹. There were four other pigs on the farm, all of which had been euthanised²¹. As the farm is non-commercial, the US Department of Agriculture (USDA) maintains that the national pork supply remains safe²¹.

On 17 November 2024, Hawai'i confirmed H5N1 in a backyard flock of birds in Central O'ahu²⁷. This is the first time H5N1-infected animals have been detected in Hawai'i²⁸. The Department of Health has identified the Mililani Pet Fair, which was held on 2 November 2024, as a potential exposure point for the public and advised anyone with symptoms to isolate at home and contact their primary care provider²⁷. They advised the risk of H5N1 spreading to the public is low, and the infected flock did not have symptoms at the time of the Pet Fair²⁷. As of 21 November, there have been no human cases of H5N1 detected in Hawai'i²⁹.

On 20 December 2024, the Los Angeles County Department of Public Health issued an animal health alert due to an increase in cases of H5 in domestic cats that had consumed raw cat food or milk³⁰. In addition, Oregon also confirmed the death of a domestic cat due to H5N1 after the cat ate infected raw pet food³¹. The supplier of this pet food, which caters to 12 US states, has recalled this food³¹. Twenty wild cats at the Wild Felid Advocacy Center of Washington have also become ill with H5N1, including one tiger, four cougars, one caracal, and 14 other types of wild cats³⁰. The center is closed to the public until further notice³⁰. The rise in cases among domestic cats, while concerning, has not led to any known cat-to-cat or cat-to-human transmission³¹. Therefore, the CDC maintains that the risk to public health remains low¹⁹.

Infected humans

Infection with HPAI A (H5N1) in humans is rare, and only sporadic infections have been reported in the US due to close contact with infected animals¹⁴. In 2024, and as of 23 December, 65 human cases of H5 (some of which have been confirmed as H5N1, however it is likely all are H5N1) have been reported from Colorado (n=10), Michigan (n=2), Missouri (n=1), Texas (n=1), Washington (n=11), Oregon (n=1), Iowa (n=1), Louisiana (n=1), Wisconsin (n=1), and California (n=36)^{19,32,33}. Due to low viral RNA levels, the US has not been able to determine the neuraminidase subtype as N1 for all cases³⁴. Most cases developed eye redness and conjunctivitis, but some reported mild respiratory symptoms³⁵. All cases except for two had known contact with infected or sick animals^{19,36}. On 22 November 2024, the CDC reported a confirmed HPAI A (H5N1) case in a child in California³⁷. This is the first child affected in the US during this outbreak so far³⁷. Household members also reported having symptoms however, they have tested negative for H5N1 but positive for other common respiratory viruses, and the CDC maintains that this is not indicative of person-to-person transmission³⁷. The child developed mild symptoms and is recovering³⁷. In Missouri, a household contact of a confirmed case became sick but was not tested, and both cases have recovered³⁶. The US Centers for Disease Control and Prevention (CDC) maintains that this is also not indicative of person-to-person transmission but likely a common exposure³⁶.

Before 2024, only one human case of HPAI A (H5N1) infection occurred in 2022 after exposure to infected poultry³². There has not been any case of human-to-human transmission yet, although a recent study suggests that the virus can transmit to the upper respiratory tract of humans, which could facilitate human transmission^{19,39}. Another study demonstrated that H5N1 from an infected human was able to transmit through air to ferrets, highlighting the importance of continued monitoring⁴⁰. While there is evidence that consumption of untreated raw milk from infected cattle could transmit the disease to other animals and pose a risk to humans, the US Food and Drug Administration (FDA) maintains that the commercial milk

supply is safe^{41,42}. To gain a better understanding of the prevalence of H5N1 in raw cow's milk, a double-blind study for gathering purposes only intends to begin on 28 October. This study will sample Grade "A" raw cow's milk from dairy processing facilities for detection of H5N1⁴¹. A recent serosurvey study of workers exposed to infected dairy cattle when milking cows or cleaning milk parlours, found that 8/115 had evidence of recent infection⁴³. Only four recall having had any symptoms, mainly conjunctivitis^{43,44}. This evidence highlights the need for strong, active monitoring of exposed workers⁴³.

