

## Outline

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Influenza A is not a reportable condition under Calif. law. However, health care providers are required to report any **UNUSUAL** disease to the local health department within **one hour**.

In the event of Avian Influenza outbreak, SFDPH will issue guidelines for case identification, infection control, and disease reporting, at [www.sfdph.org/cdcp](http://www.sfdph.org/cdcp).

SFDPH communicable disease control may be contacted by phone at 415-554-2830.

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## AGENT

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Influenza virus belongs to the Orthomyxovirus family and contains 8 different segments of negative-stranded RNA. There are 3 types: A, B, and C, distinguishable by internal virus proteins. Influenza A is responsible for most human influenza disease, causes avian influenza, and is the source of all past influenza pandemics in humans. Influenza B is a disease of humans only, while influenza C causes milder illness in both humans and swine and occurs uncommonly.

Influenza A is subtyped based on viral envelope glycoproteins hemagglutinin (HA) and neuraminidase (NA). There are 16 different HA antigens (H1 to H16) and 9 different NA antigens (N1 to N9) for influenza A. Human disease has historically been related to 3 subtypes of HA (H1, H2, and H3) and 2 subtypes of NA (N1 and N2).

Influenza A infects humans, birds, pigs, horses, whales, seals, and has recently been recognized in felines. Avian influenza A can infect a variety of domestic and wild bird species. Avian influenza in domestic chickens and turkeys is classified according to disease severity, with two recognized forms: highly pathogenic avian influenza (HPAI), and low-pathogenic avian influenza (LPAI). Avian influenza viruses that cause HPAI are highly virulent and mortality rates in infected flocks often approach 100%. All known subtypes of influenza A can be found in birds, but only subtypes H5 and H7 have caused HPAI outbreaks.

### **Influenza Pandemics**

Pandemics differ from seasonal outbreaks or “epidemics” of influenza, which are caused by subtypes of influenza viruses that already exist among people. A pandemic is a global outbreak that occurs when a new, highly pathogenic strain of influenza type A virus emerges in the human population and spreads easily from person-to-person worldwide, aided by the lack of human immunity to the novel strain.

Past influenza pandemics have led to high levels of illness, death, social disruption, and economic loss. There were 3 influenza A pandemics during the 20<sup>th</sup> century:

- 1918-19, "Spanish flu," (H1N1), caused >500,000 deaths in the USA and >50,000,000 deaths worldwide. Nearly half of those who died were young, healthy adults.
- 1957-58, "Asian flu," (H2N2), first identified in China in early 1957, it caused about 70,000 deaths in the USA by June 1957.
- 1968-69, "Hong Kong flu," (H3N2), caused about 34,000 deaths in the United States. Influenza A (H3N2) viruses still circulate today.

### **Influenza in Bird Populations**

All birds are believed susceptible to infection with avian influenza. Migratory waterfowl – most notably wild ducks – are the natural reservoir of avian influenza viruses, however domestic poultry, including chickens and turkeys, are particularly susceptible to epidemics of rapidly fatal influenza.

Recent research has shown that viruses of low pathogenicity can quickly mutate into highly pathogenic viruses. For example, during a 1999–2001 avian influenza epidemic in Italy, the H7N1 virus, initially of low pathogenicity, mutated within 9 months to a highly pathogenic form. More than 13 million birds died or were destroyed.

Standard control measures aimed at preventing spread of HPAI in a country’s poultry population include quarantining of infected farms and destruction of infected or potentially exposed flocks.

In the absence of prompt control measures backed by good surveillance, epidemics can last for years. For example, an epidemic of H5N2 avian influenza, which began in Mexico in 1992, started with low pathogenicity, evolved to the highly fatal form, and was not controlled until 1995.

### **Mechanism of Transmission to Humans**

Influenza A viruses are genetically labile and well adapted to elude host defenses. Influenza viruses lack mechanisms for the “proofreading” and repair of errors that occur during replication. As a result of these uncorrected errors, the genetic composition of a virus changes during passage through humans and animals, and the existing strain is replaced with a new antigenic variant. These changes in the antigenic composition of influenza A viruses are known as antigenic drift.

