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Summary

Avian influenza (H5N1) virus infection is a notifiable condition. Infection control measures, such as standard, droplet, contact, and airborne precautions, are recommended.

High case-fatality rate of approximately 53% among patients with laboratory-confirmed infection.

Most patients present with fever and features of lower respiratory tract infection on admission. Molecular testing is recommended to confirm diagnosis; however, it is usually not available in most clinical settings.

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

Definition

A contagious disease of animals caused by viruses that infect birds and, less commonly, pigs. Avian influenza A viruses are highly species-specific but have infected other mammals and, on rare occasions, have crossed the species barrier to infect humans. 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]

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

Avian influenza A (H5N1) virus infection

Epidemiology

Highly pathogenic avian influenza (HPAI) H5N1 virus strains have infected poultry or wild birds in more than 50 countries since 2003. Sixteen countries have reported detection of cases of human HPAI H5N1 virus infection since 2003. Between 2003 and 2018, 860 cases were reported, with 454 deaths (a case fatality rate of 53%).[26]

[WHO: cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO] (https://www.who.int/influenza/human_animal_interface/HAI_Risk_Assessment/en/)

In 2019, only one human case was reported to the World Health Organization.[27] In October 2020, the Lao People’s Democratic Republic reported a case of human infection in a one-year-old female.[28] Most human HPAI H5N1 cases have been among previously healthy children and young adults. The median age of patients is approximately 20 years, with an age range for all patients from under 1 year to 81 years.[29] The ratio of male to female cases is about equal; however, there is 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.[18] From 2003 to 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%).[18] Mortality is associated with delayed recognition of disease and hospitalisation after symptom onset.[18] One study reported that the presence of rhinorrhea appeared to indicate a better prognosis for children with HPAI H5N1.[24]

In January 2014, Canada reported identifying a human case of HPAI H5N1 in a person who travelled from China to Canada, where the patient was hospitalised and died.[30] While there is no indication that the infection was acquired within North America, this case highlights that clinicians should remain vigilant for influenza virus infections, including HPAI H5N1 and other novel influenza A viruses, in critically ill patients. Also in 2014, the United Nations Food and Agriculture Organization (FAO) reported that there were at least 6 countries with endemic HPAI H5N1 virus circulation among poultry populations: Bangladesh, the People’s Republic of China, Egypt, India, Indonesia, and Vietnam, with sporadic poultry outbreaks in other countries.[31] 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.[32] A cohort study of human avian influenza virus infections in households raising backyard poultry in Egypt found a very low prevalence of H5N1 (0.4% at baseline and 0.2% at follow up).[33] Asian lineage HPAI H5N1 virus strains have not been detected in domestic poultry in North or South America to date, though antigenically distinct HPAI H5N1 viruses not associated with human infection have been identified in birds in the US.[34]

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

Theory

Most human HPAI H5N1 cases are sporadic and associated with direct contact (e.g., touching) or very close exposure with sick or dead backyard poultry (usually chickens), and a seasonal variation observed in human cases parallels that of outbreaks in birds.[18] [36] [37] [38] However, other risk factors include visiting a live poultry market[39] [40] [41] and prolonged, unprotected close contact with a human HPAI H5N1 case.[17] In some cases, a possible exposure risk was not identified, suggesting possible environmental exposure or close contact with an unknown infected person.[42] Clustering of HPAI H5N1 cases among blood-related family members suggests the potential for increased genetic susceptibility. However, human-to-human transmission remains rare.[43] [44] [45] [46] [47] Rare nosocomial transmission has also been documented.[1] [2] [48] There is no evidence of ongoing human-to-human transmission of HPAI H5N1 virus.

Experimental studies in ferrets have demonstrated that HPAI H5N1 virus can acquire traits that improve transmissibility via respiratory droplets, and thus increase the risk of human-to-human transmission.[49] Of the several amino acid substitutions associated with increased respiratory transmission in this mammalian model, some are already found in HPAI H5N1 viruses currently circulating among poultry.[50] The odds of spontaneous mutations resulting in improved transmissibility are very low.[51] A change in the current epidemiology of HPAI H5N1 human cases, including epidemiologically related clusters or unrelated cases, could suggest increased transmissibility from viral mutations and increased pandemic potential.[52] However, investigations of a large increase in human HPAI H5N1 cases in Egypt during 2014-2015 attributed increased diagnostic testing of exposed persons and not viral mutations as the likely cause of increased case detection.[53] [54]

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).[55] [56]

Pathophysiology

Highly pathogenic avian influenza (HPAI) 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.[57] [58] Such receptors have also been reported in the human gastrointestinal tract.[59] Furthermore, specific structural conformation, not just receptor binding affinity, may be important in binding to receptors in the upper-respiratory tract.[60] HPAI H5N1 virus obtained from human clinical samples with the ability to bind upper-respiratory tract tissue has also been reported.[57] [61] High and prolonged HPAI H5N1 viral replication in the lower respiratory tract induces pro-inflammatory cytokines and chemokines,[62] [63] resulting in pulmonary capillary leak, diffuse alveolar damage, and acute lung injury, and can lead to development of ARDS. HPAI H5N1 viraemia has been reported in fatal cases,[63] and dissemination of HPAI 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.[20] [64] Reactive haemophagocytosis has also been reported.[64]

Avian influenza A viruses, including HPAI 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.[17]
• Inhalation of aerosolised material (e.g., poultry faeces) containing infectious HPAI 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 H5N1 virus (touching or cleaning infected birds) or indirect (fomite) contact transmission from surfaces contaminated with poultry faeces or products containing HPAI 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.

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 poultry. LPAI H6N1, H7N2, H7N3, H7N7, H7N9, H9N2, 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 (H7N9, H10N8).[3] [4] [5] [6] [7]
• HPAI strains identified to date are of the H5 and H7 subtypes and can cause severe illness in poultry. HPAI virus infections in humans have ranged from asymptomatic to severe or fatal disease. Rare, sporadic human cases of HPAI virus infection have been detected with H5N1, H5N6, H7N3, and H7N7 viruses and have caused a wide spectrum of illness from conjunctivitis (H7N3, H7N7) to severe pneumonia, ARDS, and fatal outcomes (H7N7, H5N1, H5N6).[8] [9] [10] [11] 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 H5N1 nomenclature.[12] According to this revised nomenclature system, circulating HPAI H5N1 virus strains among birds are classified into numerous clades, and subdivided into subclades and lineages.[13] [14] Circulating HPAI H5N1 virus strains now include clades and subclades 1.1, 2.1, 2.2, 2.3, and 7.[15] Further subdivisions of antigenically distinct circulating subclades have also been described (e.g., 1.1.1, 1.1.2, 2.1.3, 2a, 2.3.2, 2.3.4, and 7.2), and they continue to undergo antigenic drift.[12] [16] These antigenic changes have important implications for vaccine development. Clades that have infected humans include 0, 1, 2, and 7.[17] HPAI H5N1 virus continues to cause rare, sporadic human infections, including fatal outcomes. Most human HPAI H5N1 virus infections since 2005 have been with clade 2 virus strains. HPAI H5N1 virus strains continue to evolve among infected birds.
Case history

Case history #1

A previously healthy 32-year-old Egyptian 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 AST and ALT 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.

