Avian Influenza

Fowl Plague, Grippe Aviaire

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Importance

Avian influenza viruses are highly contagious, extremely variable viruses that are widespread in birds. Wild birds in aquatic habitats are thought to be their natural reservoir hosts, but domesticated poultry are readily infected. Most viruses cause only mild disease in poultry, and are called low pathogenic avian influenza (LPAI) viruses. Highly pathogenic avian influenza (HPAI) viruses can develop from certain LPAI viruses, usually while they are circulating in poultry flocks. HPAI viruses can kill up to 90-100% of the flock, and cause epidemics that may spread rapidly, devastate the poultry industry and result in severe trade restrictions. Infection of poultry with LPAI viruses capable of evolving into HPAI viruses also affects international trade. Avian influenza viruses occasionally affect mammals, including humans, usually after close contact with infected poultry. While many human cases are limited to conjunctivitis or mild respiratory disease, some viruses tend to cause severe illness. In rare cases, avian influenza viruses can become adapted to circulate in a mammalian species, and these viruses have caused or contributed to at least three pandemics in humans.

Etiology

Avian influenza results from infection by viruses belonging to the species *influenza A virus*, genus *influenzavirus A* and family Orthomyxoviridae. Influenza A viruses are classified into subtypes based on two surface proteins, the hemagglutinin (HA) and neuraminidase (NA). At least 16 hemagglutinins (H1 to H16), and 9 neuraminidases (N1 to N9) have been found in viruses from birds, while two additional HA and NA types have been identified, to date, only in bats. The viral HA, and to a lesser extent the NA, are major targets for the immune response. There is ordinarily little or no cross-protection between different HA or NA types.

Influenza viruses in birds are classified as either low pathogenic (also called low pathogenicity) or highly pathogenic (high pathogenicity) avian influenza viruses. A virus is defined as HPAI or LPAI by its ability to cause severe disease in intravenously inoculated young chickens in the laboratory, or by its possession of certain genetic features associated with HPAI viruses. To date, the fully virulent HPAI viruses found in nature have always contained H5 or H7, although there are rare examples of other viruses that could technically be considered HPAI.

Antigenic shift and drift in influenza A viruses

Influenza A viruses are very diverse, and two viruses that share a subtype may be only distantly related. Some variability results from the gradual accumulation of mutations, a process called 'antigenic drift.' Once the viral HA or NA has changed enough, immune responses generated against its former proteins may no longer be protective. More rapid changes can occur when two different influenza viruses infect the same cell. In this situation, gene segments from both viruses may be packaged into a single, novel virion, a process called genetic reassortment. Genetic reassortment can occur between any two influenza A viruses, whether they are adapted to circulate in birds or mammals. If genetic reassortment results in the acquisition of a new HA and/or NA protein, this can cause an 'antigenic shift' among the viruses circulating in a species. Antigenic shifts may be sufficient for the reassortant virus to completely evade existing immunity. After a subtype has circulated in a species for a while, genetic reassortments and antigenic drift can produce numerous viral variants, which may differ in their virulence for birds and/or mammals.

Species Affected

The vast majority of LPAI viruses are maintained in asymptomatic wild birds in aquatic habitats. These birds are thought to be their natural reservoir hosts. Infections are particularly common among members of the order Anseriformes (waterfowl, such as ducks, geese and swans) and two families within the order Charadriiformes, the Laridae (gulls and terns) and Scolopacidae (shorebirds). Some aquatic species in other orders might also be maintenance hosts. LPAI viruses seem to be uncommon in most wild birds that live on land (terrestrial birds). However, these birds can also become.

infected if they are exposed. HPAI viruses are not normally found in wild birds, although a few subtypes have been detected, and some have caused outbreaks.

Domesticated birds can be infected by avian influenza viruses, although susceptibility appears to differ between species. Poultry are readily infected by both LPAI and HPAI viruses. When LPAI viruses from wild birds are transferred to poultry, they may circulate inefficiently and die out; become adapted to the new host and continue to circulate as LPAI viruses; or if they contain H5 or H7, they may evolve into HPAI viruses. Viruses that have adapted to poultry rarely become re-established in wild birds, although they may infect them transiently. Many different viruses can cause disease in chickens and turkeys, but three viral lineages are currently of particular concern.

