

# High Pathogenicity Avian Influenza

*Fowl Plague, Grippe Aviaire*

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the Center for  
Food Security  
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IOWA STATE UNIVERSITY®

College of Veterinary Medicine  
Iowa State University  
Ames, Iowa 50011  
Phone: 515.294.7189  
Fax: 515.294.8259  
cfsph@iastate.edu  
www.cfsph.iastate.edu



INSTITUTE FOR  
INTERNATIONAL  
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## Importance

Avian influenza viruses are highly contagious, extremely variable viruses that are widespread in birds, particularly wild waterfowl and shorebirds. Most of these viruses, which are usually carried asymptotically by wild birds, cause only mild disease in poultry. These viruses are called low pathogenicity avian influenza (LPAI) viruses. Others, the high pathogenicity avian influenza (HPAI) viruses, can kill up to 90-100% of a poultry flock. Epidemics of high pathogenicity avian influenza can spread rapidly, devastate the poultry industry and result in severe trade restrictions. Some avian influenza viruses can also infect mammals including humans. The severity of zoonotic avian influenza varies with the virus. Although many human infections are limited to conjunctivitis or mild respiratory disease, some viral strains cause severe disease and death. Generally, avian influenza viruses do not spread efficiently in mammals, and infections are limited to individual animals or small groups. However, some viruses can become adapted to a new species and cause epidemics or pandemics.

HPAI viruses have been eliminated from domesticated poultry in many nations including the U.S. and Canada; however, these viruses can be reintroduced from imported poultry, wild birds or pet birds. It is possible for wild birds to carry HPAI viruses, but historically this seems to be rare. More often, wild birds transmit LPAI viruses to poultry, and these viruses then mutate to become HPAI viruses while they are circulating in poultry flocks. Although HPAI outbreaks can be devastating, the virus is successfully eradicated in most cases. However, the world is currently experiencing an extensive avian influenza outbreak that has no immediate prospects for complete, worldwide eradication. In 2003, HPAI viruses of the H5N1 subtype appeared among poultry in several nations in Southeast Asia. Although at times this epidemic appeared to be under control, eradication was never complete. The outbreaks continued to smolder and spread, and eventually Asian lineage H5N1 viruses reached other parts of Asia, Europe, Africa and the Middle East. The strains responsible for this epidemic appear to be unusually virulent. They have been found in many species of wild birds, which is unusual, and numerous deaths have been reported in these species. As of January 2010, these viruses have also been responsible for approximately 470 human infections, generally as the result of close contact with poultry; about 60% of these cases were fatal. Asian lineage H5N1 viruses have caused disease in other mammals including housecats, several species of large felids, palm civets, raccoon dogs, stone martens, a dog and a mink. Some of these infections were fatal. In addition, these viruses have been detected in pigs and pikas, and experimental infections have been established in a variety of species including foxes, ferrets, rodents and rabbits. There are fears that an Asian lineage H5N1 virus could eventually become adapted to humans, resulting in a severe human pandemic.

## Etiology

Avian influenza results from infection by viruses in the *influenzavirus A* genus and influenza A species of the family Orthomyxoviridae. These viruses are also called type A influenza viruses. In addition to avian influenza viruses, this species includes the closely related human, equine, swine and canine influenza viruses. Influenza A viruses are classified into subtypes based on two surface antigens, the hemagglutinin (H) and neuraminidase (N) proteins. There are 16 hemagglutinin antigens (H1 to H16) and nine neuraminidase antigens (N1 to N9). These two proteins are involved in cell attachment and release from cells. They are also major targets for the immune response. Subtypes of influenza A viruses are classified into strains. Strains of influenza viruses are described by their type, host, place of first isolation, strain number (if any), year of isolation, and antigenic subtype. For example, one H5N1 virus isolated from chickens in Hong Kong in 1997 is A/chicken/Hong Kong/y385/97 (H5N1). For human strains, the host is typically omitted.

Avian influenza viruses are classified as either HPAI or LPAI viruses, based on the genetic features of the virus and the severity of disease in experimentally infected chickens. Although there are exceptions (e.g., viruses that fit the genetic description of HPAI viruses but cause mild illness), HPAI viruses usually cause severe disease in

# Highly Pathogenic Avian Influenza

poultry, while LPAI infections are generally much milder. To date, only subtypes containing H5 or H7 have been highly pathogenic; subtypes that contained other hemagglutinins have been found only in the LPAI form. H5 and H7 LPAI viruses also exist, and these strains can evolve into high pathogenicity strains. The LPAI viruses found in wild birds can be divided into Eurasian and American lineages. Although viruses occasionally cross between these two geographic regions, this is uncommon. When a subtype has become established and has circulated for a time, numerous variants may occur in the population. For example, multiple genotypes and a number of clades of Asian lineage H5N1 viruses are currently found among poultry.

Waterfowl and shorebirds, which seem to be the natural reservoirs for influenza A viruses, carry all of the known H and N antigens, usually in the LPAI form. The predominant subtypes in wild ducks change periodically. H3, H4 and H6 viruses are detected most often in North American and northern European wild ducks, but nearly all hemagglutinin and neuraminidase antigens can be found. Waders (families Charadriidae and Scolopacidae) seem to have a wider variety of hemagglutinin/neuraminidase combinations than ducks. In the eastern U.S., H1 through H12 (LPAI) viruses have been isolated from these birds; H1, H2, H5, H7 and H9-H12 viruses are particularly common. Gulls are often infected with H13 LPAI viruses, which are rare in other avian species. They can also carry H16 viruses.

Limited information is available on the subtypes found in other species of birds. Subtypes that have been detected in ratites include H3N2, H4N2, H4N6, H5N1, H5N2, H5N9, H7N1, H7N3, H9N2, H10N1, H10N4 and H10N7. Isolates from cage birds usually contain H3 or H4; however, infections with high pathogenicity subtypes containing H7 or H5 can also occur. Very few avian influenza viruses were found in wild passerine birds, pigeons and doves in one survey.

## **Antigenic shift and drift in influenza A viruses**

Influenza A viruses can change frequently. Strains evolve as they accumulate point mutations during virus replication; this process is sometimes called 'antigenic drift'. A more abrupt change can occur during genetic reassortment. Reassortment is possible whenever different influenza viruses infect a cell simultaneously; when the new viruses (the 'progeny') are assembled, they may contain some genes from one parent virus and some genes from the other. Reassortment between two different strains results in the periodic emergence of novel strains. Reassortment between subtypes can result in the emergence of a new subtype. Reassortment can also occur between avian, swine, equine and human influenza A viruses. This type of reassortment can result in a 'hybrid' virus with, for example, both avian and human influenza virus proteins.

An abrupt change in the subtypes found in host species is called an 'antigenic shift.' Antigenic shifts can result from three mechanisms: 1) genetic reassortment between subtypes, 2) the direct transfer of a whole virus from one host species into another, or 3) the re-emergence of a virus that was found previously in a species but is no longer in circulation. Antigenic drift and antigenic shifts result in the periodic emergence of novel influenza viruses. By evading the immune response, these viruses can cause influenza epidemics and pandemics.