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 an 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. Clinical progression to severe lower respiratory tract disease typically occurs in patients at about days 3 to 6. [18] Multi-organ failure may occur.[19] Encephalitis and meningoencephalitis have been reported.[20] [21] 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.[22] [23] [24] At admission, most patients have fever and clinical findings similar to those of severe community-acquired pneumonia.[25]
Avian influenza A (H5N1) virus infection

Approach

People with infection due to highly pathogenic avian influenza (HPAI) H5N1 virus present with similar symptoms of pneumonia caused by other infectious aetiologies (including seasonal influenza A or B viruses and 2009 H1N1 virus). There is a wide spectrum of disease ranging from sub-clinical or only mild symptoms to severe respiratory compromise and death. However, most patients with HPAI A (H5N1) virus infection are severely ill, reflecting late clinical presentation and late antiviral treatment, identified through hospital-based case-finding.

Given that human infection with HPAI H5N1 virus is rare (even among people with high-risk exposures), diagnostic evaluation and therapy must consider alternative aetiologies. If there is concern that a patient might have HPAI H5N1 virus infection, infection control precautions should be used, including face mask, goggles, disposable gown, and gloves.

Novel influenza A virus infections are a notifiable disease in the US and some other countries.

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 H5N1 virus infection within the prior 7 days by a person with febrile respiratory illness should trigger consideration of HPAI H5N1 virus infection. A recent history of travel to an HPAI-H5N1 virus-affected country should also prompt consideration of HPAI H5N1 virus infection in the differential diagnosis of a patient presenting with fever and respiratory symptoms. 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.[21]

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, rhinorrhea, headache, sore throat, myalgia, and fatigue). Clinical progression to severe lower respiratory tract disease occurs in many patients during days 3 to 6. Clinically mild disease (fever and symptoms of upper respiratory infection) has been documented. At admission, most patients have fever and clinical findings similar to severe community-acquired pneumonia. Several non-specific primary gastrointestinal symptoms (abdominal pain, vomiting, diarrhoea) have been reported in children and adults with HPAI H5N1 virus infection.

Most patients admitted to the hospital with H5N1 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 support, disseminated intravascular coagulation, spontaneous abortions in pregnant women, and encephalitis.

Physical examination

Physical examination findings in severe infection 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).[17] Less commonly, the examination may also show evidence of signs of atypical features (e.g., altered mental status, seizures, and febrile diarrhoeal illness progressing to pneumonia).
Mild illness with HPAI H5N1 virus infection may be 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, and investigation for endemic respiratory pathogens from the region where infection may have occurred.

First-line evaluation of patients suspected of having HPAI 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. 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 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 virus infection should be considered, as it is far more common than HPAI H5N1 virus infection.
- Other respiratory virus testing may be considered in certain circumstances (e.g., respiratory syncytial virus in young children, multiple virus aetiologies in immunocompromised patients). Patients presenting with atypical symptoms (e.g., gastrointestinal or neurological) should receive a suitable work-up directed at alternative aetiologies for those processes.

We recommend that clinicians pursue alternative diagnoses whenever they encounter a patient they suspect has HPAI H5N1 virus infection. As always, work-up should be directed toward abnormal clinical findings.

**Specific viral testing**

The recommended and definitive HPAI H5N1 diagnostic testing is by reverse transcription polymerase chain reaction (RT-PCR) of respiratory specimens, including real-time or conventional RT-PCR, using H5-specific primers and probes. As HPAI H5N1 virus strains continue to evolve, testing by RT-PCR using updated primers and probes is essential. However, RT-PCR for HPAI H5N1 virus is usually not available in clinical settings. Many regional public health laboratories, most national laboratories, and some private laboratories can perform RT-PCR for HPAI H5N1 virus. In non-intubated patients, the preferred respiratory specimens are oropharyngeal and nasal swabs. Oropharyngeal swabs have a higher diagnostic yield than other upper respiratory specimens. Nasal and nasopharyngeal swabs are preferred to detect other respiratory viruses, including seasonal influenza viruses. Healthcare workers collecting clinical specimens from patients with suspected HPAI H5N1 virus infection should follow recommended infection control precautions and use appropriate personal protective equipment.[76] [77] [78] Swabs with Dacron tips or aluminium or plastic shafts should be used. Using swabs with cotton tips or wooden shafts is not recommended because they may interfere with the RT-PCR assay. Ideally, multiple respiratory specimens for testing should be collected from multiple respiratory sites from patients with suspected HPAI H5N1 virus infection, including over multiple days because testing single specimens may miss detection of HPAI H5N1 virus. Intubated patients should also have endotracheal aspirates collected for...
HPAI H5N1 testing. Bronchoscopy and thoracentesis are not recommended procedures for the sole purpose of collecting clinical specimens for HPAI H5N1 testing, but if collected for other diagnostic purposes, bronchioalveolar lavage fluid specimens and pleural fluid can also be tested. 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 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 H5N1 virus infection. The RT-PCR test takes approximately 4 hours to produce preliminary results, but transport time and testing logistics may delay testing results. Viral culture should not be undertaken except in an experienced, biosafety level 3-enhanced or greater laboratory following recommended personal protective equipment and infection control precautions.

Commercially available, point-of-care, rapid influenza diagnostic tests are insensitive and not specific for HPAI H5N1 virus and, therefore, should not be used for diagnosis of HPAI H5N1.

Paired acute and convalescent sera, collected about 2 to 3 weeks apart and tested using specialised laboratory serological methods, can potentially yield a retrospective diagnosis of HPAI H5N1 virus infection in a patient with clinically compatible illness, but cannot inform clinical management decisions.[76] All positive tests on human clinical specimens for HPAI H5N1 virus should be confirmed at a WHO H5 reference laboratory; the WHO also accepts positive H5 results from a limited number of WHO-designated national laboratories. Positive laboratory results for human infection with avian influenza A viruses, including HPAI H5N1 virus, should be reported to the WHO under international health regulations.