Influenza A viruses, including subtypes from different species, can also swap or reassort genetic materials. This process -- known as antigenic shift -- creates a novel virus subtype that differs genetically from both parent viruses. As populations will have no immunity to the new subtype, and as no existing vaccines can confer protection, antigenic shift has historically resulted in highly lethal pandemics. For this to happen, a subtype of avian influenza needs to acquire genes from human influenza viruses that enable person-to-person transmission.

Conditions favorable for the emergence of antigenic shift are thought to involve humans living in close proximity to domestic poultry and pigs. Because pigs are susceptible to infection with both avian and mammalian viruses, including human strains, they can serve as a "mixing vessel" for the scrambling of genetic material from human and avian viruses, resulting in the emergence of a novel subtype. In addition, evidence is mounting that, for at least some avian influenza virus subtypes circulating in bird populations, humans themselves can serve as the "mixing vessel".

### **The Current H5N1 Threat**

Of the avian influenza subtypes, currently the H5N1 subtype is of greatest pandemic concern for the following reasons:

- Rapid spread throughout poultry flocks in Asia; now appears to be endemic in eastern Asia
- Mutates rapidly
- Propensity to acquire genes from viruses infecting other animal species
- Causes severe disease in humans, with a high case-fatality rate (approx. 70%)
- There is ongoing exposure and infection of humans in rural Asia, where many households keep free-ranging poultry flocks for income and food

The first documented infection of humans with an avian influenza virus occurred in Hong Kong in 1997, when the H5N1 strain caused severe respiratory disease in 18 humans, of whom 6 died. The infection of humans coincided with an epidemic of HPAI, caused by the same strain, in Hong Kong's poultry population. Close contact with live infected poultry was the source of human infection, and the virus was shown to have jumped directly from birds to humans. Transmission to health care workers occurred, but did not cause severe disease. Rapid destruction of Hong Kong's entire poultry population, estimated at around 1.5 million birds, reduced opportunities for further direct transmission to humans, and may have averted a pandemic.

Alarms have continued to mount since 2003, when an outbreak of HPAI caused by the H5N1 strain spread rapidly through poultry farms in southeastern Asia. Areas currently affected by H5N1 avian influenza in poultry include Cambodia, China (both Taiwan and the People's Republic of China), Hong Kong, Indonesia, Japan, Laos, Malaysia, Philippines, South Korea, Thailand, and Vietnam. Over 140 million chickens have been slaughtered to halt spread of the virus.

The strain circulating in Asia appears highly pathogenic for humans, and immunity in the human population is generally lacking. If H5N1 continues to circulate widely among poultry, the potential

for emergence of a pandemic strain remains high. Human cases of H5N1 have been reported officially in Vietnam, Thailand, and Cambodia. Between December 26, 2003 and June 28, 2005, the WHO has tallied 108 laboratory-confirmed cases of H5N1 influenza in humans (54 of them fatal). Probable person-to-person transmission was identified in Thailand involving transmission from an ill child to her mother and aunt. However, the strain has not yet been shown to be easily transmitted between humans, and sustained person-to-person transmission has not occurred.

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## CLINICAL FEATURES

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Typical clinical features of influenza A are shown in the following table.

<b>INFLUENZA A: CLINICAL FEATURES</b>	
<b>Incubation Period</b>	1-2 days
<b>Signs &amp; Symptoms</b>	<p>Initially, systemic symptoms predominate</p> <ul style="list-style-type: none"> <li>• Fever (duration 3 days, range 2-8 days)</li> <li>• Chills, malaise, headache, myalgias, arthralgias, anorexia, toxic appearance, occasionally prostration</li> <li>• Dry cough, pharyngeal pain, rhinorrhea</li> </ul> <p>Convalescent period lasts 1-3 weeks</p> <ul style="list-style-type: none"> <li>• Cough, lassitude, and malaise</li> </ul>
<b>Complications</b>	<ul style="list-style-type: none"> <li>• Primary influenza pneumonia; rapid progression of fever, cough, dyspnea, cyanosis</li> <li>• Secondary bacterial pneumonia</li> <li>• Croup</li> <li>• Exacerbation of COPD</li> <li>• Myositis; myoglobinuria</li> <li>• Myocarditis; pericarditis</li> <li>• Toxic shock syndrome</li> <li>• Encephalitis (rare)</li> </ul>
<b>Laboratory Findings</b>	<ul style="list-style-type: none"> <li>• WBC often normal (unless secondary bacterial process: elevated with left shift)</li> <li>• Sputum gram stain unremarkable (unless secondary bacterial pneumonia)</li> <li>• CXR usually normal in uncomplicated influenza; usually shows infiltrates and/or consolidation when pneumonia present</li> </ul>