## **Avian influenza virus infections in mammals**

Avian influenza viruses are closely related to influenza A viruses found in humans, horses, pigs and dogs. Ordinarily, the influenza viruses found in each species infect only that species. However, occasionally a virus from one species may infect another species. This can happen in two ways. If two viruses from different species infect a cell simultaneously, the gene segments can reassort when new virus particles are assembled. For example, if a cell is infected by an avian and a human influenza virus, the new viruses budding from that cell might contain some segments from the avian influenza virus and others from the human influenza virus. An avian influenza virus that contained some genes from a human influenza virus might be able to establish itself in humans.

Sometimes, an influenza virus can also jump 'whole' from one species to another. For instance, avian influenza viruses have been known to jump from birds into people, cats, mink, seals, horses and other animals. Usually, the virus is poorly adapted to the new species, cannot be transmitted efficiently, and quickly dies out. Occasionally, a virus can replicate and be transmitted in the new host species, and a permanent jump is made. Although cross-species transmission is a rare event, it may be followed by an epidemic or pandemic, since the new host has no immunity to the new virus. For an epidemic to occur, three requirements must be met: 1) a new influenza virus subtype must emerge in a species with little or no immunity to that subtype, 2) the virus must produce disease in that species, and 3) there must be sustainable transmission in the new species. As of January 2010, the Asian lineage H5N1 viruses have met the first two criteria in humans and some other mammals. However, efficient or sustainable transmission has not been reported in any species with the possible exception of pikas. H5N1 viruses have recently been reported to circulate among pikas in China, apparently without causing significant illness.

## **Geographic Distribution**

Avian influenza (LPAI) viruses occur worldwide in wild birds and poultry. HPAI viruses have been eradicated from domesticated poultry in most developed nations. The Asian lineage H5N1 HPAI outbreak began among poultry in Southeast Asia in 2003. From 2003 to 2008, it spread into domesticated or wild birds in other

# Highly Pathogenic Avian Influenza

regions of Asia as well as parts of Europe, the Pacific, the Middle East and Africa. Although some countries have eradicated the virus from their domesticated poultry, this epidemic is ongoing and worldwide eradication is not expected in the short term.

## Transmission

In birds, avian influenza viruses are shed in the feces as well as in saliva and nasal secretions. The feces contain large amounts of virus, and fecal-oral transmission is usually the predominant means of spread in wild bird reservoirs. Fecal-cloacal transmission might also be possible. Fecal transmission is facilitated by the persistence of avian influenza viruses in aquatic environments for prolonged periods, particularly at low temperatures. Respiratory transmission of LPAI viruses is thought to be unimportant in most wild birds; however, it is possible that it might play a role in some species, particularly those that live on land. Some recent isolates of Asian lineage H5N1 (HPAI) viruses have been found in higher quantities in respiratory secretions than the feces. This suggests that, at least in some wild birds, these strains may no longer be transmitted primarily by the fecal-oral route.

Once an avian influenza virus has entered a poultry flock, it can spread on the farm by both the fecal-oral route and aerosols, due to the close proximity of the birds. Fomites can be important in transmission, and flies may act as mechanical vectors. HPAI viruses have also been found in the yolk and albumen of eggs from infected hens. Although these eggs are unlikely to hatch, broken shells could transmit the virus to other chicks in the incubator.

In countries where HPAI has been eradicated from domesticated poultry, influenza viruses can be introduced into flocks by migratory waterfowl or shorebirds, as well as by infected poultry, pet birds or fomites. Migrating birds, which can fly long distances, may exchange viruses with other populations at staging, stopover or wintering sites. Wild birds usually carry only the low pathogenicity form of avian influenza viruses. Once they are introduced into poultry, these viruses reassort and/or mutate to produce HPAI viruses. However, the Asian lineage HPAI H5N1 strains appear to occur regularly in wild birds, although their importance in transmitting these viruses to poultry is controversial. HPAI H5N2 viruses have also been detected recently in some asymptomatic wild ducks and geese in Africa.

### *Survival of influenza viruses in the environment*

The survival of avian influenza viruses in the environment is influenced by temperature, pH, salinity and the presence of organic material. These viruses, which are often transmitted between birds in feces, may persist for relatively long periods in aquatic environments. They appear to survive best at low temperatures and in fresh or brackish water rather than salt water. LPAI

viruses are reported to persist in distilled water for more than 100 days at 28°C (82°F) and 200 days at 17°C (63°F). These viruses also remained viable for at least 35 days in peptone water at 4°C (39°F), 30°C (86°F) or 37°C (98.6°F). Various avian influenza viruses were reported to survive for four weeks at 18°C (64°F). One recent study suggested that H5 and H7 HPAI viruses may survive for shorter periods in water than LPAI viruses; however, they still persisted in fresh water for 100 days or more at 17°C (63°F) and for approximately 26 to 30 days at 28°C (82°F). Avian influenza viruses might survive indefinitely when frozen.

A few studies have examined virus persistence in feces. In one study, LPAI viruses (H7N2) persisted for up to two weeks in feces and on cages. These viruses could survive for up to 32 days at 15-20°C (59-68°F), and for at least 20 days at 28-30°C (82-86°F), but they were inactivated more quickly when mixed with chicken manure. In other studies, LPAI viruses were reported to survive for at least 44 or 105 days in feces.

### *Transmission of avian influenza viruses to mammals*

Some avian influenza viruses can be transmitted to mammals by direct or indirect contact. Transmission is best understood for the Asian lineage H5N1 (HPAI) viruses. Close contact with dead or sick birds seems to be the principal way this virus is spread to humans, but a few cases may have resulted from indirect exposure via contaminated feces, and swimming in contaminated water is theoretically a source of exposure. Ingestion of H5N1 viruses has been reported in naturally infected housecats, other felids and dogs; experimentally infected cats, pigs, ferrets, mice and foxes; and rarely in humans. One Asian lineage H5N1 infection occurred in a dog that had eaten infected duck carcasses. Similarly, leopards and tigers in zoos, as well as some housecats, were apparently infected when they ate raw birds. Infected housecats in an animal shelter probably ingested contaminated feces from a swan while they were grooming, but aerosol transmission could not be ruled out. Infected raccoon dogs in China were fed chicken carcasses, and might have acquired the H5N1 virus from this source. In humans, the strongest evidence for oral transmission is that two people became infected with an Asian lineage H5N1 virus after eating uncooked duck blood. There are other human cases where ingestion probably occurred, but additional routes of exposure also existed.

Experimental studies suggest that Asian lineage H5N1 viruses can be transmitted to mammals by the respiratory, oral and intraocular routes; however, all routes have not been reported in each species. Infections have been established in cats by intratracheal inoculation with Asian lineage H5N1 viruses and by feeding them H5N1-infected chicks. Cats appear to shed these viruses from the intestinal tract as well as the respiratory tract.