## 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 conjunctivitis, rhinorrhea, headache, sore throat, myalgia, and fatigue).

**dyspnoea (common)**
- Ranges from mild to severe.

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

**rales, rhonchi (common)**
- Auscultatory finding described in highly pathogenic avian influenza (HPAI) H5N1 patients.
**Avian influenza A (H5N1) virus infection**

**Diagnosis**

- **wheeze (common)**
  - Auscultatory finding described in highly pathogenic avian influenza (HPAI) H5N1 patients.

- **decreased breath sounds (common)**
  - Auscultatory finding described in highly pathogenic avian influenza (HPAI) H5N1 patients.

- **tachypnoea (common)**
  - Usually develops within 5 days of illness onset.

**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) 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**
  - Direct contact (touching) or close (within ≤1 m) exposure with sick or dead poultry or other birds suspected or confirmed to have highly pathogenic avian influenza (HPAI) H5N1 virus infection.
  - Most people with HPAI 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 H5N1 virus infection. Every year, many people are exposed to HPAI H5N1 virus but only a very small proportion become infected.

- **recent travel to an HPAI-H5N1 virus infected country**
  - A recent history of travel to an HPAI-H5N1 virus-affected country should also prompt consideration of HPAI H5N1 virus infection in the differential diagnosis of a patient presenting with fever and respiratory symptoms. 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.[21]

- **environmental exposure to H5N1 virus**
  - Direct contact (touching) with poultry faeces and visiting a live poultry market in highly pathogenic avian influenza (HPAI) H5N1-endemic countries are risk factors for infection.[40] [41]
  - Exposure to pond water in regions where HPAI H5N1 has been widespread among birds has also been suggested as a possible risk factor.[65] Most people with HPAI H5N1 virus infection had unprotected direct or close unprotected exposure with infected sick or dead poultry before illness
onset, but exposure appears to rarely result in HPAI H5N1 virus infection. Every year, many people are exposed to HPAI H5N1 virus but only a small proportion become infected.

**Weak**

**close contact with infected humans**

- The risk is highest among blood-related family members.[45] Rarely implicated risk factor, usually in caregivers of an ill blood-related family member. Risk is defined as prolonged direct or close unprotected contact (within 1-2 m) with ill people suspected or confirmed to have HPAI H5N1 virus infection. Nosocomial transmission of HPAI H5N1 virus from a patient to a healthcare worker has been reported.[48] However, serological surveys of healthcare personnel using no or inadequate personal protective equipment while caring for patients with confirmed HPAI H5N1 virus infection have demonstrated very low risk of transmission.[66] [67] [68]

**laboratory work with H5N1 virus**

- HPAI H5N1 virus transmission to laboratory workers using proper techniques and personal protective equipment in appropriate biosafety precautions has not been documented.
- Biosafety level 2 practices and procedures are the minimum requirement for handling specimens suspected to contain HPAI H5N1 virus.[69] Biosafety level 3-enhanced containment standards are the minimum requirement for culture of suspected HPAI H5N1 virus.[69] A small serosurvey of laboratory workers exposed to HPAI H5N1 virus with incomplete personal protective equipment use and adherence to biosafety precautions demonstrated no serological evidence of prior HPAI H5N1 virus infection.[70]
# Investigations

## 1st test to order

<table>
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<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>FBC with differential</td>
<td><strong>leukopenia, lymphopenia, thrombocytopenia</strong></td>
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<tr>
<td>• Described in most patients in small case series.</td>
<td></td>
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<tr>
<td>LFTs</td>
<td><strong>elevated AST/ALT</strong></td>
</tr>
<tr>
<td>• Described in most patients in small case series.</td>
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<tr>
<td>chest x-ray</td>
<td><strong>may be normal; may show infiltrates consistent with pneumonia in severe cases</strong></td>
</tr>
<tr>
<td>• A chest x-ray alone cannot exclude viral or bacterial pneumonia.</td>
<td></td>
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<tr>
<td>pulse oximetry</td>
<td><strong>may show hypoxia</strong></td>
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<tr>
<td>• Indicated in patients with dyspnoea or suspected pneumonia.</td>
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<tr>
<td>sputum Gram stain</td>
<td><strong>visualisation of infecting organisms if bacterial pneumonia or potential bacterial co-infection</strong></td>
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<tr>
<td>• Primary bacterial pneumonia and potential bacterial co-infection should be evaluated. Few co-infections have been reported in highly pathogenic avian influenza (HPAI) H5N1 patients, except with ventilator-associated pneumonia.</td>
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<tr>
<td>sputum and blood bacterial culture</td>
<td><strong>growth of infecting organism if bacterial pneumonia or potential bacterial co-infection</strong></td>
</tr>
<tr>
<td>• Primary bacterial pneumonia and potential bacterial co-infection should be evaluated.</td>
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<tr>
<td>reverse transcription polymerase chain reaction (RT-PCR) of respiratory specimens</td>
<td><strong>positive for H5-specific viral RNA</strong></td>
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<tr>
<td>• Recommended clinical test for diagnosis of highly pathogenic avian influenza (HPAI) H5N1 virus infection using H5-specific primers and probes to detect HPAI H5N1 viral RNA in respiratory clinical specimens.[79] [80] Both real-time and conventional RT-PCR assays can be used to detect HPAI H5N1 viral RNA at national laboratories, highly specialised local public health laboratories, or some academic centre laboratories. RT-PCR for HPAI H5N1 virus is not available in most clinical settings. H5-specific primers and probes should be updated regularly. RT-PCR for influenza A and B viruses can confirm a diagnosis of seasonal influenza.</td>
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<tr>
<td>• H5-positive results from national laboratories should be confirmed at WHO H5 reference laboratories or World Health Organization (WHO) collaborating influenza centres. The WHO also accepts results of RT-PCR assays from some national influenza laboratories.[81] [82]</td>
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Other tests to consider

