BMJ Best Practice

Avian influenza A (H5N1) virus infection

Straight to the point of care

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Summary

Avian influenza A(H5N1) virus infection is a notifiable condition. Infection prevention and control measures such as patient isolation and standard, contact, and airborne (including eye protection) precautions are recommended.

Sporadic human infections have been reported globally since 1997; however, there has been no evidence of sustained human-to-human transmission.

High case-fatality proportion of approximately 49% among reported cases of laboratory-confirmed infection.

Most patients present with fever and features of lower respiratory tract infection on admission to hospital. Infection should be considered in anyone showing signs or symptoms of acute respiratory illness who has a relevant exposure history. Molecular testing (with subtyping) is recommended to confirm the diagnosis.

Antiviral therapy is recommended as soon as possible in symptomatic patients with suspected or confirmed infection. Supportive care and specialised intensive care management are indicated for respiratory failure and other severe complications.

Antiviral post-exposure prophylaxis and monitoring of close contacts of a confirmed or probable case are recommended.

Definition

Avian influenza A(H5N1) is a contagious disease of wild birds and poultry. Avian influenza A viruses can either be low or highly pathogenic, and can infect other animal species such as wild or domestic terrestrial mammals, and marine mammals. Different virus subtypes have sporadically infected humans to cause a wide range of pathologies. Specifically, highly pathogenic avian influenza (HPAI) A(H5N1) virus originating in poultry and wild birds can be transmitted to humans, with rare cases of infection transmitted between humans.[1] [2] Cases of human infection linked to infected dairy cows have been reported, and represent the first instances of likely mammal-to-human transmission.[3]

This topic focuses on human infection with HPAI A(H5N1) virus; Avian influenza A(H7N9) virus infection is covered in a separate topic.

[BMJ talk medicine podcast: avian influenza - a guide to recognition, reporting and referral with Dr Mary-Margaret Fill] (https://soundcloud.com/bmjpodcasts/bmj-best-practice-avian-influenza)

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THEORY

Epidemiology

Highly pathogenic avian influenza (HPAI) A(H5N1) virus strains have infected poultry or wild birds in more than 60 countries since 2003.

Globally, from May 1997 to 12 December 2024, 974 cases of human HPAI A(H5N1) infection were reported from 25 countries. This includes 18 cases and six deaths in Hong Kong during May through December 1997, and two cases and one death in Hong Kong in February 2003.[35] [36][37] From November 2003 to 12 December 2024, 49% of reported HPAI A(H5N1) cases were fatal.[37] Since a large outbreak of cases was reported in Egypt during 2015 (136 cases), few sporadic human cases have been reported worldwide until the ongoing 2024-2025 outbreak in the US.

US outbreak 2024-2025

- Since March 2024, sporadic human infections have been reported in the US associated with exposure to poultry or dairy cattle as part of ongoing multistate outbreaks among poultry and dairy cattle. As of 31 January 2025, 67 human cases and one death have been reported as part of this outbreak.[22]
- April 2024: one HPAI A(H5N1) human case was reported in Texas. The person developed conjunctivitis (eye redness) as their only symptom, and they had exposure to dairy cattle presumed to be infected with HPAI A(H5N1) virus.[43][44]
- May 2024: a second human case was reported in a dairy worker in Michigan. Similar to the case in Texas, the person worked on a dairy farm where H5N1 virus had been identified in cows, and only reported eye symptoms.[45]
- May 2024: a third human case was reported in a dairy worker in Michigan with exposure to infected cows. This was the first case in the US to report more typical upper respiratory tract symptoms including cough and eye discomfort with watery discharge.[46]
- July 2024: a fourth human case was reported in a dairy worker in Colorado with exposure to infected cows. The person reported eye symptoms only.[47]
- July 2024: a further nine confirmed cases of human infection associated with exposure to poultry at two facilities were reported in Colorado. All cases were in farm workers involved in the depopulation of poultry at a facility experiencing a H5N1 outbreak. The workers reported mild illness with conjunctivitis as the most common symptom.[48]
- September 2024: a human case was reported in Missouri, and was the first case without a known occupational exposure to sick or infected animals. The case was identified through the state's seasonal influenza surveillance system. No ongoing transmission has been reported.[49]
- October 2024: three human cases were reported in people with occupational exposure to infected dairy cows in California. All cases experienced only mild symptoms (including conjunctivitis).[50] [51] Several cases have been reported in California since these initial three cases (38 in total), including the first case in a child.[38]
- December 2024: the first case of severe infection in the US was reported in Louisiana. The patient had exposure to sick and dead birds in backyard flocks. The virus was identified as belonging to the D1.1 genotype currently detected in poultry and wild birds in the US. The patient died in early January 2025, and was the first person in the US to die as a result of H5 virus infection.[39] [40]
- Cases have also been reported in Iowa, Oregon, Washington, and Wisconsin in 2024.[22]
- Prior to this, the first human case of infection ever reported in the US was in 2022 in Colorado, and was associated with direct exposure to infected poultry during a culling process.

Cases outside of the US: January 2023 to January 2025

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- January 2025: one HPAI A(H5N1) case was reported in the West Midlands region in the UK. The case acquired the infection on a farm after close prolonged contact with a large number of infected birds. The infection was detected during routine surveillance.[42]
- November 2024: one HPAI A(H5N1) case was reported in a 13-year-old girl in British Columbia, Canada. The case was detected through enhanced hospital-based influenza surveillance, and the patient had no travel history. The source of infection is currently unknown. The patient had a history of mild asthma and elevated body mass index, and was hospitalised due to worsening respiratory symptoms and haemodynamic instability, which progressed to acute respiratory distress syndrome (ARDS). Genomic sequencing revealed the virus belonged to the 2.3.4.4b clade (D1.1. genotype), the virus currently detected in bird outbreaks in Canada and the US.[52]
- November 2024: one HPAI A(H5N1) case was reported in a 18-year-old boy in Vietnam. The patient resided in an area where a H5N1 outbreak in poultry and waterfowl had been reported, with the patient reporting exposure to sick and dead poultry. The patient was diagnosed with severe pneumonia, hospitalised, and treated with antiviral therapy, and has since recovered.[53]
- September 2024: one HPAI A(H5N1) case was reported in a 15-year-old child in Cambodia. The patient was admitted to hospital after presenting with fever, cough, sore throat, and difficulty breathing. The patient was treated with oseltamivir, but died 3 days later. The patient was exposed to potentially infected chickens in the days prior to the onset of illness.[54]
- May 2024: one HPAI A(H5N1) case was reported in Victoria, Australia. The case occurred in a child who acquired the infection in India. The child was unwell in March 2024 and experienced severe infection, but has since made a full recovery. The source of exposure to the virus in this case is currently unknown. No further cases have been connected to this case. This is the first human case of infection reported in Australia.[55]
- March 2024: one HPAI A(H5N1) case was reported in a 21-year-old man in Khanh Hoa Province, Vietnam. He developed fever and cough before being admitted to hospital with persistent abdominal pain and diarrhoea. He then developed severe pneumonia, sepsis, and acute respiratory distress syndrome, and died 12 days after initial symptom onset. The man went bird hunting in February 2024 and did not have contact with dead or sick poultry since then. No evidence of human-to-human transmission was identified.[56]
- February 2024: two HPAI A(H5N1) cases were reported in epidemiologically-unrelated people in different provinces in Cambodia. A 3-year-old child exposed to dead backyard poultry was hospitalised with mild uncomplicated upper respiratory tract illness, and a 69-year-old patient who raised domestic poultry and fighting roosters was hospitalised with difficulty breathing. Both patients recovered, and no evidence of human-to-human transmission was identified.[57]
- November 2023: two HPAI A(H5N1) cases were reported in people living in different households in the same rural village in Cambodia. After exposure to sick or dead backyard poultry, a young girl experienced mild uncomplicated upper respiratory tract illness and survived, and a previously healthy young woman developed severe pneumonia and died. No evidence of human-to-human transmission was identified.[58]
- October 2023: two HPAI A(H5N1) cases were reported in epidemiologically-unrelated people in different provinces in Cambodia. A young child and a middle-aged adult both died of severe pneumonia after close exposure to sick and dead poultry in rural villages. No evidence of human-to-human transmission was identified.[20]
- May 2023: two HPAI A(H5N1) cases were identified in poultry farm workers in the UK. Both cases were asymptomatic and were detected through a surveillance study of asymptomatic workers exposed to infected poultry. Both people have since tested negative, and work to determine whether these are

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false positives (rather than mucosal contamination of the nose with virus particles) is ongoing. No evidence of human-to-human transmission was identified.[59]

- March 2023: the first case of HPAI A(H5N1) virus infection in Chile was identified in a middle-aged man who developed severe pneumonia and respiratory failure. The man lived in an area where H5N1 virus was detected in wild birds and sea lions in northern Chile, but the source of his infection was unknown.[60] [61] [62]
- February 2023: two HPAI A(H5N1) cases were reported in family members, an 11-year-old girl and her father, in a rural Cambodian village after exposure to sick and dead infected poultry. The girl died of respiratory failure while her father only experienced mild upper respiratory tract illness. No evidence of human-to-human transmission was identified.[63]
- January 2023: one HPAI A(H5N1) case was reported in a 9-year-old girl who was admitted to hospital on December 30, 2022 for respiratory illness after exposure to sick and dead backyard poultry in a rural area of Ecuador. She was transferred to an intensive care unit of a paediatric hospital for septic shock and pneumonia, and survived. This was the first human case of HPAI A(H5N1) virus infection ever reported in South America.[64] [65]

Current situation reports are available from the World Health Organization (WHO), the US Centers for Disease Control and Prevention (CDC), and the UK Health Security Agency:

- [WHO: surveillance - avian influenza] (https://www.who.int/westernpacific/emergencies/surveillance/avian-influenza)
- [CDC: H5 bird flu - current situation] (https://www.cdc.gov/bird-flu/situation-summary)
- [UK Health Security Agency: avian influenza: guidance, data and analysis] (https://www.gov.uk/government/collections/avian-influenza-guidance-data-and-analysis)

Prior to the current 2024-2025 outbreak in the US, most human HPAI A(H5N1) cases were reported among previously healthy children and young adults. The median age of patients was approximately 20 years, with an age range for all patients from under 1 year to 81 years.[66] The ratio of male-to-female cases was about equal; however, there was a higher case-fatality proportion in females, which may be due to many different epidemiological factors, such as delay in accessing healthcare, case age, and physician testing patterns.[26] From 2003-2010, patients under 20 years of age had a significantly lower risk of dying than those aged over 20 years (case-fatality proportions: 52% vs. 66%).[26] Mortality is associated with delayed recognition of disease and hospitalisation after symptom onset.[26] One study reported that the presence of rhinorrhoea appeared to indicate a better prognosis for children with HPAI A(H5N1).[32]

While rare, asymptomatic infection with HPAI A(H5N1) virus confirmed virologically and serologically has been reported, detections of A(H5N1) viral RNA in asymptomatic individuals exposed to infected poultry are more common.[57] [67] [68] [69] [70] Most likely, this represents transient detection of viral RNA, and not evidence of HPAI A(H5N1) virus infection.[20][69]

One systematic review and meta-analysis of human seroprevalence of H5N1 in China detected an overall seroprevalence of 2.45%. A higher seroprevalence of 7.32% was detected in central China.[71] One cohort study of human infections with HPAI A(H5N1) virus in households raising backyard poultry in Egypt found a very low seroprevalence of antibodies to H5N1 virus (0.4% at baseline and 0.2% at follow-up).[72]

Aetiology

The natural reservoir for nearly all influenza A viruses is wild aquatic birds (ducks, geese). Of the 18 haemagglutinin and 11 neuraminidase subtypes of influenza A viruses identified to date, nearly all (except for H17N10, H18N11 identified in bats) have been identified among birds.[73] Other animal species can also

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be infected by influenza A viruses, including pigs, cows, wild terrestrial and marine mammals, horses, dogs, cats, and bats.[74] Highly pathogenic avian influenza (HPAI) A viruses can cause asymptomatic infection to fatal disease in wild birds and domestic poultry. HPAI A(H5N1) virus was first identified in Scotland in 1959. However, the progenitor HPAI A(H5N1) virus to all HPAI A(H5N1) viruses currently circulating among birds was identified in 1996 from an infected goose in southern China.