In an outbreak of avian influenza among humans, the clinical picture of primary viral pneumonia may predominate. However given that the virus responsible for human-to-human transmission will be a novel strain, the specifics of its clinical presentation will not be known until the outbreak actually occurs. A recent report of avian influenza A (H5N1) in 10 patients in Vietnam demonstrated the following clinical features of the illness:

- Incubation period was 2-4 days (mean 3 days)
- 10/10 presented with fever, shortness of breath, and cough

- 5/10 reported sputum production; in 3 of these, sputum was blood-tinged.
- 7/10 reported diarrhea.
- None complained of sore throat, conjunctivitis, rash, or a runny nose.
- 10/10 had abnormal CXR at the time of hospital admission (including extensive bilateral infiltration, lobar collapse, focal consolidation, and air bronchograms).
- 10/10 had lymphopenia, and 9/10 had thrombocytopenia at presentation
- 10/10 received broad-spectrum antibiotics
- 5/10 were treated with oseltamivir (4 of whom died)
- 8/10 died

A recent case report of a 4-year-old Vietnamese child with H5N1 avian influenza who presented in 2004 with encephalitis demonstrated the following features:

- The child presented with a 2-day history of fever, headache, vomiting, and severe diarrhea
- Laboratory tests on admission were unremarkable and chest x-ray was normal.
- On day 3, the child had a generalized convulsion and became comatose. He developed respiratory failure and died on day 5.
- H5N1 influenza A virus was isolated from CSF, fecal, throat, and serum specimens.
- Acute encephalitis was reported as the cause of death

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## SURVEILLANCE AND DIAGNOSIS

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As of this writing, CDC recommendations issued February 2004 (and re-affirmed February, 2005) for enhanced surveillance of patients at risk for avian influenza are still in effect. These are:

1) Testing for influenza A(H5N1) in the USA is indicated for hospitalized patients with:

- Radiographically confirmed pneumonia, acute respiratory distress syndrome (ARDS), or other severe respiratory illness for which an alternate diagnosis has not been established, AND
- History of travel within 10 days of symptom onset to a country with documented H5N1 avian influenza in poultry and/or humans. (List of H5N1-affected countries available at [www.who.int/topics/avian\\_influenza](http://www.who.int/topics/avian_influenza))

2) Testing for influenza A(H5N1) should be considered on a case-by-case basis in consultation with the local health department for hospitalized or ambulatory patients with:

- Documented temperature of >38°C (>100.4°F), AND

**If you consider testing for Avian Influenza, you should:**

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830) to facilitate testing and initiate the public health response. Testing for H5N1 subtype of influenza A occurs as specialized labs and requires SFDPH authorization.**
- **Inform your laboratory that Avian Influenza is under suspicion, so that they may follow the appropriate biosafety procedures.**

- At least one: cough, sore throat, shortness of breath, AND
- History of contact with domestic poultry (e.g., visited a poultry farm, household raising poultry, or bird market) or a known or suspected human case of influenza A(H5N1) in an H5N1-affected country within 10 days of symptom onset.

Clinical specimens from suspect influenza A(H5N1) cases may be tested by PCR assays under strict biosafety precautions at public health reference laboratories. Virus isolation studies carry higher risks of inadvertent transmission and require even more stringent precautions.