# Highly Pathogenic Avian Influenza

Pigs and foxes can also be infected by feeding them H5N1-infected poultry, as well as by intranasal or intratracheal inoculation. Infected foxes can excrete this virus in both respiratory secretions and feces, but pigs are known to shed it only from the respiratory tract. In experimentally infected dogs, Asian lineage H5N1 viruses have been found in respiratory secretions, but fecal shedding has not been reported. In one experiment, cattle excreted small amounts of H5N1 viruses from the respiratory tract after intranasal inoculation; a high dose of the virus, which had been recovered from cats, was used to inoculate the cattle. Fecal shedding of Asian lineage H5N1 virus may also be possible in humans: this virus has been recovered from a child with diarrhea. In addition, it may be found in the urine of some mammals.

The eye might act as an entry point for some HPAI viruses. After intraocular inoculation of mice and ferrets with H7 and H5N1 (HPAI) isolates, the viruses could be detected in the respiratory tract and caused systemic disease. Transplacental transmission of avian influenza viruses is not well studied in mammals; however, viral antigens and nucleic acids were detected in the fetus of a woman who died of an Asian lineage H5N1 infection.

As of January 2010, little or no host-to-host transmission of H5N1 viruses has been seen in mammals, with the possible exception of pikas. Limited animal-to-animal transmission has been reported among zoo tigers, as well as in experimentally infected housecats. No animal-to-animal transmission was reported in the asymptomatic cats infected by exposure to a sick swan, or in experimentally infected pigs. In one study, Asian lineage H5N1 virus was not transmitted to one dog or three cats in contact with four experimentally infected dogs, or to three dogs in contact with infected cats. However, there is recent evidence that these viruses might have become established among some pika populations in China. In humans, only rare cases of limited person-to-person spread have been documented, and these cases occurred after close, prolonged contact. Sustained human-to-human transmission has not been reported, as of January 2010. Viral antigens and nucleic acids were detected in the fetus of a pregnant woman who died of her illness, suggesting that transplacental transmission may be possible in some species.

## Disinfection

The influenza viruses are susceptible to a wide variety of disinfectants including sodium hypochlorite, 70% ethanol, oxidizing agents, quaternary ammonium compounds, aldehydes (formalin, glutaraldehyde, formaldehyde), phenols, acids, povidone-iodine and lipid solvents. They can also be inactivated by heating to 56°C (133°F) for a minimum of 60 minutes, as well as by ionizing radiation or low pH (pH 2). Avian influenza viruses seem to be more resistant to high temperatures and low pH than mammalian influenza viruses.

## Infections in Humans

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### Incubation Period

The incubation period for avian influenza is difficult to determine in humans. Human influenza viruses usually cause disease in one to four days. Limited data from Asian lineage H5N1 infections suggest that the incubation period for this virus may range from two to eight days and could be as long as 17 days. In most cases, the first symptoms appear in two to five days. The World Health Organization (WHO) currently suggests using an incubation period of seven days for field investigations and monitoring patient contacts.

### Clinical Signs

Infections with avian influenza viruses have occasionally been reported in humans. Healthy children and adults, as well as those with chronic medical conditions, have been affected. Some infections have been limited to conjunctivitis and/or typical influenza symptoms; other cases, especially those caused by Asian lineage H5N1 viruses, were serious or fatal.

#### *Asian lineage H5N1 viruses*

The Asian lineage H5N1 HPAI viruses appear to cause more severe disease than other HPAI viruses or LPAI viruses. High fever and upper respiratory symptoms resembling human seasonal influenza tend to be the initial signs. In some patients, there may also be mucosal bleeding, or gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain. Respiratory signs are not always present at diagnosis; two patients from southern Vietnam had acute encephalitis without symptoms to indicate respiratory involvement. Similarly, a patient from Thailand exhibited only fever and diarrhea. Many patients develop lower respiratory tract disease shortly after the first signs; the symptoms may include chest pain, dyspnea, tachypnea, hoarseness of the voice and crackles during inspiration. The respiratory secretions and sputum are sometimes blood-tinged. Most patients deteriorate rapidly. Heart failure, kidney disease, encephalitis and multiorgan dysfunction are common in the later stages, and disseminated intravascular coagulation can occur. Milder cases have been reported occasionally, particularly among children. One H5N1 infection in a child with upper respiratory signs and an uncomplicated recovery after antibiotic treatment was recognized only by routine virus surveillance. Asymptomatic infections with Asian lineage H5N1 viruses seem to be rare.

The following human infections with Asian lineage H5N1 and other HPAI and LPAI avian influenza viruses were reported between 1997 and 2009:

- In 1997, the first eighteen H5N1 HPAI infections in people were reported during an HPAI outbreak among poultry in Hong Kong. The symptoms included fever, sore throat and cough and, in some cases, severe respiratory distress and viral

# Highly Pathogenic Avian Influenza

pneumonia. Eighteen people were hospitalized and six died.

- In 1999, avian influenza (LPAI H9N2) was confirmed in two children with upper respiratory signs, fever, sore throat, abdominal pain and vomiting in Hong Kong. The illnesses were mild and both children recovered. No other cases were found. Six unrelated H9N2 infections associated with acute respiratory disease were also reported from mainland China in 1998-99; all six people recovered
- In 2002, antibodies to an avian H7N2 virus were found in one person after an LPAI outbreak among poultry in Virginia.
- In 2003, two HPAI H5N1 infections were reported in a Hong Kong family that had traveled to China. One of the two people died. Another family member died of a respiratory illness while in China, but no testing was done.
- In 2003, 347 total (suspected and confirmed) and 89 confirmed human infections were associated with an H7N7 HPAI outbreak among poultry in the Netherlands. Most cases occurred in poultry workers, but three family members also became ill. In 78 of the confirmed cases, conjunctivitis was the only sign of infection. Two people had influenza symptoms such as fever, coughing and muscle aches. Five had both conjunctivitis and influenza-like illnesses. (Four cases were classified as “other.”) The single death occurred in an otherwise healthy veterinarian who developed acute respiratory distress syndrome and other complications. His initial symptoms included a persistent high fever and headache but no signs of respiratory disease. The virus isolated from the fatal case had accumulated a significant number of mutations, while viruses from most of the other individuals had not. This virus also caused severe or fatal infections in experimentally infected ferrets and mice, while other H7 viruses from milder human cases in North America were significantly less virulent.
- Cases of conjunctivitis have been reported after contact with HPAI H7N7 avian viruses from infected seals.
- In 2003, an H9N2 LPAI infection was confirmed in a child in Hong Kong. The symptoms included mild fever, mild dehydration and cough. The child was hospitalized but recovered.
- In 2003, an LPAI H7N2 infection with respiratory signs was reported in a patient in New York. The person, who had serious underlying medical conditions, was hospitalized but recovered.
- In 2004, two cases of conjunctivitis and flu-like symptoms were confirmed in poultry workers in Canada. One virus was LPAI; the other was HPAI.

Both people recovered after treatment with an antiviral drug. Ten other infections were suspected but not confirmed; these cases included both conjunctivitis and upper respiratory symptoms. All of the infections were associated with an H7N3 virus outbreak in poultry.