Most human HPAI A(H5N1) cases are sporadic and associated with direct contact (e.g., touching) or very close exposure (within ≤1 metre [≤3 feet]) with sick or dead backyard poultry (usually chickens), and a seasonal variation observed in human cases parallels that of outbreaks in birds.[26] [75] [76] [77] However, other risk factors include visiting a live poultry market and prolonged, unprotected close contact with a symptomatic human HPAI A(H5N1) case.[78] [79] [80] Exposure to pond water in regions where HPAI A(H5N1) virus has been widespread among birds has also been suggested as a possible risk factor.[81] In some cases, a possible exposure risk was not identified, suggesting possible environmental exposure or close contact with an unknown infected person.[82] Clustering of HPAI A(H5N1) cases among genetically related family members suggests the potential for increased genetic susceptibility. However, human-to-human transmission remains rare.[83] [84] [85] [86] [87] Rare nosocomial transmission has also been documented.[1] [2] [88] There is no evidence of ongoing human-to-human transmission of HPAI A(H5N1) virus. As of May 2024, no evidence of human-to-human transmission of HPAI A(H5N1) virus has been reported since 2007.

Avian influenza A viruses, including HPAI A(H5N1) virus, can potentially be transmitted to humans through different modalities.

- Direct contact (touching) or close exposure to infected sick or dead poultry or poultry products is thought to be the major risk for transmission of avian influenza A viruses to humans.
- Inhalation of aerosolised material (e.g., poultry faeces) containing infectious HPAI A(H5N1) virus is a likely route of transmission from poultry to humans.
- Self-inoculation of the mucous membranes after direct contact with material containing HPAI A(H5N1) virus (touching or cleaning infected birds) or indirect (fomite) contact transmission from surfaces contaminated with poultry faeces or products containing HPAI A(H5N1) virus to mucous membranes has also been hypothesised.
- Consumption of uncooked poultry products, including blood from infected birds, has been identified as a potential risk factor in field investigations, but whether transmission can occur by primary HPAI H5N1 virus infection of the human gastrointestinal tract is unknown.

Transmission from mammals to humans may be possible, but it is thought to be rare. The first instance of likely mammal-to-human transmission was reported in Texas, US, in April 2024.[3] The person developed conjunctivitis as their only symptom after exposure to dairy cattle presumed to be infected with HPAI A(H5N1) virus.[43][44] Other cases of transmission from dairy cattle have been reported in the US since then.

Experimental studies in ferrets have demonstrated that HPAI A(H5N1) virus can acquire traits that improve transmissibility via respiratory droplets, and thus increase the risk of human-to-human transmission.[89] They have also shown the potential for H5N1 viruses to cause infection after exposure to virus via the eyes.[90] Ferret studies using the A(H5N1) virus from a human case in the 2024-2025 dairy cattle outbreak suggest that the virus is not capable of spreading efficiently among people via respiratory droplets or fomites, but spreads efficiently between ferrets in direct contact.[91]

Of the several amino acid substitutions associated with increased respiratory transmission in this mammalian model, some have been found in HPAI A(H5N1) viruses circulating among poultry.[92] The odds of

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spontaneous mutations resulting in improved transmissibility are very low.[93] A change in the current epidemiology of HPAI A(H5N1) human cases, including a large increase in epidemiologically related clusters or unrelated cases, could suggest increased transmissibility from viral mutations and increased pandemic potential.[94] However, investigations of a large increase in human HPAI A(H5N1) cases reported in Egypt during 2014-2015 attributed increased diagnostic testing of exposed people and not viral mutations as the likely cause of increased case detection.[67] [95]

Influenza A viruses are subject to genetic re-assortment. Previous pandemic viruses are believed to have emerged in human populations through mutation from a zoonotic reservoir (1918 H1N1), genetic re-assortment between low pathogenic avian influenza and seasonal influenza A viruses (1957 H2N2, 1968 H3N2), and genetic re-assortment between triple re-assortant swine influenza A (H1N1) and other swine influenza A viruses (2009 H1N1).[96] [97]

Pathophysiology

The incubation period has been estimated to be between 2-10 days (mean 3.3 days, median 5 days), and the infectious period has been estimated to be between 5-13 days. However, there is very limited evidence available.[98]

Highly pathogenic avian influenza (HPAI) A(H5N1) virus binds to receptors with sialic acids bound to galactose by alpha-2,3 linkages, which are primarily, but not entirely, distributed in the human lower respiratory tract.[99] [100] Such receptors have also been reported in the human gastrointestinal tract.[101] In contrast, most seasonal influenza A and B viruses bind preferentially to receptors with sialic acids bound to galactose by alpha-2,6 linkages, which are primarily distributed in the human upper respiratory tract. Furthermore, specific structural conformation, not just receptor binding affinity, may be important in binding to receptors in the upper respiratory tract.[102] HPAI A(H5N1) virus obtained from human clinical samples with the ability to bind upper respiratory tract tissue has also been reported.[99] [103] High and prolonged HPAI A(H5N1) viral replication in the lower respiratory tract induces pro-inflammatory cytokines and chemokines at much higher levels than with seasonal influenza A virus infection, resulting in pulmonary capillary leak, diffuse alveolar damage, and acute lung injury, and can lead to development of acute respiratory distress syndrome.[104] [105] HPAI A(H5N1) viraemia has been reported in fatal cases, and dissemination of HPAI A(H5N1) virus to infect brain tissue; isolation from cerebrospinal fluid, gastrointestinal infection, and vertical transmission with evidence of virus in placenta and fetal lung cells have been documented.[28] [105] [106] Reactive haemophagocytosis has also been reported.[106]

Classification

Pathogenicity

Avian influenza A virus strains are classified as low pathogenic avian influenza (LPAI) or highly pathogenic avian influenza (HPAI) on the basis of molecular and pathogenicity criteria.

- Most strains are LPAI viruses and cause asymptomatic infection or mild disease in infected poultry. LPAI H3N8, H6N1, H7N2, H7N3, H7N4, H7N7, H7N9, H9N2, H10N3, H10N7, and H10N8 virus strains have infected humans causing disease ranging from conjunctivitis to non-fatal upper respiratory and lower respiratory tract disease, to severe lower respiratory tract disease and death (H3N8, H7N9, H9N2, H10N8).[4] [5] [6] [7] [8] [9] [10] [11]

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- HPAI strains identified to date are of the H5 and H7 subtypes and can cause severe illness in poultry. HPAI A virus infections in humans have ranged from asymptomatic to severe or fatal disease. Rare, sporadic human cases of HPAI A virus infection have been detected with H5N1, H5N6, H7N3, H7N7, and H7N9 viruses and have caused a wide spectrum of illness from conjunctivitis (H7N3, H7N7) to severe pneumonia, acute respiratory distress syndrome, and fatal outcomes (H5N1, H5N6, H7N7, H7N9).[12] [13] [14] [15] Asian lineage HPAI H7N9 viruses were detected and reported in the People's Republic of China for the first time in February 2017.

Antigenic structure (clades)

In 2014, the World Health Organization/World Organisation for Animal Health/Food and Agriculture Organization H5N1 Evolution Working Group published a revision to HPAI A(H5N1) virus nomenclature.[16] According to this revised nomenclature system, circulating HPAI A(H5N1) virus strains among birds are classified into numerous clades, and subdivided into subclades and lineages.[17] [18] These antigenic changes have important implications for vaccine development. Clades that have infected humans include 0, 1, 2, and 7. HPAI A(H5N1) virus continues to cause rare, sporadic human infections, including fatal outcomes. Most human HPAI A(H5N1) virus infections since 2005 have been with clade 2 virus strains. HPAI A(H5N1) virus strains continue to evolve among infected birds through genetic reassortment and antigenic drift.[19]

In 2023, clade 2.3.4.4b viruses were the predominant HPAI A(H5N1) virus strains circulating among wild birds worldwide, resulting in outbreaks in commercial and backyard poultry, with spillover to terrestrial and marine mammals, and rare human infections.[20][21] Clade 2.3.4.4b is also responsible for the current outbreak in dairy cattle in the US and the associated human cases.[22][23] [24]

- Genotype D1.1 has been detected in human infections associated with the current outbreaks in poultry and wild birds in the US and Canada, and genotype B3.13 has been detected in human infections associated with the current outbreaks in dairy cattle in the US.[25]

Other HPAI A(H5N1) virus strains, such as clade 2.3.2.1c viruses, are circulating among poultry in some areas of the world, and have also caused sporadic human infections.

Case history

Case history #1

A previously healthy 32-year-old woman who raises backyard chickens acutely develops overwhelming fatigue and a temperature of >38.8°C (>102°F) for 2 days. She has a new cough, bloody sputum production, dyspnoea, and pleuritic chest pain. She has vague abdominal pain, as well as some watery diarrhoea. Her respiratory status declines over the following 2 days, prompting her family to bring her to hospital. A chest radiograph shows multi-lobar consolidation. Her lymphocyte and platelet counts are low, and her aspartate aminotransferase and alanine aminotransferase are high. No family members have been sick. They report that many poultry are sick or have died in the area recently, and the patient recently prepared and ate ill-appearing chickens.

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Case history #2

A 55-year-old Vietnamese-American man with hypertension develops progressive fever, productive cough, and shortness of breath soon after returning to the US in the winter from Southeast Asia. He had spent the prior 3 months in a rural area of Vietnam. His family reports that there were widespread deaths among poultry in the village where he had stayed. He had handled backyard poultry that had died 5 days before the onset of his symptoms, and he recently purchased live chickens and ducks at a live poultry market. He is tachypnoeic, has a room air oxygen saturation of 90%, and has decreased breath sounds on the posterior base of his left lung. A chest radiograph demonstrates left lower lobe consolidation. Laboratory findings include leukocytosis, anaemia, thrombocytosis, and hypoxaemia.

Other presentations

Early illness is manifested by signs and symptoms consistent with a febrile upper respiratory tract infection, and may include conjunctivitis or gastrointestinal symptoms. Clinical progression to severe lower respiratory tract disease typically occurs in patients at about days 3 to 6.[26] Multi-organ failure may occur.[27] Encephalitis and meningoencephalitis have been reported.[28] [29] Clinically mild disease (fever and symptoms of upper respiratory tract infection) has been documented, especially in children in Egypt presenting for care early, and in other countries.[30] [31] [32] At hospital admission, most patients have fever and clinical findings similar to those of severe community-acquired pneumonia.[33] In human cases linked to the 2024-2025 outbreak in the US, some farm workers with evidence of recent infection reported no symptoms or mild conjunctivitis only.[34]

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Approach

People with infection due to highly pathogenic avian influenza (HPAI) A(H5N1) virus typically present with similar signs and symptoms of pneumonia caused by other infectious aetiologies (including seasonal influenza A or B viruses). There is a wide spectrum of disease ranging from sub-clinical or only mild symptoms (e.g., upper respiratory tract symptoms, conjunctivitis) to severe respiratory compromise and multi-organ failure, which can lead to death. However, most patients with HPAI A(H5N1) virus infection reported since 1997 and before the 2024-2025 US outbreak have been severely ill, reflecting late clinical presentation and late initiation of antiviral treatment, identified through hospital-based case-finding.

Consider the possibility of infection in anyone showing signs or symptoms of acute respiratory illness or conjunctivitis who has a relevant exposure history.[41]

Given that human infection with HPAI A(H5N1) virus is rare (even among people with high-risk exposures), diagnostic evaluation and therapy must consider alternative aetiologies. See Differential diagnosis .

If there is concern that a patient might have HPAI A(H5N1) virus infection, infection prevention and control precautions (i.e., patient isolation and standard, contact, and airborne precautions including eye protection) should be used.

Human infection with an avian influenza A virus is a notifiable disease under the World Health Organization's (WHO) International Health Regulations. Cases are reportable to the WHO and local or national public health departments should be contacted for guidance. Many local health departments can directly assist clinicians to determine which people need testing, to facilitate testing, and to assist with case management.

History

A history of direct contact (touching) or close exposure with animals (predominantly sick or dead poultry) or people suspected or confirmed to have HPAI A(H5N1) virus infection within the prior 7-10 days by a person with febrile respiratory illness should trigger consideration of HPAI A(H5N1) virus infection.[119] [120] A recent history of travel to a country or area where HPAI A(H5N1) virus has been documented in wild birds, commercial or backyard poultry, or terrestrial or marine mammals, with relevant exposures (e.g., to sick/dead animals) should also prompt consideration of HPAI A(H5N1) virus infection in the differential diagnosis of a patient presenting with fever and respiratory symptoms.