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

Emerging tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>serological testing for H5N1-specific</td>
<td>fourfold increase in H5N1-</td>
</tr>
<tr>
<td>antibody for retrospective diagnosis</td>
<td>specific antibody</td>
</tr>
<tr>
<td>• Serological testing for highly</td>
<td></td>
</tr>
<tr>
<td>pathogenic avian influenza (HPAI) H5N1</td>
<td></td>
</tr>
<tr>
<td>virus antibodies is not routinely</td>
<td></td>
</tr>
<tr>
<td>available, cannot inform clinical</td>
<td></td>
</tr>
<tr>
<td>management, and should not be</td>
<td></td>
</tr>
<tr>
<td>considered for clinical diagnostic</td>
<td></td>
</tr>
<tr>
<td>purposes.</td>
<td></td>
</tr>
<tr>
<td>• It can be performed in only a few</td>
<td></td>
</tr>
<tr>
<td>specialised laboratories, such as WHO</td>
<td></td>
</tr>
<tr>
<td>H5 reference laboratories, using live</td>
<td></td>
</tr>
<tr>
<td>HPAI H5N1 virus in a microneutralisation</td>
<td></td>
</tr>
<tr>
<td>assay under biosafety level 3-enhanced</td>
<td></td>
</tr>
<tr>
<td>conditions.</td>
<td></td>
</tr>
<tr>
<td>• Other serological assays include horse</td>
<td></td>
</tr>
<tr>
<td>red blood cell haemagglutinin inhibition</td>
<td></td>
</tr>
<tr>
<td>assay or assessment of HPAI H5N1-specific</td>
<td></td>
</tr>
<tr>
<td>T-cell responses.[83] Properly timed</td>
<td></td>
</tr>
<tr>
<td>acute and convalescent sera can yield</td>
<td></td>
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<tr>
<td>a retrospective diagnosis of HPAI H5N1</td>
<td></td>
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<tr>
<td>virus infection. A fourfold increase in</td>
<td></td>
</tr>
<tr>
<td>H5N1-specific antibody level after a</td>
<td></td>
</tr>
<tr>
<td>2- to 4-week period from the initial</td>
<td></td>
</tr>
<tr>
<td>blood draw is diagnostic of HPAI H5N1</td>
<td></td>
</tr>
<tr>
<td>virus infection in a patient with</td>
<td></td>
</tr>
<tr>
<td>clinically compatible illness.</td>
<td></td>
</tr>
<tr>
<td>• Serological tests using standard influenza haemagglutination inhibition assays are</td>
<td></td>
</tr>
<tr>
<td>non-specific for HPAI H5N1 virus and are</td>
<td></td>
</tr>
<tr>
<td>not recommended.</td>
<td></td>
</tr>
</tbody>
</table>
## Differentials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Coronavirus disease 2019 (COVID-19)   | • Residence in/travel to a country/area or territory with local transmission, or close contact with a confirmed or probable case of COVID-19, in the 14 days prior to symptom onset.  
• Signs and symptoms are similar so it may be difficult to differentiate between the conditions clinically.  
• The situation is evolving rapidly; see our COVID-19 topic for further information. | • Real-time reverse transcription polymerase chain reaction (RT-PCR): positive for SARS-CoV-2 RNA.  
• 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 and 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) H5N1-specific tests do not exclude co-infection, although most HPAI H5N1 cases have not had bacterial co-infection identified except in intubated patients with ventilator-associated pneumonia. Seasonal influenza virus infection with bacterial co-infection is more common. |
<p>| 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 |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| 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) H5N1 virus infection, but co-infection with HPAI H5N1 virus and other respiratory viruses has not been reported. |
| Avian influenza A (H7N9) 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 H5N1 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) H5N1 virus infection, but co-infection with HPAI H5N1 and endemic respiratory infections has not been reported. |
## Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| **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 to 5 days and resolve within 7 to 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.[84]  
• Diagnostic tests confirming infection by another respiratory virus does not rule out highly pathogenic avian influenza (HPAI) H5N1 virus infection, but co-infection with HPAI H5N1 virus and other respiratory viruses have not been reported. |
| **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. 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 ARDS. Many also have gastro-intestinal symptoms (including diarrhoea), while others have kidney failure. | • RT-PCR is positive for MERS coronavirus. The test can be found at some international public health laboratories, particularly in regions affected by MERS. |
Criteria

Centers for Disease Control and Prevention (CDC): interim guidance on case definitions for investigations of human infection with highly pathogenic avian influenza A (H5N1) virus in the US[85]

Confirmed case:

- Highly pathogenic avian influenza (HPAI) H5N1 virus infection in a patient that is confirmed by the CDC’s Influenza Laboratory or a CDC-certified public health laboratory using methods agreed upon by the CDC and the Council of State and Territorial Epidemiologists (CSTE).
- Confirmation of infection with avian influenza A (H5N1) viruses may be made by public health laboratories following CDC-approved protocols for detection of avian influenza A (H5N1) virus, or by laboratories using a US Food and Drug Administration (FDA)-authorised test specific for detection of avian influenza A (H5N1) virus.

Probable case:

- Illness compatible with influenza in a patient meeting the exposure criteria (below) and for whom laboratory diagnostic testing is positive for influenza A, negative for H1, negative for H1pdm09, and negative for H3 by real-time reverse transcription-polymerase chain reaction (RT-PCR) and therefore unable to be subtyped.

Case under investigation:

- Illness compatible with influenza in a patient meeting any of the exposure criteria (below) and for whom confirmatory laboratory test results are not known or pending.

Exposure criteria:

- Patients with recent travel (within <10 days of illness onset) to areas where human cases of HPAI H5N1 virus infection have become infected or to areas where HPAI H5N1 viruses are known to be circulating in animals; OR
- Patients who have had recent close contact (within <10 days of illness onset) with confirmed or suspected cases of human infection with avian influenza A (H5N1) virus. Close contact may be regarded as coming within about 2 m (6 feet) of a confirmed or suspected case while the case was ill (beginning 1 day prior to illness onset and continuing until resolution of illness). This includes healthcare personnel providing care for a confirmed or suspected case, family members of a confirmed or suspected case, persons who lived with or stayed overnight with a confirmed or suspected case, and others who have had similar close physical contact; OR
- Unprotected exposure to live HPAI H5N1 virus in a laboratory.

World Health Organization (WHO): case definitions for human infections with influenza A (H5N1) virus[86]

Person under investigation:

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

Suspected H5N1 case:
Avian influenza A (H5N1) virus infection

Diagnosis

- A person presenting with unexplained acute lower respiratory illness with fever >38°C (>100.4°F) 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 m [3.2 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 H5N1 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 H5N1 infections in animals or humans have been suspected or confirmed in the last month
  - Close contact with a confirmed H5N1-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 H5N1 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 H5N1 virus
  - Positive 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 H5N1 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 H5N1 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.
Screening

There is no role for screening of the asymptomatic population outside of epidemiological research studies.
Approach

There is no standardised approach for the clinical management of humans with highly pathogenic avian influenza (HPAI) H5N1 virus infection; supportive care and neuraminidase inhibitor antiviral therapy are considered the mainstays of treatment.[87] Patients with severe illness due to H5N1 virus infection can present with clinical findings similar to those of pneumonia caused by other infectious aetiologies. Given that human infection with HPAI H5N1 virus is rare (even among people with high-risk exposures), diagnostic evaluation and therapy should also consider alternative aetiologies.