- From 2004 to 2008, sporadic human illness and deaths were associated with widespread outbreaks of Asian lineage H5N1 high pathogenicity avian influenza among poultry. As of December 31 2009, 467 confirmed human cases had been reported to WHO; 282 cases were fatal.
- In 2007, a mild LPAI H9N2 virus infection was reported in a 9-month-old child in Hong Kong.
- In 2008, an H9N2 virus was found in a 2-month-old infant in China.
- In 2009, an H9N2 virus infection was reported in a 3-year-old child with a fever, cough and rhinorrhea in Hong Kong. She was hospitalized but recovered. There is no indication in the report that this case was more severe than the previously reported infections.

## Communicability

Rare cases of probable person-to-person transmission, and no cases of sustained transmission, have been reported in humans infected with avian influenza viruses. Fecal shedding of an Asian lineage H5N1 virus has been documented in a child with diarrhea. Transplacental transmission of this virus may be possible.

## Diagnostic Tests

Avian influenza viruses can be identified by reverse transcription polymerase chain reaction (RT-PCR) tests, antigen detection or virus isolation. RT-PCR is usually the primary test for infection with Asian lineage H5N1 viruses. Virus isolation is done at World Health Organization (WHO) H5 Reference Laboratories. In the U.S., samples that test positive by RT-PCR or antigen tests are confirmed by the Centers for Disease Control and Prevention (CDC). RT-PCR and antigen testing of avian influenza viruses must be carried out in Biosafety Level (BSL) 2 laboratory conditions. Enhanced BSL 3+ laboratory conditions are required for the isolation of H5N1 HPAI viruses. Serology has been used for surveillance. The microneutralization assay is the most reliable test for detecting antibodies to avian influenza viruses.

## Treatment

Four antiviral drugs -- amantadine, rimantadine, zanamivir, and oseltamivir - are active against human influenza viruses. Studies suggest that these drugs may also be helpful in avian influenza infections in humans. Oseltamivir appears to increase the chance of survival in patients infected with Asian lineage H5N1 viruses, particularly if it is given early. Further testing, particularly

# Highly Pathogenic Avian Influenza

on the optimum dose and duration of treatment, is still needed. The H5N1 viruses currently circulating in poultry are resistant to amantadine and rimantadine. Although resistance to zanamivir and oseltamivir has been reported in these viruses, it is uncommon.

## Prevention

Controlling epidemics in poultry decreases the risk of exposure for humans. People working with infected birds should follow good hygiene practices and wear appropriate protective clothing such as boots (or shoe covers), coveralls, gloves, respirators and goggles. The specific recommendations may vary with the virus. In addition, WHO recommends prophylaxis with antiviral drugs in people who cull birds infected with H5N1 HPAI viruses. To prevent reassortment between human and avian influenza viruses, people in contact with infected birds should be vaccinated against human influenza. They are also discouraged from having contact with sick birds while suffering flu symptoms.

In areas where Asian lineage H5N1 viruses could be present in domesticated poultry, poultry farms and live bird markets should be avoided. Precautions should also be taken when handling raw meat and eggs, which can contain virus. Sanitary precautions and cooking methods recommended to destroy *Salmonella* and other poultry pathogens are sufficient to kill avian influenza viruses. The hands should be washed thoroughly with soap and warm water after handling meat or eggs. Cutting boards and utensils should be washed with soap and hot water. Poultry should be cooked to a temperature of at least 74°C (165°F). Eggs should be cooked until the whites and yolks are both firm.

Avian influenza viruses can be carried in wild birds, and these birds could be the initial source of infection in an area. Wild birds should be observed from a distance; close contact is discouraged. If birds or potentially contaminated surfaces are touched, the hands should be washed with soap and water before eating, drinking, smoking, or rubbing the eyes. Dead or diseased wildlife should be reported to state, tribal or federal natural resource agencies. Hunters should not handle or eat sick game, and should always wear rubber or latex gloves while handling and cleaning wild birds. The hands, as well as equipment and surfaces, should be thoroughly washed after dressing the carcass. All game should be cooked thoroughly.

If a human avian influenza pandemic occurs, additional precautions will be necessary. During a pandemic, crowded conditions and close contact with other people should be avoided. Respirators and other protective equipment may be advisable during close contact with an infected individual. In addition, infection control measures such as good hygiene, cancellation of social events and voluntary quarantine of infected individuals can limit the spread of disease. H5N1 vaccines have also been developed. In the U.S., these

vaccines are stockpiled by the government and will be distributed by public health officials if they are needed. Avian influenza vaccines for humans are not commercially available in the U.S.

## Morbidity and Mortality

The severity of zoonotic influenza seems to vary with the virus isolate. Particularly severe infections have been reported with Asian lineage H5N1 (HPAI) viruses. Most patients infected with these viruses have been young and have had no predisposing conditions. The overall case fatality rate, as of December 31, was 60%. Higher or lower case fatality rates have been reported in smaller series, varying with the country and the clade of the virus. A few milder cases have been documented, particularly among children. One H5N1 infection in a child with upper respiratory signs and an uncomplicated recovery after antibiotic treatment was recognized only by routine virus surveillance. The prevalence of human infections with Asian lineage H5N1 viruses is unknown; however, asymptomatic infections seem to be rare.

Human disease has also been reported occasionally after infections with various H7 viruses and H9N2 viruses. The reported infections with LPAI H9N2 viruses have resembled human influenza, and they have not been fatal. Most infections with H7 viruses, including HPAI viruses, were limited to conjunctivitis, but influenza symptoms have also been seen. A single death occurred in an otherwise healthy veterinarian who became infected with an HPAI H7N7 virus. Some isolates may also cause asymptomatic or mild, unrecognized infections. During an H7N3 LPAI outbreak in Italy in 2003, 3.8% of poultry workers tested developed antibodies to H7 viruses. Interestingly, no seropositive individuals were identified in serum samples collected during H7N1 epidemics from 1999-2002. In other studies, antibodies to H4, H5, H6, H7, H9, H10 and H11 avian influenza viruses have been found in poultry workers, veterinarians and waterfowl hunters. Whether these antibodies result from productive infections, exposure to antigens or cross-reactions with human influenza viruses remains to be determined.

## Infections in Animals

### Species Affected

#### *Birds*

Avian influenza viruses mainly infect birds. In wild species, these viruses are especially common among birds that live in wetlands and other aquatic environments. Waterfowl and shorebirds appear to be the natural reservoirs for the influenza A viruses, and carry all of the known subtypes. Important reservoir hosts include ducks, geese, swans, gulls, terns and waders. The vast majority of viruses found in birds are LPAI; HPAI viruses are usually detected mainly in poultry. Some host specificity may be seen. For example, the gallinaceous birds

# Highly Pathogenic Avian Influenza

including chickens, turkeys, quail, and pheasants often have severe infections with HPAI viruses, but the same viruses may cause only minor disease when they infect ducks, geese and other waterfowl. Among cage birds, most avian influenza virus infections have been recorded in passerine birds. Psittacine birds are rarely affected.