Early illness is manifested by signs and symptoms consistent with a febrile upper respiratory tract infection. A dry or productive cough and dyspnoea are common symptoms. Non-specific symptoms consistent with influenza-like illness have been reported (including conjunctivitis, rhinorrhoea, headache, sore throat, myalgia, and fatigue). Clinical progression to severe lower respiratory tract disease occurs in many patients during days 3-6.[26] Clinically mild disease (fever and symptoms of upper respiratory infection) has been documented.[30] [31] [32] In human cases linked to the dairy cattle outbreak in the US in 2024-2025, some dairy farm workers with evidence of recent infection reported no symptoms.[34] At hospital admission, most patients have fever and clinical findings similar to severe community-acquired pneumonia.[33] Several non-specific primary gastrointestinal symptoms (abdominal pain, vomiting, diarrhoea) have been reported in children and adults with HPAI A(H5N1) virus infection.

Most patients admitted to the hospital with HPAI A(H5N1) virus infection have severe lower respiratory tract disease, and multi-organ dysfunction or failure (renal, respiratory, hepatic, and cardiac) can occur. Other reported complications include haemophagocytosis, refractory shock requiring vasopressor

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support, disseminated intravascular coagulation, spontaneous abortions in pregnant women, and encephalitis.

Physical examination

Physical examination findings in severe disease usually are consistent with severe pneumonia due to other aetiologies and might include temperature ≥38°C (≥100.4°F), tachypnoea, and abnormalities on chest auscultation (including rales, wheezing, and focal decreased breath sounds). Less commonly, the examination may also show evidence of signs of atypical features (e.g., altered mental status, seizures, and febrile diarrhoeal illness initially complicated by progressing to pneumonia).

Mild illness with HPAI A(H5N1) virus infection is clinically indistinguishable from uncomplicated human influenza virus infection , especially in children. Physical examination findings include upper respiratory tract and constitutional signs and symptoms such as fever, cough, rhinorrhoea, and/or malaise.

Initial investigations

Given the rarity of HPAI H5N1 virus infection, it is critical that diagnostic evaluation also includes work-up for a broad range of more common disease processes that may also present as febrile respiratory illness, including respiratory viruses, and investigation for endemic respiratory pathogens from the region where infection may have occurred. Testing for other causes of acute respiratory illness, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), should be considered depending on the local epidemiology of circulating respiratory viruses. See Differential diagnosis .

First-line evaluation of patients suspected of having HPAI A(H5N1) virus infection should include the following.

- Laboratory tests, including at least an full blood count with differential, basic chemistries and hepatic enzymes, and a chest x-ray, should be performed. Common findings in severe cases may include leukopenia, lymphopenia, and mild to moderate thrombocytopenia, but these laboratory findings are not present in all cases and are unlikely to be useful to distinguish between infection by HPAI A(H5N1) virus and other respiratory pathogens.
- Pulse oximetry should be performed in patients with dyspnoea to assess their oxygenation status, as well as arterial blood gas if considered necessary.
- Sputum Gram stain and bacterial culture, and blood culture should be performed as part of the evaluation for primary bacterial pneumonia and potential bacterial co-infection. Seasonal influenza A or B virus infection should be considered, as it is far more common than HPAI A(H5N1) virus infection.
- SARS-CoV-2 diagnostic testing should be performed, as SARS-CoV-2 infection is far more common than HPAI A(H5N1) virus infection, and a positive result can inform antiviral treatment and infection prevention and control measures.
- Other respiratory virus testing may be considered in certain circumstances (e.g., respiratory syncytial virus in young children, multiple respiratory virus aetiologies in immunocompromised patients). Such testing can inform and guide appropriate treatment, including decisions on whether to initiate or discontinue antibiotic treatment, and appropriate infection prevention and control measures. Patients presenting with atypical symptoms (e.g., gastrointestinal or neurological) should receive a suitable work-up directed at alternative aetiologies for those processes.

Clinicians should pursue alternative diagnoses whenever they encounter a patient they suspect has HPAI A(H5N1) virus infection. As always, work-up should be directed toward abnormal clinical findings.

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Specific viral testing

Perform testing on people who meet epidemiological criteria and either clinical or public health response criteria.[119] For case definitions, see Criteria .

- In the context of the current outbreak in the US, as of 16 January 2025, the Centers for Disease Control and Prevention (CDC) recommends routinely testing all patients with suspected influenza and to expedite the subtyping of influenza A-positive specimens from hospitalised patients, particularly those in the intensive care unit. Subtyping should be performed as soon as possible following admission, ideally within 24 hours. The goal of this approach is to prevent delays in identifying infections.[121]

Testing of symptomatic human cases of suspected novel influenza A virus infection should be referred to the nearest public health laboratory.[122] Testing of asymptomatic people is not routinely recommended, but may be considered as part of ongoing public health investigations (e.g., workers with a high risk of exposure to infected animals who do not report wearing the recommended personal protective equipment, close contacts of a confirmed case).[41]

Reverse transcription polymerase chain reaction (RT-PCR)

- The recommended and definitive diagnostic testing is real-time RT-PCR of respiratory specimens.[122] [123] Testing for seasonal influenza A and B viruses should be performed on respiratory specimens; if influenza A is positive, then subtyping should be performed for seasonal influenza A(H1) and A(H3) viruses. If influenza A testing is positive but A(H1) and A(H3) are negative, then testing for A(H5) should be performed at a specialised public health laboratory.[124]
- RT-PCR for HPAI A(H5N1) virus may not be available in some clinical settings. Many regional public health laboratories, most national laboratories, and some private laboratories can perform testing for A(H5) virus.
- RT-PCR takes approximately 4 hours to produce preliminary results, but transport time and testing logistics may delay testing results.

Specimen collection

- Healthcare workers should follow recommended infection control precautions and use appropriate personal protective equipment when collecting clinical specimens, including respiratory and eye protection.[125]
- The preferred specimens in non-intubated patients are upper respiratory tract specimens (e.g., oropharyngeal swab, nasopharyngeal swab, nasal aspirate or wash). Two swabs may be combined into one vial (e.g., one nasal or nasopharyngeal swab and one oropharyngeal swab). Ideally both a nasopharyngeal swab, and a combined nasal swab and oropharyngeal swab should be collected and tested separately. Oropharyngeal swabs have a higher diagnostic yield for HPAI A(H5N1) virus than other upper respiratory specimens. Nasal and nasopharyngeal swabs are preferred to detect other respiratory viruses, including seasonal influenza viruses.[122] [126] A conjunctival swab (with a nasopharyngeal swab) and/or nasal swab combined with an oropharyngeal swab should be collected if the person has conjunctivitis (with or without respiratory symptoms). Sputum, if obtainable from a patient who is not intubated, could also be collected for testing.[41] [122]
- The preferred specimens in intubated patients or patients with severe lower respiratory tract illness are lower respiratory tract specimens (e.g., endotracheal aspirate, bronchoalveolar lavage fluid). These specimens have a higher yield for detecting HPAI A(H5N1) virus.[122] [126]

- Multiple respiratory specimens should be collected from different sites on at least two consecutive days for hospitalised patients, because testing single specimens may miss detection of HPAI A(H5N1) virus.[122]
- Swabs with a synthetic tip (e.g., Dacron®, polyester) and an aluminum or plastic shaft should be used. Swabs with cotton tips or wooden shafts, and calcium alginate swabs are not recommended because they may interfere with the test.[122] [126]
- Obtain specimens as soon as possible, ideally within 7 days of symptom onset. However, if earlier specimens are not available, respiratory specimens should still be collected and tested after 7 days from symptom onset, as prolonged viral shedding has been documented for critically ill patients with HPAI A(H5N1) virus infection.[122]

Other investigations

- Viral culture should not be undertaken except in an experienced, biosafety level 3-enhanced laboratory or greater following recommended personal protective equipment and infection control precautions. Viral culture is important for virological surveillance, antigenic monitoring for vaccine strain selection, and assessment and analyses of viral characteristics such as genetic re-assortment, receptor binding affinity, and antiviral susceptibility.
- Serological testing is not routinely available, cannot inform clinical management, and should not be considered for clinical diagnostic purposes. However, properly timed acute and convalescent sera tested at specialised public health laboratories for evidence of seroconversion can yield a retrospective diagnosis of HPAI A(H5N1) virus infection.
- Commercially available point-of-care rapid influenza diagnostic tests are insensitive and not specific for HPAI A(H5N1) virus and, therefore, should not be used for diagnosis of HPAI A(H5N1) virus infection.

Commercially available influenza molecular assays available in clinical settings are not specific and do not differentiate between seasonal, avian, or swine influenza A viruses.

All positive tests on human clinical specimens for influenza A(H5) virus should be confirmed at a WHO H5 reference laboratory; the WHO also accepts positive A(H5) results from a limited number of WHO-designated national laboratories. Positive laboratory results for human infection with avian influenza A viruses, including HPAI A(H5N1) virus, should be reported to the WHO under the International Health Regulations.[126]

Government public health organisations have many useful online resources to assist clinicians to determine whether a particular patient should have clinical specimens tested for HPAI A(H5N1) virus, and they have health officers available to consult and assist clinicians in the evaluation, testing, and case management of suspected or confirmed human HPAI A(H5N1) virus infection.

Starting empirical antiviral treatment

The CDC recommends starting empirical antiviral treatment immediately for patients with suspected HPAI A(H5N1) virus infection. Antiviral treatment should not be delayed by diagnostic specimen collection or pending laboratory testing results.[112]

However, the WHO recommends starting antiviral treatment prior to receiving test results only if results will be delayed for more than 24 hours (antiviral treatment can be stopped if the test is negative).[123]

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History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include close contact with infected birds and environmental exposure to highly pathogenic avian influenza (HPAI) H5N1 virus.

cough (common)

- Can be dry or productive. Blood-tinged sputum has been described but is not common.

influenza-like illness (common)

- Some non-specific symptoms consistent with influenza-like illness have been reported (including rhinorrhoea, headache, sore throat, myalgia, and fatigue).

conjunctivitis (common)

- Non-specific symptoms consistent with influenza-like illness, including conjunctivitis, have been reported.
- Conjunctivitis is part of the current US case definition, and has been the only symptom in some of the cases linked to the dairy cattle outbreak in the US in 2024-2025.[45][44]
- There is limited evidence describing the clinical characteristics of patients with conjunctivitis caused by influenza A(H5).[127]

dyspnoea (common)

- Ranges from mild to severe.

fever (common)

- Usually temperature >38°C (100.4°F) occurs early in the course of illness and often persists, especially with severe illness.

rales, rhonchi (common)

- Auscultatory finding described in patients with highly pathogenic avian influenza (HPAI) A(H5N1) virus infection.

wheeze (common)

- Auscultatory finding described in patients with highly pathogenic avian influenza (HPAI) A(H5N1) virus infection.

decreased breath sounds (common)

- Auscultatory finding described in patients with highly pathogenic avian influenza (HPAI) A(H5N1) virus infection.

tachypnoea (common)

- Usually develops within 5 days of illness onset in patients with severe disease.

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Other diagnostic factors

abdominal pain, vomiting, diarrhoea (uncommon)

- Several non-specific primary gastrointestinal symptoms have been reported in children and adults with highly pathogenic avian influenza (HPAI) A(H5N1) virus infection.

altered mental status (uncommon)

- Non-specific neurological symptoms have been reported.

seizures (uncommon)

- Non-specific neurological symptoms have been reported.