Many local and national health departments, and the World Health Organization (WHO), have excellent online guidance documents:


[CDC: avian influenza - information for health professionals and laboratorians] (http://www.cdc.gov/flu/avianflu/healthprofessionals.htm)

Many local health departments can directly assist clinicians to determine which people need testing, to facilitate testing, and to assist with case management.

Unprotected exposure to a suspected or confirmed case: antiviral chemoprophylaxis

The decision to use antiviral chemoprophylaxis should be considered on a case-by-case basis and guided by the nature of HPAI H5N1 virus exposure and subsequent risk of developing infection. No prospective clinical trials exist to guide WHO antiviral chemoprophylaxis recommendations.[88] [89] Guidelines are based on observational data for HPAI H5N1 virus cases and studies of patients with seasonal influenza.[89]

Close observation and post-exposure oseltamivir or zanamivir chemoprophylaxis is recommended for healthcare workers after unprotected close exposure to a symptomatic, suspected, or confirmed HPAI H5N1 case (within 2 m) in the healthcare setting, as well as for household members and close contacts of a person with suspected or confirmed HPAI H5N1 virus infection. Local or national public health departments should be contacted for guidance. If post-exposure antiviral chemoprophylaxis is administered, it should be given twice daily (treatment dosing frequency) rather than once daily because of potential that HPAI H5N1 virus infection may have already occurred.[90] If exposure was time-limited and not ongoing, chemoprophylaxis 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.[90]

Suspected HPAI A (H5N1) virus infection

When HPAI H5N1 virus infection is highly suspected, isolating the patient and treating early with empiric neuraminidase inhibitor according to existing guidelines while waiting for the results of specific laboratory tests is appropriate. Oral or enterically-administered oseltamivir is the preferred primary treatment. Inhaled zanamivir might be used as an alternative regimen in non-intubated patients.[88] It is important to note that HPAI H5N1 virus infection of humans appears to be very rare, and physicians must consider alternative diagnoses when evaluating patients with suspected HPAI H5N1.
Contacting local or national public health departments for guidance is highly recommended. Antiviral therapy should not be delayed by diagnostic specimen collection or laboratory testing. Available evidence suggests that early diagnosis is associated with improved clinical outcomes.[91]

**Confirmed avian influenza A (H5N1) virus infection**

Most patients admitted to the hospital with HPAI H5N1 virus infection have rapidly progressive viral pneumonia leading to ARDS and multi-organ failure.[17] Patients with early recognition of disease and initiation of antiviral and supportive therapies may have improved clinical outcomes. Local or national public health departments should be contacted for guidance.

While there is no standardised approach for the clinical management of humans with HPAI 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).[17] According to the WHO, patients who have severe or progressive clinical illness, including viral pneumonitis, respiratory failure, and ARDS due to influenza virus infection, should not be given systemic corticosteroids unless indicated for other reasons (e.g., adrenal insufficiency, refractory septic shock) or as part of an approved research protocol.[88]

If exposure risk factors are present or suspected, empiric antiviral therapy should be initiated as early as possible. Antiviral therapy (neuraminidase inhibitors) should not be delayed by diagnostic specimen collection or laboratory testing. Oral or enterically-administered oseltamivir is the preferred primary treatment. No published controlled clinical trial data are available on efficacy of oseltamivir in treating HPAI H5N1 patients. Nevertheless, the WHO strongly recommends oseltamivir therapy for patients with HPAI H5N1 virus infection based on retrospective data.[89] 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 ARDS.[17] Treatment with oseltamivir for HPAI H5N1 virus infection in children aged under 1 year is recommended by the US Centers for Disease Control and Prevention (CDC) and the WHO. The dosage for children is based on weight. Children may experience unique cutaneous, behavioural, and neurological adverse events; therefore, extra caution should be used in this population. Serious adverse events were generally not reported during treatment of HPAI H5N1 patients or in systematic reviews in adults with seasonal influenza. Inhaled zanamivir might be used as an alternative regimen in non-intubated patients.[88]

Where the clinical course remains severe or progressive, despite ≥5 days of antiviral treatment, the WHO recommends monitoring of virus replication and shedding, and antiviral drug susceptibility testing, if possible. Emergence of oseltamivir resistance during treatment of patients with HPAI H5N1 virus infection has been reported.[95] Additionally, HPAI A (H5N1) virus infection with de novo reduced susceptibility to oseltamivir (before oseltamivir exposure) has been reported.[97] In 2010, none of the HPAI H5N1 virus isolates tested by the WHO had neuraminidase mutations known to predict resistance to oseltamivir.[18] Combination oseltamivir and zanamivir treatment is not recommended because of the potential for antagonism.[98]

Giving M2 inhibitors (amantadine or rimantadine) alone as a first-line therapy is not recommended. According to the WHO, a combination of a neuraminidase inhibitor and an M2 inhibitor should be considered if local surveillance data show that the HPAI H5N1 virus is known or likely to be susceptible, but this should be done only in the context of research or prospective data collection.[89] Clinicians should carefully determine which patients could receive combination therapy.[89]
Infection control procedures

Given the potential infectiousness and virulence of HPAI H5N1 virus, enhanced infection control precautions are recommended. All infection control strategies include standard hand hygiene precautions. There may be slight infection control recommendation differences between the WHO and some national public health organisations; therefore, if HPAI H5N1 virus infection is considered in a patient, it is recommended that clinicians consult national infection control guidelines.

The WHO recommends using the following personal protective equipment before patient contact:[99]

- Clean, non-sterile, long-sleeved gown; if cloth gowns are used, a plastic apron should be added if splashing of blood or body fluids is anticipated
- Clean, non-sterile gloves
- Face protection: either (1) medical mask and eye visor or goggles, or (2) a face shield.

The duration of the above precautions depends on the age of the HPAI H5N1 patient:

- Patients aged ≥12 years: 7 days after fever resolves
- Patients aged <12 years: up to 21 days after symptom onset.