On 13 November, Canada reported its first domestically acquired human case of H5N1⁴⁵. This was confirmed in a teenager in British Columbia⁴⁵. Genomic sequencing showed the virus is related to the H5N1 virus that currently affects poultry in British Columbia: clade 2.3.4.4b, genotype D1.1⁴⁵. This is different from the genotype circulating in cattle in the US⁴⁵. The previously healthy teenager is now hospitalised and in critical condition⁴⁵. Investigations were unable to determine how this individual became exposed to the virus^{45,46}. No other cases have been reported so far, and the Canadian government advises the risk to public health remains low⁴⁵. The virus affecting this teenager has shown some mutations suggesting adaptation to humans, which has raised some concerns and may explain the severity of the illness⁴⁷. However, there remains no evidence that the virus can be transmitted from human to human⁴⁷.

Most cases in the US have developed mild symptoms so far. However, a recently detected presumptive H5N1 case in Louisiana has been hospitalised as reported by the State Department of Health on 13 December 2024³⁸. The individual affected was exposed to sick and dead birds suspected of having H5N1³⁸. Genomic analysis reveals that genetic sequences in the specimen collected from the individual affected in Louisiana differ from those found in cattle and poultry⁴⁸. The analysis found mutations that had likely emerged during the individual's illness^{48,49}. These mutations may enable greater transmission of the virus and upper airway infection⁴⁹. In addition, one of the changes identified was also found in the infected teenager from British Columbia^{48,49}. This suggests that viral changes have occurred during illness in individuals who suffered severe illnesses⁴⁹. The CDC states that while these changes are concerning, they would be more concerning had they been found in animal hosts or occurred in the early stages of infection⁴⁸. There has been no onward transmission of H5N1 from the Louisiana case⁴⁸.

Public Health Response and Risk Assessments

While the spread of H5N1 to cattle and between cattle has caused some concern about the transmissibility of the virus, the US CDC states that the risk of H5N1 spread to the public is low¹⁹. This is in line with the Food and Agriculture Organization (FAO), the World Health Organization (WHO), and the World Organisation for Animal Health (WOAH) which also state the risk to the public is low however, the risk to persons exposed is low to moderate depending on the nature of the exposure⁵⁰.

An NIH-funded study by Lin et al. found that one mutation of the virus, called Q226L, could lead to increased human-to-human transmissibility and a pandemic. The US CDC continues to monitor the situation closely to identify any genetic changes that could suggest increased transmissibility, increased disease severity, and reduced susceptibility to antivirals⁵¹. They are also conducting wastewater surveillance to complement influenza surveillance systems however this cannot distinguish the subtype or source of influenza A viruses³². Even with a strong surveillance system, there are several barriers to detecting H5N1 in humans and the likely number of infections may be higher than what is reported⁵². Barriers to detection include asymptomatic infection, limited access to rural farm workers who may be hesitant to seek medical care (especially without health insurance or with concerns about immigration status), and a lack of incentive to report infections in cattle⁵².

As part of a CDC initiative, over 100,000 seasonal influenza vaccine doses have been administered to individuals from 12 states with infected dairy cattle⁵³. The vaccine does not protect against H5N1 however, it could reduce illness severity⁵³. Further, with a reduction in seasonal influenza, HPAI (H5) cases may be

better detected⁵³. In addition, the USDA has approved two vaccine candidates for research trials to develop vaccines that protect cattle from H5N1²¹.

A recent survey study of dairy farmworkers in Colorado found that very few used respiratory personal protective equipment (PPE) when working with confirmed infected cattle⁵⁴. Less than half of workers report using eye protection⁵⁴. Considering recent evidence, the CDC has expanded recommended testing to all individuals (including asymptomatic) who have been exposed to infected animals, particularly if PPE was not worn⁴⁴. In addition, the CDC now recommends offering Oseltamivir (Tamiflu) to all exposed individuals regardless of symptoms⁴⁴. However, a recent study demonstrated that H5N1 extracted from an infected human was less sensitive to oseltamivir and more sensitive to favipiravir, baloxavir marboxil, and zanamivir⁴⁰.

Useful Resources

- Pandemic PACT has a dedicated [H5N1 page](#) in the Outbreak section of the website which provides information and analyses of active mpox research and funding globally since 2020.
- The most up-to-date information and guidance can be found on the US CDC's [webpage](#) dedicated to H5 Bird Flu.
- The US Department of Health and Human Services has published '[U.S. Highly Pathogenic Avian Influenza a\(H5N1\) Research Priorities: October 2024](#)'.
- The US CDC published a '[Public Health Science Agenda for Highly Pathogenic Avian Influenza A\(H5N1\)](#)' with strategic priorities to guide research and surveillance activities.
- NIAID published a '[Research Agenda for 2024 H5N1 Influenza – May 2024](#)'.
- The WHO published a '[Summary status of development and availability of A\(H5N1\) candidate vaccine viruses and potency testing reagents](#)' in February 2024.

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