Risk factors

Strong

close contact with infected birds or poultry

- Direct contact (touching) or close (within ≤1 metre [≤3 feet]) exposure with sick or dead poultry or other birds suspected or confirmed to have highly pathogenic avian influenza (HPAI) A(H5N1) virus infection is a risk factor for infection.[26] [75] [76] [77]
- Most people with HPAI A(H5N1) virus infection had direct or close unprotected exposure with infected sick or dead poultry before illness onset, but exposure appears to rarely result in HPAI A(H5N1) virus infection. Every year, many people are exposed to HPAI A(H5N1) virus but only a very small proportion become infected.

close contact with infected animals or mammals

- Animal species other than birds can be infected by influenza A viruses, including pigs, cows, wild terrestrial and marine mammals, horses, dogs, cats, and bats.[74]
- Transmission from animals or mammals to humans may be possible, but it is thought to be rare. The first instance of likely mammal-to-human transmission was reported in Texas, US, in April 2024.[3] The person developed conjunctivitis as their only symptom after exposure to dairy cattle presumed to be infected with highly pathogenic avian influenza (HPAI) A(H5N1) virus.[43][44] Other cases of transmission from dairy cattle have been reported in the US since then.

recent travel to a country with H5N1 virus outbreaks

- A recent history of travel to a country with outbreaks of highly pathogenic avian influenza (HPAI) A(H5N1) virus in birds (or other animals) should prompt consideration of HPAI A(H5N1) virus infection in the differential diagnosis of a patient presenting with fever and respiratory symptoms, especially if there is a history of exposure to sick or dead poultry or wild birds, or visiting live poultry markets. For example, a traveller who had returned to Canada after visiting China presented with fever, pleuritic chest pain, and abdominal pain, and progressed to lower respiratory tract disease with meningoencephalitis and died of HPAI H5N1 virus infection.[29]

environmental exposure to H5N1 virus

- Direct contact (touching) with surfaces contaminated with poultry faeces and visiting a live poultry market in highly pathogenic avian influenza (HPAI) A(H5N1) virus-endemic countries are risk factors for infection.[78] [79] [80] Inhalation of aerosolised material (e.g., faeces) containing infectious virus is

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a likely route of transmission from poultry to humans. Consumption of uncooked poultry or dairy cattle products also may be a potential risk factor.[107]

- Exposure to pond water in regions where HPAI A(H5N1) virus has been widespread among birds has also been suggested as a possible risk factor.[81]

Weak

close contact with infected humans

- Unprotected close contact with a symptomatic human case of highly pathogenic avian influenza (HPAI) A(H5N1) virus infection may be a risk factor. Risk is defined as prolonged direct or close unprotected contact (within 1-2 metres [3-6 feet]) with ill people suspected or confirmed to have HPAI H5N1 virus infection. However, human-to-human transmission remains rare, and there is no evidence of ongoing human-to-human transmission of HPAI H5N1 virus.[83] [84] [85] [86] [87]
- The risk is highest among related family members, usually in carers of an ill, gentically related family member.[85] Although limited, non-sustained human-to-human transmission among genetically related family members has typically occurred in households before a sick patient was hospitalised, and this has also been reported in hospitals.[1] [2]
- Nosocomial transmission of HPAI A(H5N1) virus from a patient to a healthcare worker has been reported.[1] [2] [88] However, serological surveys of healthcare personnel using no or inadequate personal protective equipment while caring for patients with confirmed HPAI A(H5N1) virus infection have demonstrated a very low risk of transmission.[108] [109] [110]

laboratory work with H5N1 virus

- Highly pathogenic avian influenza (HPAI) A(H5N1) virus transmission to laboratory workers using proper techniques and personal protective equipment in appropriate biosafety precautions has not been documented. A small serosurvey of laboratory workers exposed to HPAI A(H5N1) virus with incomplete personal protective equipment use and adherence to biosafety precautions demonstrated no serological evidence of prior HPAI A(H5N1) virus infection.[111]

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Investigations

1st test to order

Test	Result
FBC with differential • Described in most patients in small case series.	**leukopenia, lymphopenia, thrombocytopenia**
LFTs • Described in most patients in small case series.	**elevated aspartate aminotransferase/alanine aminotransferase**
chest x-ray • A chest x-ray alone cannot exclude viral or bacterial pneumonia.	**may be normal; may show infiltrates consistent with pneumonia in severe cases**
pulse oximetry • Indicated in patients with dyspnoea or suspected pneumonia.	**may show hypoxia**
sputum Gram stain • Primary bacterial pneumonia and potential bacterial co-infection should be evaluated. Few co-infections have been reported in highly pathogenic avian influenza (HPAI) A(H5N1) patients, except with ventilator-associated pneumonia.	**visualisation of infecting organisms if bacterial pneumonia or potential bacterial co-infection**
sputum and blood bacterial culture • Primary bacterial pneumonia and potential bacterial co-infection should be evaluated.	**growth of infecting organism if bacterial pneumonia or potential bacterial co-infection**
real-time reverse transcription polymerase chain reaction (rtRT-PCR) • Recommended for diagnosis of highly pathogenic avian influenza (HPAI) A(H5N1) virus infection.[122] [123] If influenza A is positive, then subtyping should be performed for seasonal influenza A(H1) and A(H3) viruses. If influenza A testing is positive but A(H1) and A(H3) are negative, then testing for A(H5) should be performed at a specialised public health laboratory.[124] • Perform testing on people who meet epidemiological criteria and either clinical or public health response criteria.[119] • Testing of asymptomatic people is not routinely recommended, but may be considered as part of public health investigations (e.g., workers with a high risk of exposure to infected animals who do not report wearing the recommended personal protective equipment, close contacts of a confirmed case).[41] • Infection prevention and control precautions are recommended when collecting specimens. Preferred specimens in non-intubated patients are upper respiratory tract specimens (e.g., oropharyngeal swab, nasopharyngeal swab, nasal aspirate or wash). Two swabs may be combined into one vial (e.g., one nasal or nasopharyngeal swab and one oropharyngeal swab). Ideally both a nasopharyngeal swab, and a combined nasal swab and oropharyngeal swab should be collected and tested separately.[122] [126] • Preferred specimens in intubated patients or patients with severe lower respiratory tract illness are lower respiratory tract specimens (e.g., endotracheal aspirate, bronchoalveolar lavage fluid). Multiple	**positive for H5-specific viral RNA**

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Test	Result
respiratory specimens should be collected from different sites on at least two consecutive days for hospitalised patients.[122] [126] • A conjunctival swab (with a nasopharyngeal swab) and/or nasal swab combined with an oropharyngeal swab should be collected if the person has conjunctivitis (with or without respiratory symptoms).[41] [122] • Swabs with a synthetic tip (e.g., Dacron®, polyester) and an aluminum or plastic shaft should be used. Obtain specimens as soon as possible, ideally within 7 days of symptom onset.[122] [126] • Specific A(H5) testing may not be available in some clinical settings. Many regional public health laboratories, most national laboratories, and some private laboratories can perform this test. It takes approximately 4 hours to produce preliminary results, but transport time and testing logistics may delay testing results. • In the context of the current outbreak in the US, as of 16 January 2025, the Centers for Disease Control and Prevention (CDC) recommends routinely testing all patients with suspected influenza and to expedite the subtyping of influenza A-positive specimens from hospitalised patients, particularly those in the intensive care unit. Subtyping should be performed as soon as possible following admission, ideally within 24 hours. The goal of this approach is to prevent delays in identifying infections.[121]	

Other tests to consider

Test	Result
viral culture • Virus culture will not produce timely results for clinical management and must be performed in a biosafety level 3-enhanced laboratory. Viral culture can be performed at WHO H5 reference laboratories and WHO collaborating influenza centres. • Viral culture is important for virological surveillance, antigenic monitoring for vaccine strain selection, and assessment and analyses of viral characteristics such as genetic re-assortment, receptor binding affinity, and antiviral susceptibility. • Clinical specimens testing positive for highly pathogenic avian influenza (HPAI) A(H5N1) viral RNA by RT-PCR should be cultured by a WHO H5 Reference Laboratory or WHO collaborating influenza centre laboratory.[126]	**positive for H5N1 virus**

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Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Coronavirus disease 2019 (COVID-19)	• Important to consider the current COVID-19 epidemiological situation and any recent outbreaks. May give history of COVID-19 exposure. • Signs and symptoms are similar so it may be difficult to differentiate between the conditions clinically.	• Real-time reverse transcription polymerase chain reaction (RT-PCR): positive for SARS-CoV-2 RNA. Rapid antigen tests may also be used. • It is not possible to differentiate COVID-19 from other causes of pneumonia on chest imaging.
Community-acquired pneumonia	• No differentiating signs/ symptoms.	• Diagnostic studies should be considered based on local guidance as well as microbial patterns in a particular community. • Isolation of organisms such as *Streptococcus pneumoniae* , *Staphylococcus aureus* or group A *Streptococcus* from sputum and blood culture, and response to typical therapy confirms diagnosis. • Chest x-ray findings for typical pneumonia are consistent with consolidation. • Positive highly pathogenic avian influenza (HPAI) A(H5N1) virus-specific tests do not exclude co-infection, although most HPAI A(H5N1) cases have not had community-acquired bacterial co-infection identified except in intubated patients with ventilator-associated pneumonia. Seasonal influenza virus infection with bacterial co-infection is more common.
Atypical pneumonia	• No differentiating signs/ symptoms.	• Confirmation of infection by atypical pathogens (including atypical pneumonia pathogens such as *Mycoplasma pneumoniae* and *Legionella pneumophila*) by sputum culture, blood culture, or other specific tests.

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Condition	Differentiating signs / symptoms	Differentiating tests
		• A diagnosis of atypical pneumonia does not rule out highly pathogenic avian influenza (HPAI) A(H5N1) virus infection, but co-infection with HPAI A(H5N1) virus and atypical pneumonia pathogens has not been reported.
Seasonal influenza virus infection	• More common cause of severe morbidity in young children, older adults, and people with underlying chronic medical conditions (e.g., cardiopulmonary disease, immunosuppressed). • More likely to be a self-limited condition with milder symptoms among previously healthy people. Severe lower respiratory tract disease can occur among previously healthy children, young adults, pregnant women, and people with class III obesity.	• Diagnostic tests confirming infection by another respiratory virus does not rule out highly pathogenic avian influenza (HPAI) A(H5N1) virus infection, but co-infection with HPAI A(H5N1) virus and other respiratory viruses is uncommon.
Avian influenza A (H7N9) virus infection	• Epidemic has been geographically focused in China. • Most patients require hospitalisation for management of pneumonia and/or respiratory failure and often present soon after the onset of symptoms, in contrast to the late presentation often seen with A(H5N1) virus infection. • No differentiating signs/ symptoms.	• Reverse transcription-polymerase chain reaction (RT-PCR) is positive for H7-specific viral RNA.
Endemic respiratory infections	• Respiratory infections due to pathogens endemic to the region where infection occurred should be considered (e.g., endemic mycotic infection, melioidosis in parts of Southeast Asia). • No differentiating signs/ symptoms.	• Diagnostic tests confirming infection by an atypical pneumonia do not rule out highly pathogenic avian influenza (HPAI) A(H5N1) virus infection, but co-infection with HPAI A(H5N1) and endemic respiratory infections has not been reported.

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Condition	Differentiating signs / symptoms	Differentiating tests
Respiratory syncytial virus infection	• Most common cause of lower respiratory tract infection in children aged less than 1 year. • Significant and often unrecognised cause of lower respiratory tract infection in both older and immunosuppressed patients. • Gives rise to upper and lower respiratory symptoms that peak in 3-5 days and resolve within 7-10 days.	• Rapid assays using antigen capture technology are the mainstay of the diagnostic algorithm, as the identification by culture can take from 4 days to 2 weeks. • Diagnostic tests confirming infection by another respiratory virus does not rule out highly pathogenic avian influenza (HPAI) A(H5N1) virus infection, but co-infection with HPAI A(H5N1) virus and other respiratory viruses is uncommon.
Severe acute respiratory syndrome (SARS)	• No differentiating signs/ symptoms. • Both can have rapid onset of fever, cough, and pneumonia. • The absence of confirmed cases since 2004 makes the diagnosis of SARS outside of re-emergence of the virus very unlikely.	• The diagnosis of SARS requires high clinical suspicion and should be informed by global surveillance for infections by SARS-associated coronavirus (SARS-CoV). Tests for influenza virus are negative. Real-time reverse transcription polymerase chain reaction (RT-PCR) is positive for SARS-CoV.
Middle East respiratory syndrome (MERS)	• Most cases are epidemiologically linked to the Arabian Peninsula. Many cases are associated with nosocomial transmission. Zoonotic transmission from dromedary camels and limited non-sustained human-to-human transmission have occurred. • No differentiating signs/ symptoms. Common symptoms are acute, serious respiratory illness with fever, cough, shortness of breath, and breathing difficulties. Most patients have pneumonia, respiratory failure, and acute respiratory distress syndrome. Many also have gastro-intestinal symptoms (including diarrhoea), while others have kidney failure.	• Real-time reverse transcription polymerase chain reaction (RT-PCR) is positive for MERS coronavirus. The test can be found at some international public health laboratories, particularly in regions affected by MERS.