If the patient leaves the hospital before this time, continued home quarantine is 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

<table>
<thead>
<tr>
<th>Initial</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>unprotected exposed healthcare workers and close contacts of suspected/confirmed case</td>
<td>1st observation ± post-exposure neuraminidase inhibitor</td>
</tr>
<tr>
<td>suspected infection</td>
<td>1st isolation + neuraminidase inhibitor plus infection control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>confirmed illness</td>
<td>1st supportive care plus neuraminidase inhibitors plus infection control adjunct M2 inhibitors</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>1st</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>observation ± post-exposure neuraminidase inhibitor</strong></td>
</tr>
</tbody>
</table>

#### 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 >15-23 kg body weight: 45 mg orally twice daily for 5-10 days; children >23-40 kg body weight: 60 mg orally twice daily for 5-10 days; children >40 kg body weight and adults: 75 mg orally twice daily for 5-10 days
  

- **zanamivir**: children ≥5 years of age and adults: 10 mg (2 puffs) inhaled twice daily for 5-10 days
  

#### Secondary 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 >15-23 kg body weight: 45 mg orally twice daily for 5-10 days; children >23-40 kg body weight: 60 mg orally twice daily for 5-10 days; children >40 kg body weight and adults: 75 mg orally twice daily for 5-10 days
  
Avian influenza A (H5N1) virus infection

Management

Initial

» The decision to use antiviral chemoprophylaxis should be considered on a case-by-case basis and guided by assessment of highly pathogenic avian influenza (HPAI) H5N1 virus exposure and subsequent risk of developing infection. No prospective clinical trials exist to guide World Health Organization (WHO) chemoprophylaxis recommendations. Guidelines are based on observational data for HPAI H5N1 cases and their contacts, and studies of seasonal influenza.[89]

» Close observation and post-exposure oseltamivir or zanamivir chemoprophylaxis is recommended for healthcare workers after unprotected close exposure to a symptomatic, suspected, or confirmed HPAI H5N1 case (within 2 m) in the healthcare setting, as well as for household members and close contacts of a person with suspected or confirmed HPAI H5N1 virus infection. Local or national public health departments should be contacted for guidance.

» Oseltamivir is the preferred option in pregnant women.[100]

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

» If post-exposure antiviral chemoprophylaxis is administered, it should be given twice daily (treatment dosing frequency) rather than once daily because of potential that HPAI H5N1 virus infection may have already occurred.[90]

» If exposure was time-limited and not ongoing, chemoprophylaxis 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.[90]

» Recommended doses are based on guidelines from the US Centers for Disease Control and Prevention (CDC).[100]

suspected infection

1st isolation + neuraminidase inhibitor

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 >15-23 kg
### Management

**Initial**

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 mg</td>
<td>45 mg orally twice daily for 5 days</td>
</tr>
<tr>
<td>23-40 kg</td>
<td>60 mg orally twice daily for 5 days</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>75 mg orally twice daily for 5 days</td>
</tr>
</tbody>
</table>


**Secondary options**

- **zanamivir**: children ≥7 years of age and adults: 10 mg (2 puffs) inhaled twice daily for 5 days

When highly pathogenic avian influenza (HPAI) H5N1 is highly suspected, isolating the patient and treating early with empiric neuraminidase inhibitor according to existing guidelines while waiting for the results of specific laboratory tests is appropriate. It is important to note that HPAI A (H5N1) virus infection of humans appears to be very rare, and physicians must consider alternative diagnoses when evaluating patients with suspected HPAI H5N1 virus infection.

- Oral or enterically-administered oseltamivir is the recommended antiviral medication treatment.[17] [22] [42] [63] Inhaled zanamivir might be used as an alternative regimen in non-intubated patients.[88]

- Oseltamivir is the preferred option in pregnant women.[100]

- Children may experience unique cutaneous, behavioural, and neurological adverse events with neuraminidase inhibitors; therefore, extra caution should be used in this population.
<table>
<thead>
<tr>
<th><strong>Initial</strong></th>
<th><strong>Management</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination oseltamivir and zanamivir treatment is not recommended because of the potential for antagonism.[98]</td>
<td></td>
</tr>
<tr>
<td>Recommended doses are based on guidelines from the US Centers for Disease Control and Prevention (CDC).[100]</td>
<td></td>
</tr>
<tr>
<td><strong>plus</strong> infection control</td>
<td></td>
</tr>
<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
<td></td>
</tr>
<tr>
<td>Given the potential infectiousness and virulence of highly pathogenic avian influenza (HPAI) A (H5N1) virus, enhanced infection control precautions are recommended. All infection control strategies include standard hand hygiene precautions. There may be slight infection control recommendation differences between the WHO[99] and some national public health organisations; therefore, if HPAI H5N1 is considered in a patient, it is recommended that clinicians consult national infection control guidelines.</td>
<td></td>
</tr>
</tbody>
</table>
Acute

confirmed illness

1st supportivc care

» Most patients admitted to the hospital with highly pathogenic avian influenza (HPAI) H5N1 virus infection have had rapidly progressive pneumonia leading to ARDS and multi-organ failure.[17] Patients with early recognition of disease and initiation of antiviral and supportive therapies may have improved clinical outcomes.[102] [103]

» While there is no standardised approach for the clinical management of humans with HPAI 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).[17] [92] According to the WHO, patients who have severe or progressive clinical illness, including viral pneumonitis, respiratory failure, and ARDS due to influenza virus infection, should not be given systemic corticosteroids unless indicated for other reasons (e.g., adrenal insufficiency, refractory septic shock) or as part of an approved research protocol.[88]

plus neuraminidase inhibitors

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/ dose twice daily for 5 days; children >1 year of age and ≤15 kg body weight: 30 mg orally twice daily for 5 days; children >15-23 kg body weight: 45 mg orally twice daily for 5 days; children >23-40 kg body weight: 60 mg orally twice daily for 5 days; children >40 kg body weight and adults: 75 mg orally twice daily for 5 days

### Acute

Table showing antiviral medications: summary for clinicians. Oct 2020 [internet publication]. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Lower doses should be considered for infants who are not receiving regular oral feedings and/or those who have a concomitant medical condition that is expected to reduce significantly renal function. An adult dose of 150 mg twice daily is often used for critically ill patients.