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## TREATMENT AND PROPHYLAXIS

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**Detailed guidelines for Avian Influenza treatment/prophylaxis have not yet been issued. For updates and situational guidance in response to events, check [www.sfdph.org/cdcp](http://www.sfdph.org/cdcp).**

### Antiviral Agents

There are 2 key uncertainties that challenge planning for administration of antiviral agents in the event of an avian influenza outbreak among humans. First, it is unclear how much antiviral drug will be available in the event of a large-scale outbreak. Second, the influenza strain responsible for the outbreak and its profile of antibiotic resistance may not be fully known in advance.

There are 2 classes of antiviral agents for influenza: adamantanes (amantadine and rimantadine), and neuraminidase inhibitors (zanamivir and oseltamivir). The drugs differ in cost, routes of administration, adverse events, contraindications, and potential for antiviral resistance.

<b>CHARACTERISTICS OF ANTI-INFLUENZA ANTIVIRAL AGENTS</b>				
	<b>Adamantane Derivatives</b>		<b>Neuraminidase Inhibitors</b>	
	<b>Amantadine</b>	<b>Rimantadine</b>	<b>Oseltamivir</b>	<b>Zanamivir</b>
<b>Route</b>	Oral	Oral	Oral	Inhalation
<b>Treatment License</b>	≥1 year old	>1 year old	≥13 years old	Not FDA Approved
<b>Prophylaxis License</b>	≥1 year old	Adults	≥1 year old	≥7 years old
<b>Selected Adverse Events</b>	CNS (dizziness, insomnia, seizures, suicidality); GI (nausea); some reports cardiac toxicity	CNS (e.g. insomnia, dizziness), GI (e.g. nausea, vomiting)	GI (principally nausea, vomiting)	Poss. bronchospasm and decrease in lung function, esp. in patients with underlying airway disease

*Adapted from: DHHS Pandemic Influenza Response & Preparedness Plan, Aug. 26, 2004*

Both classes of drugs reduce duration of uncomplicated influenza when started within 2 days of illness onset. However, there are no controlled studies of patients infected with influenza A(H5N1).

### **Vaccine Development**

Influenza vaccine must be both subtype- and strain-specific. Candidate vaccines against H5N1 subtype were developed during 2003 for protection against the strain that was isolated from humans in Hong Kong in February of that year. However, the current strain is different. Clinical trials of additional candidate H5N1 vaccines are currently under way. However, it is not clear if prototype H5 vaccines will offer protection against an emergent pandemic strain, and WHO has indicated that 4-6 months (minimum) would be needed to develop a vaccine against a novel strain.

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## **INFECTION CONTROL\***

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**These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events ([www.sfdph.org/cdcp](http://www.sfdph.org/cdcp)).**

### **Poultry Workers**

Birds that are infected with avian influenza viruses can shed virus in saliva, nasal secretions, and feces. Activities that could result in exposure to avian influenza-infected poultry include euthanasia, carcass disposal, and cleaning and disinfection of premises affected by avian influenza. These activities are unlikely to occur in an urban area such as San Francisco. However, the CDC has written interim guidance for protection of persons involved in control of avian influenza outbreaks among poultry in the USA ([www.cdc.gov/flu/avian/professional/protect-guid.htm](http://www.cdc.gov/flu/avian/professional/protect-guid.htm)).

### **Health Care Providers**

Human influenza is transmitted primarily via large respiratory droplets, and isolation precautions for typical human influenza include Standard plus Droplet Precautions. However, the CDC has recommended additional precautions for healthcare workers involved in the care of patients with documented or suspected avian influenza, for the following reasons: 1) higher risk of serious disease and increased mortality from HPAI; 2) each human infection represents an important opportunity for avian influenza to further adapt to humans and gain the ability to transmit more easily among people; and 3) any opportunities for human-to-human transmission of avian influenza may increase opportunities for genetic reassortment and possible emergence of a pandemic strain.