Several clades of H5N1 viruses are currently circulating in poultry. These viruses can infect and cause disease in many species of birds in addition to poultry. Unusually, they have caused severe disease and deaths in some species of wild waterfowl and shorebirds, which usually carry avian influenza viruses asymptotically. Many Asian lineage H5N1 viruses have been isolated from birds in the order Anseriformes, particularly the families Anatidae (ducks, swans and geese) and Charadriiformes (shorebirds, gulls and terns). Symptomatic infections have also been reported in pheasants, partridges, quail, jungle fowl, guineafowl and peafowl (order Galliformes); egrets, storks and herons (order Ciconiiformes); pigeons (order Columbiformes); eagles, falcons, kites, kestrels, goshawks and buzzards/ vultures (order Falconiformes); owls (order Strigiformes); cranes, cranes, moorhens, bustards, watercocks, coots and sultans (order Gruiformes); cormorants and pelicans (order Pelecaniformes), emus (order Struthioniformes), grebes (order Podicipediformes), budgerigars (order Psittaciformes), hornbills (order Coraciiformes) and flamingos (order Phoenicopteriformes). Symptomatic natural or experimental infections have been reported in passeriform birds including various finches, house sparrows (*Passer domesticus*), Eurasian tree sparrows (*Passer montanus*), mynahs, crows, ravens, jackdaws, Oriental magpie robins (*Copsychus saularis*), munias, orioles, shrikes, starlings, mesias, red-billed leiothrix (*Leiothrix lutea*), Japanese white-eye (*Zosterops japonicus*) and magpies. Asian lineage H5N1 viruses have also been found in a variety of birds that appeared healthy. In a recent study from Thailand, there was no apparent difference in the prevalence of the H5N1 virus between waterfowl and other birds.

## Mammals

Some strains of avian influenza viruses may occasionally cause disease in mammals including pigs, horses, mink, cats, dogs, ferrets, stone martens, palm civets, marine mammals and other species.

The Asian lineage H5N1 (HPAI) viruses seem to have a particularly broad host range. Symptomatic infections with these viruses have been reported in captive tigers (*Panthera tigris*), leopards (*Panthera pardus*), clouded leopards (*Neofelis nebulos*), lions (*Panthera leo*) and Asiatic golden cats (*Catopuma temminckii*), as well as housecats, a dog, stone martens (*Mustela foina*), a wild mink (*Mustela vison*), raccoon dogs and captive palm civets (*Chrotogale owstoni*). Asymptomatic infections have been reported in some housecats, and Asian lineage H5N1 viruses have been recovered from populations of

apparently healthy wild pikas. During outbreaks in poultry, serological evidence of infection or exposure has been reported in cats, dogs and swine, and viruses have been isolated rarely from pigs in China. Unpublished research suggests that some raccoons in Japan also have antibodies to H5N1 viruses. Experimental infections have been established in housecats, dogs, foxes, pigs, ferrets, rodents, cynomolgus macaques and rabbits. Cattle can be experimentally infected with viruses isolated from cats. The Asian lineage H5N1 viruses are continuing to evolve, and other species may also be susceptible to infection and/or disease.

## Incubation Period

The incubation period in poultry is one to seven days. A 21-day incubation period, which takes into account the transmission dynamics of the virus, is used for an avian population in the context of disease control. The incubation period for avian influenza viruses in mammals is also thought to be short.

## Clinical Signs

### Birds

In contrast to LPAI viruses, which usually cause asymptomatic infections, mild respiratory disease or decreased egg production and other reproductive signs, the HPAI viruses are highly virulent. HPAI viruses can cause severe infections in some species of birds on a farm while leaving others unaffected. The clinical signs are variable. Sudden death of large numbers of birds is a common presentation. Systemic signs, and in some cases, respiratory signs, may be noted in chickens, turkeys and other gallinaceous birds. The birds can be markedly depressed, with decreased feed and water consumption, and ruffled feathers. Sinusitis, lacrimation, cyanosis of the head, comb and wattle, edema of the head, and green to white diarrhea may be present in some poultry. In addition, there can be coughing, sneezing, blood-tinged oral and nasal discharges, ecchymoses on the shanks and feet, neurological disease, decreased egg production, loss of egg pigmentation and deformed or shell-less eggs. However, none of these clinical signs is pathognomonic, and sudden death can occur with few other signs. Most of the flock usually dies. Because HPAI viruses are partly defined by their genetic composition, it is also possible for an HPAI virus to be isolated from gallinaceous birds showing mild signs consistent with LPAI.

Clinical signs are minimal in ducks and geese infected with most HPAI viruses. In domesticated ducks, the most common signs are sinusitis, diarrhea and an increased mortality rate in the flock. However, some recent H5N1 isolates have caused severe, acute disease with neurological signs and high mortality rates. There are few descriptions of the clinical signs in other domesticated birds. Ostriches that were experimentally infected with an HPAI H7N1 virus developed mild depression and hemorrhagic diarrhea.

# Highly Pathogenic Avian Influenza

Avian influenza is often subclinical in wild birds, but some strains can cause illness and death. Strains known to cause fatal illness include some of the currently circulating Asian lineage H5N1 viruses. Some captive wild birds infected with these viruses have died suddenly, within a few hours, without apparent clinical signs. In other cases, anorexia, extreme lethargy, dark green diarrhea, respiratory distress and/or neurological signs were seen, with death within 1-2 days. Swans have been severely affected by H5N1 viruses; these birds are generally found dead. Experimental infections with H5N1 viruses resulted in severe neurological disease in some mute swans and sudden death in others, while some birds shed virus subclinically. Diving ducks, grebes and mergansers also seem to be highly susceptible to these viruses. Experimental infections with H5N1 viruses in call ducks (*Anas platyrhynchos* var. *domestica*), a cross between wild and domesticated ducks, resulted in drowsiness, ataxia, torticollis, circling and seizures. Experimental infections in wood ducks (*Aix sponsa*) caused severe weakness and incoordination, cloudy eyes, ruffled feathers, rhythmic dilation and constriction of the pupils, tremors, seizures and death. Other indigenous North American ducks including mallards (*Anas platyrhynchos*), northern pintails (*Anas acuta*), blue-winged teals (*Anas crecca*) and redheads (*Aythya americana*) remained asymptomatic when inoculated with the same strain.

Symptomatic infections with H5N1 viruses have also been reported in experimentally infected gulls and passerine or psittacine birds. Laughing gulls (*Larus atricilla*) developed severe neurological disease; the signs included weakness, cloudy eyes, ruffled feathers, incoordination and torticollis. Most infected gulls died. One gull that recovered had a persistent head tilt; the other recovered completely. Anorexia and depression occurred in experimentally infected zebra finches, and 100% of the birds died within five days of inoculation. House finches and budgerigars developed anorexia, depression and neurological signs, and died rapidly. In one study, H5N1 infections were mild in house sparrows, which experienced only mild depression and survived, and starlings, which remained asymptomatic. In another study, house sparrows but not starlings had severe, often fatal infections.