### Secondary options

- **zanamivir**: children ≥7 years of age and adults: 10 mg (2 puffs) inhaled twice daily for 5 days

- Oral or enterically-administered oseltamivir is the recommended antiviral medication treatment.[17] [22] [42] [63] Inhaled zanamivir might be used as an alternative regimen in non-intubated patients.[88]

- Oseltamivir is the preferred option in pregnant women.[100]

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

- Modified regimens with higher doses of oseltamivir and longer duration of treatment may be considered in a case-by-case basis, but there are no available clinical trial data to inform recommendations.[88]

- Oseltamivir has been shown to be adequately absorbed following nasogastric administration to mechanically ventilated adults with severe highly pathogenic avian influenza (HPAI) H5N1 disease.[104]

- Combination oseltamivir and zanamivir treatment is not recommended because of the potential for antagonism.[98]

- Recommended doses are based on guidelines from the US Centers for Disease Control and Prevention (CDC).[100]

---

**plus** infection control
### Acute

Treatment recommended for ALL patients in selected patient group

» Given the potential infectiousness and virulence of highly pathogenic avian influenza (HPAI) A (H5N1) virus, enhanced infection control precautions are recommended. All infection control strategies include standard hand hygiene precautions. There may be slight infection control recommendation differences between the WHO[99] and some national public health organisations; therefore, if HPAI H5N1 is considered in a patient, it is recommended that clinicians consult national infection control guidelines.

adjunct **M2 inhibitors**

Treatment recommended for SOME patients in selected patient group

**Primary options**

» **amantadine**: see local, national, or WHO guidelines for dosing recommendations

Not recommended for monotherapy of HPAI H5N1.

OR

» **rimantadine**: see local, national, or WHO guidelines for dosing recommendations

Not recommended for monotherapy of HPAI H5N1.

» Giving M2 inhibitors (amantadine or rimantadine) alone as a first-line therapy is not recommended.

» According to the WHO, a combination of a neuraminidase inhibitor and an M2 inhibitor should be considered if local surveillance data show that the highly pathogenic avian influenza (HPAI) H5N1 virus is known or likely to be susceptible, but this should be done only in the context of research or prospective data collection.[89]
Avian influenza A (H5N1) virus infection

Management

Emerging

Convalescent plasma

In June 2006, a 31-year-old male patient with highly pathogenic avian influenza (HPAI) H5N1 virus infection was treated with convalescent plasma that was obtained from a patient who had recovered from HPAI H5N1 illness earlier that year. HPAI H5N1 viral load from respiratory specimens decreased after 3 doses of convalescent plasma, with undetectable levels within 32 hours.[105] Two other HPAI H5N1 patients who received convalescent plasma from an HPAI H5N1 case or an H5N1 vaccine recipient have been reported.[106] One systematic review on the effectiveness of convalescent plasma and hyperimmune immunoglobulin in the treatment of severe acute respiratory infections of viral aetiology suggested that such treatment is safe and may reduce mortality.[107] Convalescent plasma therapy is experimental and not yet approved for clinical use.

Intravenous neuraminidase inhibitors

Parenteral formulations of neuraminidase inhibitors have been developed and include intravenous peramivir and intravenous forms of oseltamivir and zanamivir, but they are not licensed or available in most countries. Intravenous peramivir is currently approved in the US and Europe for the treatment of acute uncomplicated influenza in patients 2 years and older who have been symptomatic for no more than two days. Intravenous zanamivir is currently available on a compassionate use basis through investigational new drug (IND) application. The WHO recommends that treatment with intravenous neuraminidase inhibitors should be used in accordance with relevant emergency-use provisions. Intravenous neuraminidase inhibitors are not recommended for use outside of the context of clinical trials.[88]

Laninamivir

A new inhaled long-acting neuraminidase inhibitor that was approved in Japan for use against human influenza. It is chemically similar to zanamivir and is converted into its active form in the lungs where higher concentrations of drug persist, permitting treatment of seasonal influenza with a single drug dose. Little is known about the clinical efficacy of laninamivir against HPAI H5N1, and it is not currently recommended for this purpose.[108]

Ribavirin

Although not licensed for the treatment of influenza in most countries, it has been demonstrated to increase efficacy with oseltamivir against some HPAI H5N1 viruses in mouse models.[109] However, studies of SARS patients treated with ribavirin have found strong associations between high-dose therapy and progressive haemolytic anaemia.[110] A World Health Organization (WHO) panel concluded that there is insufficient data on either its efficacy or safety to recommend its use for the treatment of influenza.[88]

Corticosteroids

The WHO recommends against the use of corticosteroids in the management of HPAI H5N1 disease in humans. In seasonal influenza virus infection, studies have demonstrated that corticosteroid use is associated with persistent viral replication 7 days after symptom onset.[111] One study reported that early use of glucocorticoids is a risk factor for critical illness and death with 2009 H1N1 virus infection.[112] Corticosteroids should be used, though, when indicated for other reasons (e.g., asthma exacerbation, adrenal insufficiency, preterm labour).

Primary prevention

The primary means of containing highly pathogenic avian influenza (HPAI) H5N1 virus in communities and decreasing the risk to human health is through H5N1 poultry immunisation or prompt culling of poultry suspected of HPAI H5N1 virus infection with disinfection of the contaminated environment. The most
effective way to prevent HPAI H5N1 virus infection is to minimise exposure by avoiding direct or close contact with sick or dead poultry in HPAI H5N1 virus-affected countries.

The WHO and national public health organisations do not recommend travel restrictions to HPAI H5N1-affected countries. It is recommended, however, that people avoid contact with poultry suspected of HPAI H5N1 virus infection, animals in live food markets in HPAI H5N1-affected countries, and any surfaces that may be contaminated by faeces from poultry or other animals suspected of HPAI H5N1 virus infection.[17]

Influenza A (H5N1) vaccines have been found to be safe and immunogenic.[71] [72] [73] Various vaccines are licensed around the world, including Europe and the US, for use in children and adults in pandemic situations. The US contains a national stockpile that could be used if the virus begins transmitting easily from person to person.[74] Development and availability status of candidate vaccines is available from the WHO.

Healthcare workers in HPAI H5N1 virus endemic countries are recommended to receive annual seasonal influenza vaccine to decrease the risk of nosocomial transmission of seasonal influenza viruses in the healthcare setting. Preventing seasonal influenza among people exposed to HPAI H5N1 virus may also decrease the theoretical risk of human co-infection with seasonal influenza A and HPAI H5N1 viruses and of viral reassortment (an event that could lead to the emergence of a potential pandemic virus strain).

Most public health organisations consider the use of oral oseltamivir or inhaled zanamivir antiviral chemoprophylaxis for primary prevention to be unnecessary if appropriate personal protective equipment and infection control precautions are followed.

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:[75]

• 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.

**Patient discussions**

Any patient with suspected or confirmed HPAI 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 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 H5N1 virus transmission among exposed people in the community. Physicians are not recommended to manage HPAI H5N1 cases without close guidance and involvement by local or national public health departments.

[CDC: information on avian influenza] (http://www.cdc.gov/flu/avianflu/)
Monitoring

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. Once surviving patients have clinically improved and have been discharged, they may be immune to subsequent infection by antigenically similar highly pathogenic avian influenza (HPAI) H5N1 virus strains.