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Criteria

Centers for Disease Control and Prevention (CDC): case definitions for investigations of human infection with avian influenza A viruses in the United States[119]

Perform testing on people who meet epidemiological criteria and either clinical or public health response criteria.

Confirmed case:

- Avian influenza A virus infection in a person that is confirmed by the CDC's Influenza Division Laboratory or a CDC-designated laboratory using methods mutually agreed upon by the CDC and the Council of State and Territorial Epidemiologists (CSTE).

Probable case:

- A person meeting criteria for avian influenza A virus infection (below) and for whom confirmatory laboratory test results do not provide a sufficient level of detail to confirm highly pathogenic avian influenza (HPAI) A(H5) virus infection.

Suspected case (case under investigation):

- A person meeting criteria for avian influenza A virus infection (below) and for whom confirmatory laboratory test results are not known or pending.

Epidemiological criteria:

- People with recent exposure (within 10 days) to avian influenza A viruses through one of the following:
  - Exposure to A(H5), A(H7), or A(H9) virus-infected birds
  - Exposure to an infected person
  - Laboratory exposure.

Clinical criteria:

- People with signs and symptoms consistent with acute or lower respiratory tract infection or conjunctivitis, or complications of acute respiratory illness without an identified cause.

Public health response criteria:

- Asymptomatic people for whom public health authorities, in consultation with the CDC, determine that testing is needed in order to assess the clinical spectrum of infection with avian influenza A virus as part of public health investigations.

[CDC: case definitions for investigations of human infection with avian influenza A viruses in the United States] (https://www.cdc.gov/bird-flu/hcp/case-definition/index.html)

World Health Organization (WHO): case definitions for human infections with influenza A (H5N1) virus[120]

Person under investigation:

- A person whom public health authorities have decided to investigate for possible influenza A(H5N1) virus infection.

Suspected H5N1 case:

- A person presenting with unexplained acute lower respiratory illness with fever >38ºC (>100.4ºF) and cough, shortness of breath, or difficulty breathing AND one or more of the following exposures in the 7 days prior to symptom onset:
    - Close contact (within 1 metre [3 feet]) with a person (e.g., caring for, speaking with, or touching) who is a suspected, probable, or confirmed H5N1 case
    - Exposure (e.g., handling, slaughtering, defeathering, butchering, preparation for consumption) to poultry or wild birds or their remains or to environments contaminated by their faeces in an area where influenza A(H5N1) virus infections in animals or humans have been suspected or confirmed in the last month
    - Consumption of raw or undercooked poultry products in an area where influenza A(H5N1) virus infections in animals or humans have been suspected or confirmed in the last month
    - Close contact with a confirmed influenza A(H5N1) virus-infected animal other than poultry or wild birds (e.g., cat or pig)
    - Handling samples (animal or human) suspected of containing H5N1 virus in a laboratory or other setting.

Probable H5N1 case (notify WHO):

- Probable definition 1: a person meeting the criteria for a suspected case AND one of the following additional criteria:
    - Infiltrates or evidence of an acute pneumonia on chest radiograph plus evidence of respiratory failure (hypoxaemia, severe tachypnoea); or
    - Positive laboratory confirmation of an influenza A infection but insufficient laboratory evidence for influenza A(H5N1) virus infection.
- Probable definition 2: a person dying of an unexplained acute respiratory illness who is considered to be epidemiologically linked by time, place, and exposure to a probable or confirmed H5N1 case.

Confirmed H5N1 case (notify WHO):

- A person meeting the criteria for a suspected or probable case AND one of the following positive results conducted in a national, regional, or international influenza laboratory whose H5N1 test results are accepted by WHO as confirmatory:
    - Isolation of an influenza A(H5N1) virus
    - Positive influenza A(H5) PCR results from tests using two different PCR targets (e.g., primers specific for influenza A and H5 haemagglutinin)
    - A fourfold or greater rise in neutralisation antibody titre for influenza A(H5N1) virus based on testing of an acute serum specimen (collected 7 days or less after symptom onset) and a convalescent serum specimen. The convalescent neutralising antibody titre must also be 1:80 or higher
    - A microneutralisation antibody titre for influenza A(H5N1) virus of 1:80 or greater in a single serum specimen collected at day 14 or later after symptom onset and a positive result using a different serological assay: for example, a horse red blood cell haemagglutination inhibition titre of 1:160 or greater or an H5-specific western blot positive result.

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UK Health Security Agency (UKHSA): case definition for possible cases of avian influenza with potential to cause severe human disease[128]

Possible cases must fulfil the clinical AND exposure criteria below.

Clinical criteria:

- Fever >38ºC (>100.4ºF); or
- Acute respiratory symptoms (e.g., cough, hoarseness, nasal discharge or congestion, shortness of breath, sore throat, wheezing, or sneezing); or
- Other severe or life-threatening illness that is suggestive of an infectious process.

Exposure criteria:

- Close contact (within 1 metre [3 feet]) with live, dying, or dead domestic poultry or wild birds (including live bird markets), in an area of the world affected by avian influenza, or with any confirmed infected animal, in the 10 days before the onset of symptoms; or
- Close contact with a confirmed human case of avian influenza, or human case(s) of severe unexplained respiratory illness from avian influenza-affected areas, or human case(s) of unexplained illness resulting in death from avian influenza-infected areas, in the 10 days before the onset of symptoms.
    - Close contact includes handling laboratory specimens from cases without appropriate precautions, within 1 metre distance, directly providing care, touching a case, or within close vicinity of an aerosol-generating procedure, from 1 day prior to symptom onset and for duration of symptoms or positive virological detection.

Screening

Asymptomatic people

- There is currently no role for routine screening of the asymptomatic population outside of epidemiological research studies. However, testing of asymptomatic people may be considered as part of ongoing public health investigations when feasible (e.g., workers with a high risk of exposure to infected animals who do not report wearing the recommended personal protective equipment, close contacts of a confirmed case). Any person who develops signs or symptoms of acute respiratory illness or conjunctivitis after a high risk of exposure to highly pathogenic avian influenza (HPAI) A(H5N1) virus should be isolated and tested.[41]

Symptom monitoring in people with exposures

- All people who have been exposed to highly pathogenic avian influenza (HPAI) A(H5N1) virus-infected birds, cattle, or other animals should be monitored for symptoms consistent with infection starting on the first day of exposure and continuing until 10 days after the last exposure.[129]
- Exposures include, but are not limited to, contact with:
    - Infected birds, livestock, or other animals
    - Carcasses of birds, livestock, or other animals
    - Faeces or litter
    - Raw cow milk
    - Surfaces and water that may be contaminated with animal excretions.
- There are two types of monitoring recommended.

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- Active monitoring: local or state health departments contact exposed people directly about the development of signs and symptoms of infection on a specific schedule (this can be done using an application, email, or phone calls). This type of monitoring is recommended for people who have had unprotected exposures (e.g., dairy farm workers).
- Self-monitoring: exposed people are provided with information about signs and symptoms of infection and who to contact if they develop these symptoms. This type of monitoring is recommended for people who used the recommended personal protective equipment (e.g., workers who are culling poultry).

- If an exposed person becomes ill during this period, antiviral treatment should be started and the person should be treated as a possible case.

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Approach

There is no standardised approach for the clinical management of humans with highly pathogenic avian influenza (HPAI) A(H5N1) virus infection. Optimal supportive care and prompt initiation of antiviral therapy are considered the mainstays of treatment.

Patients with severe illness due to HPAI A(H5N1) virus infection can present with clinical findings similar to those of pneumonia caused by other infectious aetiologies. Given that human infection with HPAI A(H5N1) virus is rare (even among people with high-risk exposures), diagnostic evaluation and therapy should also consider alternative aetiologies.

Avian influenza A virus infection of humans is a notifiable disease. Local or national public health departments should be contacted for guidance. Many local health departments can directly assist clinicians to determine which people need testing, to facilitate testing, and to assist with case management.

Antiviral post-exposure prophylaxis for close contacts

The decision to start antiviral post-exposure prophylaxis should be considered on a case-by-case basis and guided by the nature of HPAI A(H5N1) virus exposure and subsequent risk of developing infection. Local or national public health departments should be contacted for guidance.

The US Centers for Disease Control and Prevention (CDC) recommends post-exposure prophylaxis for asymptomatic close contacts of human cases, according to their risk of exposure (see below for categories).[130]

- A close contact is defined as a person with close contact (within 2 meters [6 feet]) within a room or care area or other enclosed space, who had unprotected (i.e., without use of recommended personal protective equipment) exposure to a person who is a symptomatic confirmed or probable human case of novel influenza A virus infection for a prolonged period of time, or who had direct contact with infectious secretions while the case was likely to be infectious (beginning 1 day prior to illness onset and continuing until resolution of illness).

Highest-risk exposure groups

- Includes household members or other persons, including healthcare personnel, with unprotected, prolonged close contact to a symptomatic confirmed or probable case in a room or other enclosed space, including a healthcare setting.
- These people have a recognised risk of transmission, and post-exposure prophylaxis is recommended.

Moderate-risk exposure groups

- Includes people with unprotected, prolonged close contact to a symptomatic confirmed or probable case outside of a room or other enclosed space. It also includes laboratory personnel with unprotected direct or close exposure to a novel influenza A virus.
- These people have a variable risk of transmission, and post-exposure prophylaxis may be considered on a case-by-case basis.

Low-risk exposure groups

- Includes people and healthcare personnel wearing all recommended personal protective equipment, with prolonged close contact to a symptomatic confirmed, probable, or suspected case in a room or other enclosed space, including healthcare settings. It also includes people who are

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not household members (e.g., work, school, or social contacts) with a short duration of unprotected close contact to a symptomatic confirmed or probable case in a nonhospital setting outside of the home.
- Transmission is unlikely in these people, and post-exposure prophylaxis is not routinely recommended.

Post-exposure prophylaxis can be considered for any person who meets epidemiological exposure criteria. The decision to start post-exposure prophylaxis in low- or moderate-risk groups should be based on clinical judgement, consideration of the type of exposure, and whether the contact is at high risk for complications.[130]

The CDC does not routinely recommend post-exposure prophylaxis for people handling sick or potentially infected birds or other sick or dead animals or decontaminating infected environments who properly use (including removing) the recommended personal protective equipment, provided there are no breaches. However, post-exposure prophylaxis and influenza A(H5) testing can be offered to asymptomatic people who experience a high risk of exposure to animals confirmed or highly suspected to be infected with HPAI A(H5N1) virus without using the recommended personal protective equipment (or if there are breaches in or failures of the recommended personal protective equipment).[41]

The CDC recommends oral oseltamivir for post-exposure prophylaxis. It is recommended for people of any age, including newborn infants, and pregnant women. Administration should begin as soon as possible, ideally within 48 hours after first exposure.[130]

- Treatment should continue for 5 or 10 days. If exposure was time-limited and not ongoing, post-exposure prophylaxis is recommended for 5 days from the last known exposure. If exposure is likely to be ongoing (e.g., household setting), 10 days is recommended.
- The CDC recommends that post-exposure prophylaxis should be given twice daily (i.e., the treatment dosing frequency) rather than once daily (i.e., the typical seasonal influenza antiviral post-exposure prophylaxis dose) because of the potential that HPAI A(H5N1) virus infection may have already occurred. However, the dose may vary depending on location, and local guidelines should be consulted.

Contacts of symptomatic confirmed or probable cases should be monitored closely for signs and symptoms of illness for up to 10 days following the date of last exposure.[130]

- This includes daily assessment for acute respiratory symptoms and temperature measurement.
- Close contacts of suspected cases may also be monitored until test results are available, if resources are available to do this.