Other subtypes can also be pathogenic to some wild birds. One H7N1 virus caused conjunctivitis, apathy and anorexia, with a high mortality rate, in canaries and a siskin. An H5N3 HPAI virus caused an outbreak with a high mortality rate among South African terns in the 1960s.

## **Mammals infected with Asian lineage H5N1 viruses**

Both symptomatic and subclinical Asian lineage H5N1 virus infections have been seen in felids. Although fatal infections have been reported in some housecats, little is known about the clinical signs after natural

exposure in this species. One cat had fever, depression, dyspnea, convulsions and ataxia, and a few infected housecats were found dead. One of the latter cats was apparently well up to 24 hours before its death. In contrast, asymptomatic infections were reported in housecats that had been accidentally exposed to a sick, H5N1-infected swan. In experimentally infected housecats, the clinical signs included fever, lethargy, conjunctivitis, protrusion of the third eyelid, dyspnea and death. Fatal infections have also been reported in some captive tigers and leopards. Some of these animals exhibited respiratory distress, serosanguineous nasal discharge, high fever and neurological signs before death. During an outbreak in Cambodia, captive lions, tigers, leopards and Asiatic golden cats were lethargic and had decreased appetites without respiratory signs for 5-7 days, but recovered.

Other mammals may also be affected by Asian lineage H5N1 viruses. A dog that ate infected poultry developed a high fever, with panting and lethargy, and died the following day. Experimentally infected dogs have been asymptomatic or developed only transient fever and conjunctivitis. Fatal respiratory disease was reported in infected raccoon dogs. Other raccoon dogs on the same farm had died with respiratory signs and/or diarrhea before the virus was found. Captive palm civets had neurological signs, with evidence of interstitial pneumonia, encephalitis and hepatitis at necropsy. Some infections in palm civets were fatal. A wild stone marten was also found with neurological signs. HPAI H5N1 viruses have been isolated from wild pikas; however, there was no evidence that the pika population was seriously affected.

Asian lineage H5N1 infections in pigs appear to be mild or asymptomatic. Mild respiratory signs including coughing, fever and transient anorexia were observed in some experimentally infected pigs. In another study, some Asian lineage H5N1 strains caused slight and transient weight loss, but other clinical signs were not seen, and lung lesions were much less severe than those caused by swine influenza viruses. One group reported that miniature pigs were resistant to infection.

Experimental infections have been established in foxes, ferrets, mice and cattle, although no naturally infected animals have been reported. Some infected foxes developed a fever but no other clinical signs; however, lung lesions were reported at necropsy. In ferrets, the syndromes ranged from very mild upper respiratory infections to severe, fatal disease; the pathogenicity varied with the specific isolate and the route of inoculation (intranasal or intragastric). The clinical signs in severe cases included high fever, extreme lethargy, anorexia, weight loss, respiratory disease, diarrhea and neurological signs. Similarly, infections in mice varied with the isolate and the route of inoculation (respiratory or intragastric). Cattle inoculated with high titers of H5N1 viruses isolated

# Highly Pathogenic Avian Influenza

from infected cats remained asymptomatic but could transiently shed virus.

## ***Mammals infected with other subtypes***

Ferrets have been infected experimentally with a few LPAI or HPAI avian influenza viruses. In one early study, ferrets inoculated with influenza viruses from various species, including birds, developed rhinitis, with sneezing and shivering, but did not have an elevated temperature. Animals inoculated with avian H7 (LPAI and HPAI) viruses from recent outbreaks developed illness of varying severity. Although most viruses (including H7N7 HPAI viruses) caused relatively mild illness with fever, transient weight loss and respiratory signs, the inoculation of an HPAI H7N7 virus from a fatal case in a Dutch veterinarian resulted in severe disease with fever, lethargy, anorexia, severe weight loss, nasal discharge, diarrhea, dyspnea and neurological signs. In another experiment, ferrets infected with an H7N3 (LPAI) virus had only a transient elevation in temperature, and developed no other clinical signs.

Infections with influenza A viruses, apparently of avian origin, have been associated with outbreaks of pneumonia in seals and disease in a pilot whale. The clinical signs in seals included weakness, incoordination, dyspnea and subcutaneous emphysema of the neck. A white or bloody nasal discharge was seen in some animals. Experimental infections with these viruses were milder or asymptomatic, suggesting that co-infections may have increased the severity of the clinical signs. In the single known case in a whale, the clinical signs were extreme emaciation, difficulty maneuvering and sloughing skin.

## **Communicability**

Avian influenza viruses are transmitted readily between birds. Virus shedding can begin as early as 1 to 2 days after infection. Most chickens shed LPAI influenza viruses for only a week, but a minority of the flock can excrete the virus in the feces for up to two weeks, and shedding for as long as 36 days has been reported in experimentally infected birds. Turkeys may excrete some avian influenza viruses for up to 72 days. Waterfowl are often infected subclinically, and ducks can shed these viruses for up to 30 days. Transmission from birds to mammals seems to be uncommon.

## ***Asian lineage H5N1 viruses in mammals***

Cats that were experimentally infected with the Asian lineage H5N1 virus shed the virus by the third day post-inoculation, and were able to infect two sentinel cats in close contact. Naturally infected, asymptomatic cats appeared to excrete virus only sporadically, and for less than two weeks. Horizontal transmission was not observed in this instance. Cats appear to shed avian influenza viruses from the intestinal tract as well as the respiratory tract. Limited animal-to-animal transmission was reported among tigers in a zoo.

Dogs, foxes, pigs and cattle can also shed HPAI viruses, but horizontal transmission has not been reported. In experimentally infected foxes, Asian lineage H5N1 viruses were detected in both respiratory secretions and feces. In experimentally infected dogs, pigs and cattle, this virus has been found only in respiratory secretions. In cattle, the shedding was transient and occurred after high dose inoculation with a virus isolated from cats. Sustained or prolonged transmission has not been reported with Asian lineage H5N1 viruses in any of these mammals. However, the recent isolation of H5N1 viruses from pikas suggests that these viruses may be maintained in this population.

## **Post Mortem Lesions** [Click to view images](#)

The lesions in chickens and turkeys are highly variable and resemble those found in other systemic avian diseases. Birds that die peracutely and young birds may have few or no lesions. In other cases, the sinuses may be swollen, and the comb and wattle are often edematous, hemorrhagic, congested and/or cyanotic. There may be subcutaneous edema on the head and neck, edema and diffuse subcutaneous hemorrhages on the feet and shanks, fluid (which may contain blood) in the nares and oral cavity, and congestion, swelling and hemorrhages of the conjunctivae. Hemorrhagic tracheitis can be seen in some birds; in others, the tracheal lesions may be limited to excess mucoid exudate. The lungs may be reddened from hemorrhages and congestion, and they may exude fluid when cut. Petechiae may be noted throughout the abdominal fat, on serosal surfaces and on the peritoneum, and they can sometimes be found in the muscles. Hemorrhages may also be seen on the mucosa and in the glands of the proventriculus, beneath the lining of the gizzard, and in the intestinal mucosa. The kidneys can be severely congested and they are sometimes plugged with urate deposits. The ovaries may be hemorrhagic or degenerated, with areas of necrosis. The peritoneal cavity often contains yolk from ruptured ova, which may cause severe airsacculitis and peritonitis. A study of the 2003 H7N7 outbreak in the Netherlands suggested that the occurrence of peritonitis, tracheitis, edema of the wattles and/or neck, or petechial hemorrhages in the proventriculus may be particularly suggestive of an HPAI infection, especially when there is acute high morbidity in the flock.