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\* For description of Precautions, see Chapter on Infection Control

The most recent (May, 2004) CDC recommendations state:

- All patients who present to a health-care setting with fever and respiratory symptoms should be managed according to recommendations for respiratory hygiene and cough etiquette ([www.cdc.gov/flu/professionals/infectioncontrol](http://www.cdc.gov/flu/professionals/infectioncontrol)) and questioned regarding their recent travel history.
- Patients with a history of travel within 10 days to a country with avian influenza activity and who are hospitalized with a severe febrile respiratory illness, or are otherwise under evaluation for avian influenza, should be managed using **Standard plus Contact plus Airborne Precautions**. In addition, **Eye Protection** should be utilized when within 3 feet of the patient. These precautions should be continued for 14 days after onset of symptoms or until either an alternative diagnosis is established or diagnostic test results indicate that the patient is not infected with influenza A virus.
- Patients managed as outpatients or hospitalized patients discharged before 14 days with suspected avian influenza should be isolated in the home setting, following CDC guidelines for home isolation of SARS patients ([www.cdc.gov/ncidod/sars/guidance/i/pdf/i.pdf](http://www.cdc.gov/ncidod/sars/guidance/i/pdf/i.pdf)).

CDC guidance also recommends that healthcare workers who may come into contact with the H5N1 virus or with infected patients should be vaccinated with the most recent seasonal influenza vaccine. Although this will not protect against H5N1 influenza A, it will help avoid simultaneous infection with other influenza strains and may thereby decrease the risk of genetic reassortment.

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## REFERENCES

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CDC. Interim Guidance for Protection of Persons Involved in U.S. Avian Influenza Outbreak Disease Control and Eradication Activities. Feb. 17, 2004. ([www.cdc.gov/flu/avian/professional/protect-guid.htm](http://www.cdc.gov/flu/avian/professional/protect-guid.htm))

CDC. Update on Influenza A(H5N1) and SARS: Interim Recommendations for Enhanced U.S. Surveillance, Testing, and Infection Controls. February 3, 2004. ([www.cdc.gov/flu/avian/professional/han020302.htm](http://www.cdc.gov/flu/avian/professional/han020302.htm))

CDC. Interim Recommendations for Infection Control in Health-Care Facilities Caring for Patients with Known or Suspected Avian Influenza. May 21, 2004. ([www.cdc.gov/flu/avian/professional/infect-control.htm](http://www.cdc.gov/flu/avian/professional/infect-control.htm))

CIDRAP. Pandemic Influenza. July 1, 2005. ([www.cidrap.umn.edu/cidrap/content/influenza](http://www.cidrap.umn.edu/cidrap/content/influenza))

CIDRAP. Avian Influenza (Bird Flu): Implications for Human Disease. July 13, 2005. ([www.cidrap.umn.edu/cidrap/content/influenza](http://www.cidrap.umn.edu/cidrap/content/influenza))

De Jong MD et al. Fatal avian influenza A (H5N1) in a child presenting with diarrhea followed by coma. *N Engl J Med* 2005; 352: 686-91.

DHHS: Department of Health and Human Services Pandemic Influenza Response and Preparedness Plan. August 26, 2004. ([www.dhhs.gov/nvpo/pandemicplan](http://www.dhhs.gov/nvpo/pandemicplan))

Hien TT et al. Avian influenza (H5N1) in 10 patients in Vietnam. *NEJM* 2004; 350(12): 1179-88.

Treanor, JJ. Influenza Virus. In: *Principles and Practice of Infectious Diseases*, 6th edition; Gerald Mandell et al, Eds. Elsevier, 2005.

WHO. Global Influenza Preparedness Plan 2005 (WHO/CDS/CSR/GIP/2005.5). Available at: <http://www.who.int/csr/disease/influenza/inforesources/en/>

WHO. Avian influenza ("bird flu") and the significance of its transmission to humans. 15 January 2004. ([www.who.int/mediacentre/factsheets/avian\\_influenza](http://www.who.int/mediacentre/factsheets/avian_influenza))

WHO. International conference draws up strategy to fight avian influenza. 06 July 2005 ([www.wpro.who.int/health\\_topics/avian\\_influenza/](http://www.wpro.who.int/health_topics/avian_influenza/))

WHO. Cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO. 28 June 2005.