If the person develops a compatible illness during this time, the person should be referred for prompt medical evaluation and testing, and treated as a suspected case (including isolation and starting antiviral post-exposure prophylaxis if not already on it).[130]

- If a close contact becomes symptomatic or has worsening of symptoms during or after use of post-exposure prophylaxis, appropriate infection prevention and control measures should be instituted and respiratory specimens collected for testing as soon as possible.
- If a close contact tests positive and has been taking oseltamivir post-exposure prophylaxis for ≥3 days before becoming symptomatic, oseltamivir should be stopped and inhaled zanamivir or oral baloxavir initiated, as some novel influenza A viruses may rapidly become oseltamivir-resistant.

Post-exposure prophylaxis may also be considered for people with recent close exposure (within approximately 2 meters [6 feet]) to A(H5) virus-infected animals.

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- An exposure may include animals or animal parts, food products, contaminated surfaces, or environments (e.g., farms).
- The decision to initiate post-exposure prophylaxis in these people should be based on clinical judgement, with consideration given to the type (e.g., without use or personal protective equipment) and duration of exposure, time since exposure, known infection status of bird(s) or other animals, and whether the exposed person is at higher risk for complications.

The World Health Organization (WHO) conditionally recommends using oseltamivir for asymptomatic people exposed to zoonotic influenza viruses associated with high mortality in humans or with an unknown risk of causing severe disease in the prior 2 days (based on low-quality evidence).[123] The WHO also conditionally recommends zanamivir, baloxavir, or laninamivir as other options, but the CDC does not currently recommend these agents.[123] [130]

Infection prevention and control

Patients with suspected, probable, or confirmed HPAI A(H5N1) virus infection should be isolated and local infection control recommendations should be followed. If an airborne infection isolation room (e.g., with negative pressure and HEPA filtration) is not available, the patient should be isolated in a private room.[125]

Given the potential infectiousness and virulence of HPAI A(H5N1) virus, enhanced infection control precautions are recommended, including airborne and contact precautions (with the use of eye protection), in addition to standard precautions.[125]

There may be slight infection control recommendation differences between national public health organisations; therefore, if HPAI A(H5N1) virus infection is considered in a patient, it is recommended that clinicians consult national infection control guidelines.

Patients may be treated as outpatients or in hospital depending on disease severity and clinical presentation.

Antiviral treatment

Antiviral treatment is recommended as soon as possible for outpatients and hospitalised patients who are suspected, probable, or confirmed cases of HPAI A(H5N1) virus infection. Antiviral treatment should not be delayed by diagnostic specimen collection or laboratory testing.[112] Available evidence suggests that early diagnosis is associated with improved clinical outcomes.[131] Antiviral therapy can be discontinued in patients who are not hospitalised and who test negative for HPAI A(H5N1) virus infection (or other influenza viruses).

People who are asymptomatic but test positive for influenza A (H5) infection after exposure to infected animals (and who report not wearing or a breach in the recommended personal protective equipment) should be offered antiviral treatment, unless they are already receiving post-exposure prophylaxis, and actively monitored for the development of signs and symptoms for 10 days after the last known exposure.[41]

Neuraminidase inhibitors are widely available and active against all currently circulating zoonotic influenza A viruses. There are four commercially available neuraminidase inhibitors (depending on location), and they vary by route of administration, dosing and duration of treatment, contraindications, and adverse effects:

- Oseltamivir

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- Zanamivir
- Peramivir
- Laninamivir.

Oral or enterically administered oseltamivir is the most widely studied and available, and it is recommended first-line in all patients with suspected, probable, or confirmed HPAI A(H5N1) virus infection.

- The WHO conditionally recommends oseltamivir for people with suspected or confirmed severe influenza virus infection, based on very low-quality evidence. This includes patients with novel influenza A virus infection associated with high mortality, or with an unknown risk of severe disease, even if they do not otherwise fulfil criteria for severe infection. Treatment should be administered as early as possible and within 2 days of onset of symptoms.[123]
- The CDC recommends oseltamivir treatment for all hospitalised patients regardless of time since onset of illness, and all symptomatic outpatients. Oseltamivir is recommended for all patients with conjunctivitis or acute respiratory illness due to the potential for progression to severe disease, but clinical judgement may be used to decide whether to initiate treatment in untreated patients with uncomplicated disease in whom symptoms are nearly resolved and there is an absence of fever.[112]
- Oseltamivir is recommended for people of any age, including newborn infants. It is the preferred option in pregnant women.[132]
- No completed randomised, placebo-controlled trials exist for oseltamivir in hospitalised influenza patients. However, observational uncontrolled studies have suggested a survival benefit to early oseltamivir therapy in these patients, especially when antivirals are started early in the clinical course, or before the onset of acute respiratory distress syndrome (ARDS).[30] [32] [82] [105] [133] [134]

Inhaled zanamivir may be an alternative option in non-intubated patients who do not have underlying airway disease (e.g., COPD, asthma).

- The WHO suggests not administering inhaled zanamivir to people with suspected or confirmed severe influenza virus infection, based on very low-quality evidence. The recommendation is based on the very low certainty of benefit on critical outcomes of mortality, hospitalisation, or intensive care unit admission, rather than on evidence of harm. The WHO acknowledges that this recommendation does not apply to situations where the causative strain is known or at high risk of being resistant to oseltamivir.[123]
- The CDC does not currently recommend inhaled zanamivir in outpatients or hospitalised patients due to a lack of data in these patients.[112]

Other neuraminidase inhibitors may be available in certain jurisdictions.

- The WHO suggests not administering intravenous peramivir or inhaled laninamivir to patients with suspected or confirmed severe influenza virus infection, based on very low-quality evidence.[123]
- The CDC recommends intravenous peramivir as an alternative to oseltamivir only in hospitalised patients who cannot tolerate or absorb oral or enterically administered oseltamivir because of suspected or known gastric stasis, malabsorption, or gastrointestinal bleeding. If used, a minimum of 5 days of treatment is recommended.[112]
- Intravenous zanamivir may be available in some countries for hospitalised patients with severe or critical illness, especially if oseltamivir-resistant virus infection is suspected.
- Combination therapy with more than one neuraminidase inhibitor is not recommended because of the potential for antagonism.[135]

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Oral baloxavir is a newer antiviral agent with a different mechanism of action to neuraminidase inhibitors (selective inhibitor of influenza cap-dependent endonuclease).

- The WHO recommends considering baloxavir as an alternative to oseltamivir when oseltamivir is not available for patients with suspected or confirmed severe influenza virus infection. However, this recommendation is based on indirect evidence from nonsevere seasonal influenza and is of very low certainty.[123]
- The CDC does not currently recommend baloxavir monotherapy in outpatients or hospitalised patients due to a lack of data in these patients.[112]

Recommendations for antiviral therapy are based on observational studies and indirect evidence from studies of antiviral treatment of seasonal influenza. There are no data from randomised trials in patients with novel influenza A virus infections.[112]

Children may experience unique cutaneous, behavioural, and neurological adverse events with neuraminidase inhibitors; therefore, extra caution should be used in this population.

Combination antiviral treatment with oseltamivir plus baloxavir (drugs from two different classes of medications) may be considered in immunocompromised patients and hospitalised patients due to concerns about resistance. Seek guidance from your local public health authority for antiviral treatment in patients who are immunocompromised.[112]

Most avian influenza viruses, including HPAI A(H5N1), are susceptible to neuraminidase inhibitors and baloxavir. M2 inhibitors (amantadine or rimantadine) are not recommended for the treatment of novel influenza A virus infections, including HPAI A(H5N1) virus infection, due to the high prevalence of resistance to this class of antivirals in viruses circulating among wild birds and poultry.[112]

Supportive care

Most patients admitted to the hospital with HPAI A(H5N1) virus infection have rapidly progressive viral pneumonia leading to ARDS and multi-organ failure. Patients with early recognition of disease and initiation of antiviral and supportive therapies may have improved clinical outcomes.[136] [137]

While there is no standardised approach for the clinical management of humans with HPAI A(H5N1) virus infection, the WHO recommends that supportive care follow published evidence-based guidelines for the clinical syndrome present (e.g., septic shock, respiratory failure, and ARDS).[138]

The WHO suggests not administering corticosteroids to patients with suspected or confirmed severe influenza virus infection, based on very low-quality evidence. However, there is a possibility of important benefit, especially where the clinical diagnosis overlaps with acute respiratory distress syndrome (ARDS). Corticosteroids possibly decrease mortality in the late phase of ARDS, but there was no direct evidence for patients with ARDS caused by influenza virus. The WHO also suggests not administering other adjunctive immunomodulatory therapies (macrolides, non-steroidal anti-inflammatory drugs [NSAIDs], mTOR inhibitors, or passive immune therapy).[123]

Antiviral resistance

Where the clinical course remains severe or progressive, investigations for antiviral resistance should be performed, if possible. Emergence of oseltamivir and peramivir resistance during treatment of patients with HPAI A(H5N1) virus infection has been reported.[112][139] [140] Additionally, HPAI A(H5N1) virus infection with de novo reduced susceptibility to oseltamivir (before oseltamivir exposure) has been

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reported.[141] Contacting local or national public health departments for information about antiviral resistance and antiviral treatment guidance is highly recommended.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial		(summary)
close contact of confirmed or probable case		
	1st	**observation ± post-exposure prophylaxis**

Acute		(summary)
suspected or probable or confirmed infection		
	1st	**infection prevention and control**
	plus	**antiviral treatment**
	adjunct	**supportive care**

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Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial

close contact of confirmed or probable case

1st **observation ± post-exposure prophylaxis**

Primary options

» oseltamivir: children ≥3 months of age: 3 mg/kg orally twice daily for 5-10 days; children ≥1 year of age and ≤15 kg body weight: 30 mg orally twice daily for 5-10 days; children ≥1 year of age and >15-23 kg body weight: 45 mg orally twice daily for 5-10 days; children ≥1 year of age and >23-40 kg body weight: 60 mg orally twice daily for 5-10 days; children ≥1 year of age and >40 kg body weight and adults: 75 mg orally twice daily for 5-10 days
The CDC recommends twice-daily dosing instead of the typical once-daily post-exposure prophylaxis regimen.[130] Dose may vary depending on location, and local guidelines should be consulted.

Not recommended for post-exposure prophylaxis in children <3 months of age unless the situation is judged to be critical.[132]

» Contacts of symptomatic confirmed or probable cases should be monitored closely for signs of illness for up to 10 days following the date of last exposure. This includes daily assessment for acute respiratory symptoms and temperature measurement. If the person develops a compatible illness during this time, the person should be referred for prompt medical evaluation and testing, and treated as a suspected case (including isolation and starting antiviral post-exposure prophylaxis if not already on it).[130]

» Post-exposure prophylaxis can be considered for any person who meets epidemiological exposure criteria. The decision to start antiviral post-exposure prophylaxis should be considered on a case-by-case basis and guided by assessment of highly pathogenic avian influenza (HPAI) A(H5N1) virus exposure and subsequent risk of developing infection. Local or national public health departments should be contacted for guidance.

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Initial

» The US Centers for Disease Control and Prevention (CDC) recommends post-exposure prophylaxis in highest-risk exposure groups. It may be considered in moderate-risk exposure groups, and is not routinely recommended in low-risk exposure groups. The decision to start post-exposure prophylaxis in low or moderate risk groups should be based on clinical judgement, consideration of the type of exposure, and whether the contact is at high risk for complications.[130]

» Post-exposure prophylaxis may also be considered for people with recent close exposure (within approximately 2 meters [6 feet]) to A(H5) virus-infected animals. The decision to initiate post-exposure prophylaxis in these people should be based on clinical judgement, with consideration given to the type (e.g., without use or personal protective equipment) and duration of exposure, time since exposure, known infection status of bird(s), and whether the exposed person is at higher risk for complications.[142]

» The CDC does not routinely recommend post-exposure prophylaxis for people handling sick or potentially infected birds or other sick or dead animals or decontaminating infected environments who properly use (including removing) the recommended personal protective equipment, provided there are no breaches. However, post-exposure prophylaxis and influenza A(H5) testing can be offered to asymptomatic people who experience a high risk of exposure to animals confirmed or highly suspected to be infected with HPAI A(H5N1) virus without using the recommended personal protective equipment (or if there are breaches in or failures of the recommended personal protective equipment).[41]

» The CDC recommends oral oseltamivir for post-exposure prophylaxis. Administration should begin as soon as possible, ideally within 48 hours after first exposure, and continue for 5 or 10 days. If exposure was time-limited and not ongoing, post-exposure prophylaxis is recommended for 5 days from the last known exposure. If exposure is likely to be ongoing (e.g., household setting), 10 days is recommended.[130]

» Oseltamivir is recommended for people of any age, including newborn infants, and pregnant women.[130] [132]

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Initial

» The CDC recommends that post-exposure prophylaxis should be given twice daily (i.e., the treatment dosing frequency) rather than once daily (i.e., the typical seasonal influenza antiviral post-exposure prophylaxis dose) because of the potential that HPAI A(H5N1) virus infection may have already occurred. However, the dose may vary depending on location, and local guidelines should be consulted.