Postmortem lesions have occasionally been described in wild birds infected with Asian lineage H5N1 viruses. Experimentally infected wood ducks had multiple petechial hemorrhages in the pancreas. More extensive lesions were reported in experimentally infected laughing gulls; in these birds, petechial hemorrhages were found in the ventriculus, apex of the heart, cerebrum and pancreas. In naturally infected swans, one study reported that the most consistent lesions were multifocal hemorrhagic necrosis in the pancreas, subepicardial hemorrhages, and pulmonary congestion and edema. Pancreatic lesions alone or no gross lesions have also been seen in some

# Highly Pathogenic Avian Influenza

swans. Mild or absent gross lesions were reported in experimentally infected zebra finches, house finches and budgerigars despite high mortality rates in these species.

Pulmonary edema; pneumonia; conjunctivitis; cerebral, renal and splenic congestion; multifocal hepatic necrosis; hemorrhages in the intestinal serosa, lymph nodes, perirenal tissue and/or diaphragm; and severe hemorrhagic pancreatitis have been reported in naturally infected cats. The lungs were also affected in experimentally infected cats, with multiple to coalescing foci of pulmonary consolidation. These lesions were similar whether the cats were infected intratracheally or by the ingestion of infected chicks. In one study, cats infected by ingestion also had enlarged tonsils with multifocal petechial hemorrhages, as well as enlarged mandibular and/ or retropharyngeal lymph nodes. Petechial hemorrhages occurred in the liver of some cats, and in one cat, the liver lesions were accompanied by generalized icterus. In naturally infected tigers and leopards, the gross lesions included severe pulmonary consolidation and multifocal hemorrhages in multiple organs including the lung, heart, thymus, stomach, intestines, liver and lymph nodes.

Bloody nasal discharge, severe pulmonary congestion and edema, and congestion of the spleen, kidney and liver were reported in a naturally infected dog. Pulmonary lesions including interstitial pneumonia have been reported in some experimentally infected pigs. In one study, Asian lineage H5N1-infected pigs had mild to minimal gross lung lesions, with mild to moderate bronchiolitis and alveolitis detected on histopathological examination. Experimentally infected foxes also developed lesions mainly in the lung. More severe lesions were seen in foxes inoculated intratracheally than in animals fed infected birds, and some of these animals also had histopathological evidence of encephalitis and myocarditis.

## Diagnostic Tests

Avian influenza can be diagnosed by variety of techniques including virus isolation. The virus can be recovered from oropharyngeal, tracheal and/or cloacal swabs in live birds. Feces can be substituted in small birds if cloacal samples are not practical (e.g., cannot be collected without harming the bird). Oropharyngeal, tracheal or cloacal swabs (or intestinal contents), and organ samples (trachea, lungs, air sacs, intestine, spleen, kidney, brain, liver and heart) are tested in dead birds. Virus isolation is performed in embryonated eggs; hemagglutinating activity indicates the presence of influenza virus. The identity of the virus can be confirmed with agar gel immunodiffusion (AGID) or ELISAs. Avian influenza viruses are subtyped with specific antisera in AGID or hemagglutination and neuraminidase inhibition tests. Virulence tests in susceptible birds, together with genetic tests to identify

characteristic patterns in the hemagglutinin, are used to differentiate LPAI from HPAI viruses.

RT-PCR assays can identify avian influenza viruses in clinical samples, and can replace virus isolation in some cases. These tests can also distinguish some subtypes. Real-time RT-PCR is the method of choice for diagnosis in many laboratories. Viral antigens can be detected with ELISAs including rapid tests. As of 2008, the World Organization for Animal Health (OIE) recommended that antigen detection tests be used to identify avian influenza only in flocks and not in individual birds.

Serological tests including agar gel immunodiffusion, hemagglutination, hemagglutination inhibition and ELISAs are useful as supplemental tests. Although most gallinaceous birds and other susceptible birds die before developing antibodies, serology can be valuable for surveillance and to demonstrate freedom from infection. AGID tests can recognize all avian influenza subtypes in poultry, but hemagglutination inhibition tests are subtype specific and may miss some infections. AGID tests are not reliable for detecting avian influenza in ducks or geese. In wild birds, some serological tests may underestimate the prevalence of H5N1 infections.

## Treatment

In most countries including the U.S. and Canada, high pathogenicity avian influenza in poultry is not treated; outbreaks are controlled by eradication.

## Prevention

Poultry can be infected by contact with newly introduced birds or fomites, as well as by contact with wild birds, particularly waterfowl. The risk of infection can be decreased by all-in/all-out flock management, and by preventing any contact with wild birds or their water sources. Birds should not be returned to the farm from live bird markets or other slaughter channels. In addition, strict hygiene and biosecurity measures are necessary to prevent virus transmission on fomites.

Outbreaks can be controlled by rapid depopulation of infected and exposed flocks, proper disposal of carcasses and contaminated materials, and strict biosecurity measures. Farms should be quarantined, and movement controls and surveillance should be established. Infected premises must be thoroughly cleaned and disinfected. Insects and mice on the premises should be eliminated, then the flock depopulated and the carcasses destroyed by burying, composting or rendering. Once the birds have been killed, the manure and feed should be removed down to a bare concrete floor. If the floor is earthen, one inch or more of soil should be removed. The manure can be buried at least five feet deep. It may also be composted for 90 days or longer, depending on the environmental conditions. The compost should be covered tightly with black polyethylene sheets to prevent the entry of birds,

# Highly Pathogenic Avian Influenza

insects and rodents. Feathers can be burned or composted; alternatively, they may be removed and the area wet down with disinfectant. High-pressure spray equipment should be used to clean all equipment and building surfaces. Once all surfaces are clean and free of all organic material, the entire premises should be sprayed with an approved residual disinfectant.

H5N1 vaccines are not used routinely in the U.S. or most other countries; however, nations may consider vaccination as a preventative or adjunct control measure during an outbreak. Avian vaccines are usually autogenous or from viruses of the same subtype or hemagglutinin type. Currently licensed vaccines in the U.S. include inactivated whole virus and recombinant fowlpox-H5 vaccines. The use of these vaccines requires the approval of the state veterinarian and, in the case of H5 and H7 vaccines, USDA approval. Because vaccines can allow birds to shed virus while remaining asymptomatic, good surveillance and movement controls are critical in a vaccination campaign. Methods used to recognize infections with field viruses in vaccinated flocks include a "DIVA" (differentiating vaccinated from infected animals) strategy, and the use of sentinel birds. Vaccination may place selection pressures on avian influenza viruses, and might eventually result in the evolution of vaccine-resistant isolates.