Long-term sequelae of ARDS include neuromuscular weakness, diminished lung function, post-traumatic stress disorder, and cognitive decline in older patients.[113] [114]

Close observation and post-exposure oseltamivir or zanamivir chemoprophylaxis is recommended for healthcare workers after unprotected close exposure to a symptomatic, suspected, or confirmed HPAI H5N1 case (within 2 m) in the healthcare setting, as well as for household and close contacts of a patient with suspected or confirmed HPAI H5N1 virus infection.

Suspected cases should be reported immediately to public health authorities, who will assist with diagnostic evaluation, case management, and contact investigation.
# Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>primary influenza pneumonia</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Common complication of highly pathogenic avian influenza (HPAI) 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>respiratory failure</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>This is a common complication of highly pathogenic avian influenza (HPAI) H5N1 virus infection, usually due to ARDS. Has been documented among all affected age groups. Antiviral and supportive therapy is necessary.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute respiratory distress syndrome</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>The most common cause of respiratory failure. Evidence-based, lung protective ventilation strategies are recommended.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>multi-organ failure</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Multi-organ failure, including renal or cardiac compromise, is a common complication of severely ill highly pathogenic avian influenza (HPAI) H5N1 patients. Supportive therapy is crucial, as is targeted therapy where applicable. Management should follow evidence-based management guidelines.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sepsis</td>
<td>short term</td>
<td>medium</td>
</tr>
<tr>
<td>Septic shock requiring vasopressor support is a common complication of highly pathogenic avian influenza (HPAI) H5N1 virus infection. Treatment is supportive and should follow existing evidence-based guidelines for the management of septic shock.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>encephalitis</td>
<td>short term</td>
<td>low</td>
</tr>
<tr>
<td>Patients have headaches, behavioural disturbances, and altered mental status, and may have seizures and coma, as a direct result of virus infection. Encephalitis is an uncommon complication of highly pathogenic avian influenza (HPAI) H5N1 virus infection, but cases of CNS infection and detection of virus in CSF have been described. The underlying infection should be treated with antivirals as soon as possible, and supportive care provided as indicated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>death</td>
<td>variable</td>
<td>high</td>
</tr>
</tbody>
</table>
Avian influenza A (H5N1) virus infection

Follow up

Complications | Timeframe | Likelihood |
--- | --- | --- |
Occurs in about 53% of patients with highly pathogenic avian influenza (HPAI) H5N1 virus infection reported to WHO.[26] |  |  |

**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 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 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 rarely reported in highly pathogenic avian influenza (HPAI) H5N1 patients.[17]

Evaluation and treatment should follow evidence-based guidelines.

---

**Prognosis**

Nearly 53% of patients with confirmed highly pathogenic avian influenza (HPAI) H5N1 virus infection reported to the World Health Organization (WHO) have died since 2003.[26] Those who had progressive disease generally died from complications of ARDS and multi-organ failure. Early recognition of disease and early initiation of oseltamivir treatment may be associated with improved outcomes. The presence of rhinorrhoea appears to indicate a better prognosis for children with HPAI H5N1.[24]

Management should follow evidence-based clinical care guidelines for ARDS, septic shock, and other critical care illness. No studies have assessed the long-term sequelae of infection among survivors, but most survivors had only mild disease.
# Diagnostic guidelines

## Europe


*Published by:* Public Health England  
*Last published:* 2020

## International

**Clinical management of human infection with avian influenza A (H5N1) virus** (https://www.who.int/influenza/resources/documents/clinical_management_h5n1_15_08_2007/en/)

*Published by:* World Health Organization  
*Last published:* 2007

**Collecting, preserving and shipping specimens for the diagnosis of avian influenza A(H5N1) virus infection** (https://www.who.int/ihr/publications/WHO_CDS_EPR_ARO_2006_1/en/)

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

## North America

**Interim guidance on testing, specimen collection, and processing for patients with suspected infection with novel influenza A viruses with the potential to cause severe disease in humans** (https://www.cdc.gov/flu/avianflu/severe-potential.htm)

*Published by:* Centers for Disease Control and Prevention  
*Last published:* 2015

**Interim guidance for specimen collection, processing, and testing for patients with suspected infection with novel influenza A viruses associated with severe disease in humans** (https://www.cdc.gov/flu/avianflu/h7n9/specimen-collection.htm)

*Published by:* Centers for Disease Control and Prevention  
*Last published:* 2014

## Treatment guidelines

## Europe


*Published by:* Public Health England  
*Last published:* 2019
## International

**WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses**


**Published by:** World Health Organization  
**Last published:** 2010

**Clinical management of human infection with avian influenza A (H5N1) virus**


**Published by:** World Health Organization  
**Last published:** 2007

**WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus**


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

## North America

**CDC health information for international travel (Yellow Book) - influenza**


**Published by:** CDC health information for international travel (Yellow Book) - influenza  
**Last published:** 2019

**Community mitigation guidelines to prevent pandemic influenza - United States, 2017**


**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2017

**Interim guidance on follow-up of close contacts of persons infected with novel influenza A viruses associated with severe human disease and on the use of antiviral medications for chemoprophylaxis**


**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2015

**Interim guidance on the use of antiviral medications for treatment of human infections with novel influenza A viruses associated with severe human disease**


**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2015

**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**


**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2014
Online resources


2. WHO: cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO (https://www.who.int/influenza/human_animal_interface/HAI_Risk_Assessment/en/) (external link)

3. WHO: candidate vaccine viruses and potency testing reagents for influenza A (H5N1) (http://www.who.int/influenza/vaccines/virus/candidates_reagents/a_h5n1/en/) (external link)


5. CDC: avian influenza - information for health professionals and laboratorians (http://www.cdc.gov/flu/avianflu/healthprofessionals.htm) (external link)

6. CDC: information on avian influenza (http://www.cdc.gov/flu/avianflu/) (external link)
Key articles


• World Health Organization. WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. February 2010 [internet publication]. Full text (http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/)


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80. World Health Organization. WHO criteria for accepting positive PCR test results of H5 infection in humans from national reference laboratories. May 2011 [internet publication]. Full text (http://who.int/influenza/gisrs_laboratory/h5_reflabs/h5acceptancecriteria.pdf?ua=1)

81. World Health Organization. WHO accepts positive PCR test results of H5 infection in humans from the following laboratories. May 2011 [internet publication]. Full text (http://www.who.int/influenza/resources/documents/h5n1_PCR_laboratories/en/)


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Figure 1 – BMJ Best Practice Numeral Style
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