» The World Health Organization (WHO) conditionally recommends using oseltamivir for asymptomatic people exposed to zoonotic influenza viruses associated with high mortality in humans or with an unknown risk of causing severe disease in the prior 2 days (based on low-quality evidence).[123] The WHO also conditionally recommends zanamivir, baloxavir, or laninamivir as other options, but the CDC does not currently recommend these agents.[123] [130]

» Children may experience unique cutaneous, behavioural, and neurological adverse events with neuraminidase inhibitors; therefore, extra caution should be used in this population.

» Recommended doses are based on guidelines from the CDC.[132]

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Acute

suspected or probable or confirmed infection

1st **infection prevention and control**

» Patients with suspected, probable, or confirmed highly pathogenic avian influenza (HPAI) A(H5N1) virus infection should be isolated and local infection control recommendations should be followed. Given the potential infectiousness and virulence of HPAI A(H5N1) virus, enhanced infection control precautions are recommended, including airborne and contact precautions (with the use of eye protection), in addition to standard precautions.[125]

» There may be slight infection control recommendation differences between national public health organisations; therefore, if HPAI A(H5N1) virus infection is considered in a patient, it is recommended that clinicians consult national infection control guidelines.

» Patients may be treated as outpatients or in hospital depending on disease severity and clinical presentation.

plus **antiviral treatment**

Treatment recommended for ALL patients in selected patient group

Primary options

» oseltamivir: children <14 days of age: consult specialist for guidance on dose; children 14 days to 1 year of age: 3 mg/kg orally twice daily for 5 days; children ≥1 year of age and ≤15 kg body weight: 30 mg orally twice daily for 5 days; children ≥1 year of age and >15-23 kg body weight: 45 mg orally twice daily for 5 days; children ≥1 year of age and >23-40 kg body weight: 60 mg orally twice daily for 5 days; children ≥1 year of age and >40 kg body weight and adults: 75 mg orally twice daily for 5 days

Secondary options

» peramivir: children and adults: consult specialist for guidance on dose

OR

» baloxavir marboxil: children and adults: consult specialist for guidance on dose

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Acute

» Antiviral treatment is recommended as soon as possible for outpatients and hospitalised patients who are suspected, probable, or confirmed cases of highly pathogenic avian influenza (HPAI) A(H5N1) virus infection. Antiviral treatment should not be delayed by diagnostic specimen collection or laboratory testing.[112] Antiviral therapy can be discontinued in patients who are not hospitalised and who test negative for HPAI A(H5N1) virus infection (or other influenza viruses).

» People who are asymptomatic but test positive for influenza A (H5) infection after exposure to infected animals (and who report not wearing or a breach in the recommended personal protective equipment) should be offered antiviral treatment, unless they are already receiving post-exposure prophylaxis, and actively monitored for the development of signs and symptoms for 10 days after the last known exposure.[41]

» Oral or enterically administered oseltamivir is the most widely studied and available antiviral agent for the treatment of HPAI A(H5N1) virus infection. It is recommended for people of any age, including newborn infants, and is the preferred option in pregnant women.[132]

» The World Health Organization (WHO) conditionally recommends oseltamivir for people with suspected or confirmed severe influenza virus infection, based on very low-quality evidence. This includes patients with novel influenza A virus infection associated with high mortality, or with an unknown risk of severe disease, even if they do not otherwise fulfill criteria for severe infection. Treatment should be administered as early as possible and within 2 days of onset of symptoms.[123]

» The US Centers for Disease Control and Prevention (CDC) recommends oseltamivir for all hospitalised patients regardless of time since onset of illness, and all symptomatic outpatients. Oseltamivir is recommended for all patients with conjunctivitis or acute respiratory illness due to the potential for progression to severe disease, but clinical judgement may be used to decide whether to initiate treatment in untreated patients with uncomplicated disease in whom symptoms are nearly resolved and there is an absence of fever.[112]

» Other neuraminidase inhibitors may be available in certain jurisdictions. The CDC recommends intravenous peramivir as an

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Acute

alternative to oseltamivir only in hospitalised patients who cannot tolerate or absorb oral or enterically administered oseltamivir because of suspected or known gastric stasis, malabsorption, or gastrointestinal bleeding. If used, a minimum of 5 days treatment is recommended.[112] However, the WHO suggests not administering intravenous peramivir to patients with suspected or confirmed severe influenza virus infection, based on very low-quality evidence.[123]

» Children may experience unique cutaneous, behavioural, and neurological adverse events with neuraminidase inhibitors; therefore, extra caution should be used in this population.

» The CDC does not currently recommend baloxavir (a selective inhibitor of influenza cap-dependent endonuclease) in outpatients or hospitalised patients due to a lack of data in these patients.[112] However, the WHO recommends considering baloxavir as an alternative to oseltamivir when oseltamivir is not available for patients with suspected or confirmed severe influenza virus infection. However, this recommendation is based on indirect evidence from nonsevere seasonal influenza and is of very low certainty.[123]

» Combination antiviral treatment with oseltamivir plus baloxavir may be considered in immunocompromised patients and hospitalised patients due to concerns about resistance. Seek guidance from your local public health authority for antiviral treatment in patients who are immunocompromised.[112]

» Modified regimens with higher doses and longer duration of treatment (e.g., 10 days) may be considered on a case-by-case basis under specialist guidance (e.g., severely immunocompromised patients, severe or critical disease), but there are no available clinical trial data to inform recommendations.[112] Consult an infectious disease specialist for guidance.

» Oral oseltamivir may be given enterically/nasogastrically. Limited data suggest that oseltamivir given orally or by orogastric/nasogastric tube is well absorbed in critically ill patients, including those in the intensive care unit, or on extracorporeal membrane oxygenation or renal replacement therapy.[112] Oseltamivir has been shown to be adequately absorbed following nasogastric administration to mechanically ventilated adults with severe

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Acute

disease caused by HPAI A(H5N1) virus infection.[143]

» Where the clinical course remains severe or progressive, investigations for antiviral resistance should be performed, if possible. Contacting local or national public health departments for guidance is highly recommended.[112] [139] [140]

» Recommended doses are based on guidelines from the CDC.[132]

adjunct **supportive care**

Treatment recommended for SOME patients in selected patient group

» Most patients admitted to the hospital with highly pathogenic avian influenza (HPAI) A(H5N1) virus infection have had rapidly progressive pneumonia leading to acute respiratory distress syndrome (ARDS) and multi-organ failure. Patients with early recognition of disease and initiation of antiviral and supportive therapies may have improved clinical outcomes.[136] [137]

» While there is no standardised approach for the clinical management of humans with HPAI A(H5N1) virus infection, the World Health Organization (WHO) recommends that supportive care follow published evidence-based guidelines for the clinical syndrome present (e.g., septic shock, respiratory failure, and ARDS).[138]

» The WHO suggests not administering corticosteroids to patients with suspected or confirmed severe influenza virus infection, based on very low-quality evidence. However, there is a possibility of important benefit, especially where the clinical diagnosis overlaps with acute respiratory distress syndrome (ARDS). Corticosteroids possibly decrease mortality in the late phase of ARDS, but there was no direct evidence for patients with ARDS caused by influenza virus.[123]

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Emerging

Convalescent plasma

A 31-year-old male patient with highly pathogenic avian influenza (HPAI) A(H5N1) virus infection was treated in 2006 with convalescent plasma that was obtained from a patient who had recovered from HPAI A(H5N1) illness earlier that year. HPAI A(H5N1) viral load from respiratory specimens decreased after 3 doses of convalescent plasma, with undetectable levels within 32 hours.[144] Two other HPAI A(H5N1) patients who received convalescent plasma from an HPAI A(H5N1) case or an H5N1 vaccine recipient have been reported.[145] Convalescent plasma therapy for patients with seasonal influenza or HPAI A(H5N1) virus infection is experimental and not approved for clinical use. The World Health Organization suggests not administering passive immune therapy to patients with suspected or confirmed influenza virus infection (including zoonotic influenza) with or at risk of severe illness, based on very low-quality evidence.[123]

Primary prevention

The primary means of containing highly pathogenic avian influenza (HPAI) A(H5N1) virus in communities and decreasing the risk to human health is through H5N1 poultry immunisation or prompt culling of poultry with suspected or confirmed HPAI A(H5N1) virus infection and disinfection of the contaminated environment.

The most effective way to prevent HPAI A(H5N1) virus infection in humans is to minimise exposure by avoiding direct or close contact with sick or dead poultry (or other animals) in HPAI A(H5N1) virus-affected countries.

- The World Health Organization (WHO) recommends:[107]
    - Avoiding contact with animals (including wild animals) that are sick or dead from unknown causes
    - Reporting sick or unexpectedly dead animals to local authorities or a veterinarian
    - Following good food safety and personal hygiene practices, particularly hand washing
    - Properly handling and cooking poultry meat, eggs, and other animal products
    - Only slaughtering healthy animals for human consumption
    - Avoiding consuming raw or unpasteurised milk
    - Seeking health care if feeling unwell and reporting any possible exposure to sick animals
    - Wearing appropriate personal protective equipment when in direct or indirect contact with infected (or potentially infected) animals or their environment (e.g., occupational exposure).
- The US Centers for Disease Control and Prevention (CDC) recommends:[112]
    - Avoiding unprotected (i.e., not using eye or respiratory protection) exposures to sick or dead animals including poultry, wild or domesticated birds, and other wild or domesticated animals, as well as animal faeces, litter, or materials contaminated by birds or other animals with suspected or confirmed HPAI A(H5N1) infection.
    - Wearing appropriate personal protective equipment (i.e., safety goggles, disposable gloves, boots or boot covers, approved particulate respirator, disposable fluid-resistant overalls, disposable head/hair cover) when in direct or close contact with sick or dead animals or potentially contaminated materials.
    - Cooking poultry, eggs, and beef to safe internal temperatures to kill bacteria and viruses. Avoiding consuming unpasteurised milk (and milk products) is recommended.
- The CDC offers specific guidance for employers to reduce the risk of infection in people working with or exposed to animals, such as poultry and dairy farmers and workers, and veterinarians and their staff.

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- [CDC: interim guidance for employers to reduce exposure to avian influenza A viruses for people working with animals] (https://www.cdc.gov/bird-flu/prevention/worker-protection-ppe.html)

- For people raising poultry or exotic birds in HPAI A(H5N1) virus-affected countries, efforts should be made to keep such birds away from wild waterfowl or other wild birds and their faeces, and away from water sources that are shared by wild waterfowl. Personal protective equipment should also be worn at all times when working in a potentially infected environment.[113]

Vaccines

- Influenza A(H5N1) vaccines have been found to be safe and immunogenic in people when adjuvant is used.[114] [115] [116]
- Various H5N1 vaccines are licensed around the world, including Europe and the US, for use in children and adults in pandemic situations. The US has a national stockpile that includes H5 vaccines that could be used if the virus begins transmitting easily from person to person.[117]
- Information on the development and availability status of candidate vaccines is available from the WHO. [WHO: zoonotic influenza – candidate vaccine viruses and potency testing reagents] (https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations/zoonotic-influenza-viruses-and-candidate-vaccine-viruses)
- Healthcare workers worldwide are recommended to receive an annual seasonal influenza vaccine to decrease their risk of seasonal influenza and also to reduce the potential for nosocomial transmission of seasonal influenza viruses in the healthcare setting. Preventing seasonal influenza among people exposed to or infected with HPAI A(H5N1) virus may also decrease the theoretical risk of human co-infection with seasonal influenza A viruses and HPAI A(H5N1) virus and of viral genetic re-assortment (an event that could lead to the emergence of a potential pandemic influenza virus strain). However, seasonal influenza vaccination does not provide any protection against human infection with HPAI A(H5N1) virus infection.