Mammals should not be fed poultry or other birds that may be infected with Asian lineage H5N1 viruses or other HPAI avian influenza viruses. They should also be kept from contact with potentially infected flocks and wild birds. During outbreaks, cats and dogs should be kept indoors whenever possible.

## Morbidity and Mortality

In domesticated poultry (particularly chickens), HPAI viruses are often associated with morbidity and mortality rates that approach 90-100%. Any survivors are usually in poor condition and do not begin laying again for several weeks. Ducks and geese are clinically unaffected by many HPAI viruses.

Avian influenza virus infections in wild birds are typically asymptomatic; however, some of the Asian lineage H5N1 viruses have resulted in high mortality rates in wild birds. In April 2005, an outbreak at Qinghai Lake in central China caused the death of more than 6000 migratory wild birds. H5N1 viruses have also been isolated from a variety of dead birds, including waterfowl, in a number of other countries. High mortality rates have been reported in some but not all experimentally infected wild birds. All six laughing gulls infected with recent strains of H5N1 became severely ill, and four died. Four of six infected wood ducks also became severely ill while two others remained asymptomatic. Three of the sick ducks died and one recovered. Mallard, northern pintail, blue-winged teal and redhead ducks inoculated with the same viral strains did not become ill.

Morbidity and mortality rates in passerine and psittacine birds have varied with the species. In one study, mortality rates approached 100% in experimentally infected zebra finches, house finches and budgerigars, but all house sparrows experienced mild disease and survived, and all starlings remained asymptomatic. In a study with a different H5N1 virus, the mortality rate was 66-100% in house sparrows, but no deaths were seen in starlings.

Asian lineage H5N1 viruses have been reported in a variety of mammalian species. In an unpublished study from Thailand, antibodies to these viruses were found in 8 of 11 cats and 160 of 629 dogs. In contrast, no antibodies were detected in 171 cats from areas of Austria and Germany where infections had been reported in wild birds. Some infections with Asian lineage H5N1 viruses have been fatal; deaths have occurred in housecats, some large felids, a dog, raccoon dogs, palm civets and experimentally infected ferrets. However, both mild and severe cases have been seen in several of these species. A few fatal cases have been documented in naturally infected housecats, and some experimentally infected cats exhibited severe disease and high mortality rates. In contrast, asymptomatic infections were reported in cats that had been exposed to an infected swan in an animal shelter. Few of the latter cats shed virus, and none became ill despite the presence of other viral and bacterial infections, and high stress levels in this population. Similarly, fatal cases were reported among captive tigers and leopards in Thailand, but captive leopards, tigers, Asiatic golden cats and lions at a wildlife rescue center in Cambodia all recovered after an illness lasting 5-7 days. Asymptomatic or mild infections were seen in experimentally infected dogs, but one death was reported in a naturally infected dog. In experimentally infected ferrets and mice, the severity of the clinical signs varied with the specific isolate and the route of inoculation (intranasal or intragastric). Interestingly, there is no evidence that HPAI H5N1 viruses are causing significant illness among infected pikas in China, and Asian lineage H5N1 viruses isolated from Indonesian pigs were less virulent in mice than isolates from poultry.

Although Asian lineage H5N1 viruses have been reported in pigs, severe disease does not seem to occur in this species. A serological study conducted in Vietnam found that a low percentage of pigs (0.25%) had been exposed to H5N1 influenza viruses in 2004. Asian lineage H5N1 viruses have also been detected in swine in Indonesia, and these viruses have been isolated rarely from pigs in China. However, there are no reports of severe illness among swine. Experimental infections also suggest that the clinical signs may be mild in this species, and miniature pigs were resistant to infection in one study.

# Highly Pathogenic Avian Influenza

## Internet Resources

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- Canadian Food Inspection Agency [CFIA]. Fact Sheet - Avian Influenza  
[http://www.inspection.gc.ca/english/anima/heasan/dise\\_mala/avflu/avflufse.shtml](http://www.inspection.gc.ca/english/anima/heasan/dise_mala/avflu/avflufse.shtml)
- CFIA Notifiable Avian Influenza Hazard Specific Plan  
[http://www.inspection.gc.ca/english/anima/heasan/dise\\_mala/avflu/plan/plane.shtml](http://www.inspection.gc.ca/english/anima/heasan/dise_mala/avflu/plan/plane.shtml)
- Centers for Disease Control and Prevention. Avian Influenza  
<http://www.cdc.gov/flu/avian/>
- Public Health Agency of Canada. Material Safety Data Sheets  
<http://www.phac-aspc.gc.ca/msds-ftss/index.html>
- The Merck Manual  
<http://www.merck.com/pubs/mmanual/>
- The Merck Veterinary Manual  
<http://www.merckvetmanual.com/mvm/index.jsp>
- United States Animal Health Association. Foreign Animal Diseases.  
[http://www.vet.uga.edu/vpp/gray\\_book02/fad/index.php](http://www.vet.uga.edu/vpp/gray_book02/fad/index.php)
- United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS). Avian Influenza.  
[http://www.aphis.usda.gov/newsroom/hot\\_issues/avian\\_influenza/avian\\_influenza.shtml](http://www.aphis.usda.gov/newsroom/hot_issues/avian_influenza/avian_influenza.shtml)
- USDAAPHIS. Avian Influenza Portal  
[http://www.usda.gov/wps/portal/tut/p/\\_s.7\\_0\\_A/7\\_0\\_1OB?navid=AVIAN\\_INFLUENZA&navtype=SU](http://www.usda.gov/wps/portal/tut/p/_s.7_0_A/7_0_1OB?navid=AVIAN_INFLUENZA&navtype=SU)
- USDA APHIS. Biosecurity for the Birds  
[http://www.aphis.usda.gov/animal\\_health/birdbiosecurity/](http://www.aphis.usda.gov/animal_health/birdbiosecurity/)
- United States Geological Survey (USGS). National Wildlife Health Center. List of species affected by H5N1 (avian influenza)  
[http://www.nwhc.usgs.gov/disease\\_information/avian\\_influenza/affected\\_species\\_chart.jsp](http://www.nwhc.usgs.gov/disease_information/avian_influenza/affected_species_chart.jsp)
- World Health Organization. Avian Influenza  
[http://www.who.int/csr/disease/avian\\_influenza/en/](http://www.who.int/csr/disease/avian_influenza/en/)
- World Organization for Animal Health (OIE)  
<http://www.oie.int>
- OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals  
[http://www.oie.int/eng/normes/mmanual/a\\_summry.htm](http://www.oie.int/eng/normes/mmanual/a_summry.htm)
- OIE Terrestrial Animal Health Code  
[http://www.oie.int/eng/normes/mcode/A\\_summry.htm](http://www.oie.int/eng/normes/mcode/A_summry.htm)

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# Highly Pathogenic Avian Influenza

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