Standard personal protective measures (e.g., home isolation, respiratory etiquette, hand hygiene) are recommended to slow the spread of infection; however, additional measures may also be recommended during pandemics, including:[118]

- Voluntary home quarantine
- Use of face masks by people who are ill (or who are well)
- School, university, or child-care facility closures
- Social distancing measures (e.g., workplaces, mass gatherings)
- Environmental surface cleaning measures.

Post-exposure prophylaxis

- Antiviral post-exposure prophylaxis may be recommended for close contacts.
- See Treatment algorithm .

Patient discussions

Any patient with suspected or confirmed highly pathogenic avian influenza (HPAI) A(H5N1) virus infection should be started on antiviral treatment as soon as possible and isolated following recommended infection control precautions. Local and national public health authorities should be contacted immediately. Instructions for discharge or home care and risk management of clinically mild illness with HPAI A(H5N1) virus infection should be provided by local or national public health departments to fit the needs of the particular case. The health department will determine whether quarantine of exposed people, other forms of social distancing, and other pharmacological and non-pharmacological measures must be undertaken to prevent HPAI A(H5N1) virus transmission among exposed people in the community. Physicians are not recommended to manage HPAI A(H5N1) cases without close guidance and involvement by local or national public health departments.

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Further information is available from the World Health Organization (WHO), the US Centers for Disease Control and Prevention (CDC) and the UK Health Security Agency:

- [WHO: influenza (avian and other zoonotic)] (https://www.who.int/health-topics/influenza-avian-and-other-zoonotic)
- [WHO: influenza (avian and other zoonotic) fact sheet] (https://www.who.int/news-room/fact-sheets/detail/influenza-(avian-and-other-zoonotic))
- [CDC: avian influenza (bird flu)] (https://www.cdc.gov/bird-flu)
- [UK Health Security Agency: avian influenza: guidance, data and analysis] (https://www.gov.uk/government/collections/avian-influenza-guidance-data-and-analysis)

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Monitoring

Monitoring

Highly pathogenic avian influenza A(H5N1) virus infection is an acute infectious disease. Patients may experience prolonged virus replication and viral shedding, and their hospital course may last up to 3 weeks or longer after disease onset. Patients should be monitored for progression of illness.

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FOLLOW UP

Complications

Complications	Timeframe	Likelihood
primary influenza pneumonia	**short term**	**high**
Common complication of highly pathogenic avian influenza (HPAI) A(H5N1)virus infection. Treatment is with antivirals as soon as possible, supplemental oxygen, and supportive therapy. Respiratory status should be monitored, and early ventilatory support considered.		
respiratory failure	**short term**	**high**
This is a common complication of highly pathogenic avian influenza (HPAI) H5N1 virus infection, usually due to acute respiratory distress syndrome. Has been documented among all affected age groups. Antiviral and supportive therapy is necessary.		
acute respiratory distress syndrome	**short term**	**high**
The most common cause of respiratory failure. Evidence-based, lung protective ventilation strategies are recommended.		
multi-organ failure	**short term**	**high**
Multi-organ failure, including renal or cardiac compromise, is a common complication of severely ill highly pathogenic avian influenza (HPAI) A(H5N1) patients. Supportive therapy is crucial, as is targeted therapy where applicable. Management should follow evidence-based management guidelines.		
sepsis	**short term**	**medium**
Septic shock requiring vasopressor support is a common complication of highly pathogenic avian influenza (HPAI) A(H5N1) virus infection. Treatment is supportive and should follow existing evidence-based guidelines for the management of septic shock.		
encephalitis	**short term**	**low**
Encephalitis is an uncommon complication of highly pathogenic avian influenza (HPAI) A(H5N1) virus infection, but fatal cases of central nervous system infection and detection of virus in cerebrospinal fluid have been described. A fatal case of meningoencephalitis has also been reported. Patients have headaches, behavioural disturbances, and altered mental status, and may have seizures and coma, as a direct result of virus infection. The underlying infection should be treated with antivirals as soon as possible, and supportive care provided as indicated.		

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Complications	Timeframe	Likelihood
death	**variable**	**high**
Occurs in about 49% of patients with highly pathogenic avian influenza (HPAI) A(H5N1) virus infection reported to the World Health Organization.[37]		
community-acquired pneumonia	**variable**	**low**
While superinfection with bacterial pneumonia pathogens (*Staphylococcus aureus* , *Streptococcus pneumoniae* , group A streptococcus) is well described with seasonal influenza A or B virus infections, as well as with influenza A (H1N1)pdm09 virus infection, concurrent community-acquired bacterial pneumonia with highly pathogenic avian influenza (HPAI) H5N1 virus infection has rarely been reported. In most cases, empiric therapies for bacterial pneumonia and influenza virus infection are initiated before the HPAI A(H5N1) diagnosis is confirmed. Antibacterial therapy should follow evidence-based treatment guidelines, conform to regional standards of care, and target common community-acquired pneumonia pathogens from the region where infection occurred.		
hospital-acquired pneumonia	**variable**	**low**
Common complication of mechanical ventilation and one of the most frequent of all healthcare-associated infections. However, it has been infrequently reported in highly pathogenic avian influenza (HPAI) A(H5N1) patients. Evaluation and treatment should follow evidence-based guidelines.		

Prognosis

Between November 2003 and July 2024, approximately 49% of patients with confirmed highly pathogenic avian influenza (HPAI) A(H5N1) virus infection reported to the World Health Organization have died.[37] The case fatality rate is subject to selection bias as more severe/hospitalised cases are likely to be tested, and the true figure may be lower. Those who had progressive disease generally died from complications of acute respiratory distress syndrome (ARDS) and multi-organ failure. Early recognition of disease and early initiation of antiviral and supportive treatment may be associated with improved outcomes.[136] [137] The presence of rhinorrhoea appears to indicate a better prognosis for children with HPAI A(H5N1) virus infection.[32]

HPAI A(H5N1) virus infection is an acute infectious disease. Patients may experience prolonged virus replication and viral shedding, and their hospital course may last up to 3 weeks or longer after disease onset.

No studies have assessed the long-term sequelae of infection among survivors, but most survivors had only mild disease. Long-term sequelae of ARDS include neuromuscular weakness, diminished lung function, post-traumatic stress disorder, and cognitive decline in older patients.[146] [147]

Surviving patients may be immune to subsequent infection by antigenically similar HPAI A(H5N1) virus strains.

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Diagnostic guidelines

United Kingdom

Avian influenza: guidance for managing human cases (https://www.gov.uk/government/publications/avian-influenza-guidance-and-algorithms-for-managing-human-cases)

Published by: UK Health Security Agency **Last published:** 2024

International

Collecting, preserving and shipping specimens for the diagnosis of avian influenza A(H5N1) virus infection (https://apps.who.int/iris/handle/10665/69392)

Published by: World Health Organization **Last published:** 2006

North America

Highly pathogenic avian influenza A(H5N1) virus: interim recommendations for prevention, monitoring, and public health investigations (https://www.cdc.gov/bird-flu/prevention/hpai-interim-recommendations.html)

Published by: Centers for Disease Control and Prevention **Last published:** 2024

Clinician brief: evaluating and managing patients exposed to animals or persons infected with novel influenza A viruses of public health concern (https://www.cdc.gov/bird-flu/hcp/clinicians-evaluating-patients)

Published by: Centers for Disease Control and Prevention **Last published:** 2024

Interim guidance on specimen collection and testing for patients with suspected infection with novel influenza A viruses associated with severe disease or with the potential to cause severe disease in humans (https://www.cdc.gov/bird-flu/php/severe-potential)

Published by: Centers for Disease Control and Prevention **Last published:** 2024

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Treatment guidelines

United Kingdom

Avian influenza: guidance and algorithms for managing incidents in birds (https://www.gov.uk/government/publications/avian-influenza-guidance-and-algorithms-for-managing-incidents-in-birds)

Published by: UK Health Security Agency **Last published:** 2025

Avian influenza: guidance, data and analysis (https://www.gov.uk/government/collections/avian-influenza-guidance-data-and-analysis)

Published by: UK Health Security Agency **Last published:** 2025

Avian influenza: guidance for managing human cases (https://www.gov.uk/government/publications/avian-influenza-guidance-and-algorithms-for-managing-human-cases)

Published by: UK Health Security Agency **Last published:** 2024

International

Zoonotic influenza A virus outbreak toolbox (https://www.who.int/emergencies/outbreak-toolkit/disease-outbreak-toolboxes/zoonotic-influenza-a-virus-outbreak-toolbox)

Published by: World Health Organization **Last published:** 2024

Clinical practice guidelines for influenza (https://www.who.int/publications/i/item/9789240097759)

Published by: World Health Organization **Last published:** 2024

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North America

Interim guidance on the use of antiviral medications for treatment of human infections with novel influenza A viruses associated with severe human disease (https://www.cdc.gov/bird-flu/hcp/novel-av-treatment-guidance)

Published by: Centers for Disease Control and Prevention **Last published:** 2024

Interim guidance for follow-up of close contacts of persons infected with novel influenza A viruses associated with severe human disease or with potential to cause severe human disease, and use of antiviral medications for post-exposure prophylaxis (https://www.cdc.gov/bird-flu/php/novel-av-chemoprophylaxis-guidance)

Published by: Centers for Disease Control and Prevention **Last published:** 2024

Interim guidance on influenza antiviral post-exposure prophylaxis of persons exposed to birds or other animals with novel influenza A viruses associated with severe human disease or with the potential to cause severe human disease (https://www.cdc.gov/bird-flu/hcp/guidance-exposed-persons)

Published by: Centers for Disease Control and Prevention **Last published:** 2024

CDC Yellow Book 2024: health information for international travel: influenza (https://wwwnc.cdc.gov/travel/page/yellowbook-home)

Published by: Centers for Disease Control and Prevention **Last published:** 2023

Interim guidance for infection control within healthcare settings when caring for confirmed cases, probable cases, and cases under investigation for infection with novel influenza A viruses associated with severe disease (https://www.cdc.gov/bird-flu/hcp/novel-flu-infection-control)

Published by: Centers for Disease Control and Prevention **Last published:** 2022

Oceania

Avian influenza in humans (bird flu) (https://www.health.gov.au/diseases/avian-influenza-in-humans-bird-flu)

Published by: Australian Government Department of Health and Aged Care **Last published:** 2024

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Online resources

1. BMJ talk medicine podcast: avian influenza - a guide to recognition, reporting and referral with Dr Mary-Margaret Fill (https://soundcloud.com/bmjpodcasts/bmj-best-practice-avian-influenza) *(external link)*
2. CDC: H5 bird flu - current situation (https://www.cdc.gov/bird-flu/situation-summary) *(external link)*
3. WHO: surveillance - avian influenza (https://www.who.int/westernpacific/emergencies/surveillance/avian-influenza) *(external link)*
4. UK Health Security Agency: avian influenza: guidance, data and analysis (https://www.gov.uk/government/collections/avian-influenza-guidance-data-and-analysis) *(external link)*
5. CDC: interim guidance for employers to reduce exposure to avian influenza A viruses for people working with animals (https://www.cdc.gov/bird-flu/prevention/worker-protection-ppe.html) *(external link)*
6. WHO: zoonotic influenza – candidate vaccine viruses and potency testing reagents (https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations/zoonotic-influenza-viruses-and-candidate-vaccine-viruses) *(external link)*
7. CDC: case definitions for investigations of human infection with avian influenza A viruses in the United States (https://www.cdc.gov/bird-flu/hcp/case-definition/index.html) *(external link)*
8. WHO: influenza (avian and other zoonotic) (https://www.who.int/health-topics/influenza-avian-and-other-zoonotic) *(external link)*
9. WHO: influenza (avian and other zoonotic) fact sheet (https://www.who.int/news-room/fact-sheets/detail/influenza-(avian-and-other-zoonotic)) *(external link)*
10. CDC: avian influenza (bird flu) (https://www.cdc.gov/bird-flu) *(external link)*

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Key articles

- Centers for Disease Control and Prevention. Highly pathogenic avian influenza A(H5N1) virus: interim recommendations for prevention, monitoring, and public health investigations. Dec 2024 [internet publication]. Full text (https://www.cdc.gov/bird-flu/prevention/hpai-interim-recommendations.html)
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Figure 1 – BMJ Best Practice Numeral Style

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