Asian lineage H5N1 avian influenza viruses

The A/goose/Guangdong/1996 lineage ('Asian lineage') of H5N1 HPAI viruses seems to have a particularly wide host range. In addition to domesticated birds, these viruses have been found in a large number of wild or captive avian species. Whether wild birds can maintain these viruses for long periods (or indefinitely), or are repeatedly infected from poultry, is still controversial. Asian lineage H5N1 HPAI viruses can also infect many species of mammals, and their full host range is probably not yet known. To date, they have been found in pigs, housecats, several species of large felids in zoos, dogs, donkeys, stone martens (*Mustela foina*), raccoon dogs (*Nyctereutes procyonoides*), palm civets (*Chrotogale owstoni*), plateau pikas (*Ochotona curzoniae*) and a wild mink (*Mustela vison*). Serological evidence of infection or exposure has been reported in horses and raccoons. Experimental infections have been established in cats, dogs, foxes, pigs, ferrets, laboratory rodents, cynomolgus macaques (*Macaca fascicularis*) and rabbits. Cattle could be experimentally infected with viruses isolated from cats, but serological studies in Egypt suggest that cattle, buffalo, sheep and goats are not normally infected. Reassortants that contain gene segments from H5N1 viruses (e.g., H5N2, H5N5 and H5N8 HPAI viruses) have also been found among poultry, and some of these viruses can cause illness in mammals.

H9N2 (LPAI) avian influenza viruses

H9N2 (LPAI) viruses have become widespread among poultry in some areas, and they have also been detected in wild birds. These viruses have been found occasionally in pigs and dogs. Serological evidence of infection was detected in performing macaques in Bangladesh, and in wild plateau pikas in China, and pikas could be infected experimentally.

Zoonotic H7N9 avian influenza viruses in China

An H7N9 LPAI virus, which has recently caused serious human outbreaks in China, circulates there in poultry. Evidence of infection has also been reported in a few other birds including pigeons, an asymptomatic tree sparrow and wild waterfowl. Whether wild birds play any role in spreading this virus is uncertain. Based on experimental infections, chickens and quail are most likely to maintain this H7N9 virus, but several species of ducks, geese, pigeons, parakeets (*Melopsittacus undulates*) and various passerine birds could also be infected. There have been no reports of naturally acquired illnesses or infections in mammals, as of September 2014. In experimental studies, isolates from humans could infect miniature pigs, ferrets, laboratory mice and cynomolgus macaques.

Other avian influenza viruses reported in mammals

In addition to H5N1 and H9N2 viruses, diverse subtypes (e.g., H4, H5N2, H6N6, H7, H10N5 and H11N2) have been detected occasionally in pigs, especially in Asia. An H10N4 virus was responsible for an epidemic in farmed mink, and experimental infections with several other avian subtypes have been established in this species. One avian H3N8 virus affected horses in China for a short time. Cats and dogs can also be infected experimentally with some LPAI and/or HPAI viruses, and a clinical case caused by an H5N2 HPAI virus (related to Asian lineage H5N1 HPAI viruses) was reported in a dog. Domesticated guinea pigs in South America had antibodies to H5 influenza viruses. Few studies have investigated wild animals; however, antibodies to a few subtypes have been found in raccoons, and experimental infections were established in raccoons, skunks and wild mice (*Mus musculus*).

Zoonotic potential

Although clinical cases are usually uncommon in people, they have been caused by multiple avian influenza subtypes. Asian lineage H5N1 HPAI viruses and H7N9 LPAI viruses in China have been isolated repeatedly. Other subtypes that have caused illnesses in people include H9N2, H6N1 and various H7 and H10 viruses. Serological surveys in some highly exposed populations have also found antibodies to other HA types. Experimental infections with some subtypes (e.g., H4N8, H10N7 and H6N1), have been established in human volunteers, and some of these viruses caused mild influenza symptoms. Adaptation to humans is possible, though rare, and some previous human pandemics were caused by partially or wholly avian viruses.

Geographic Distribution

LPAI viruses are cosmopolitan in wild birds. Different viral lineages circulate in North America and Eurasia, although reassortment occurs between these lineages at some locations. LPAI viruses are usually absent from commercial poultry in developed nations, but they may be present in other domesticated birds. The H9N2 viruses circulating in poultry are currently limited to Eurasia. The zoonotic H7N9 LPAI viruses causing outbreaks in mainland China have not been reported from other regions, except as imported cases in travelers.

HPAI viruses are eradicated from all domesticated birds, whenever possible, and developed countries are usually HPAI-free. Asian lineage H5N1 HPAI viruses are currently considered to be endemic among poultry in a few Asian or Middle Eastern countries, with outbreaks occurring at times in other parts of the Eastern Hemisphere.

Transmission

In birds, avian influenza viruses are shed in the feces and respiratory secretions. Fecal-oral transmission is the predominant means of spread in aquatic wild bird reservoirs. Respiratory transmission is thought to be unimportant in most wild birds, but it can occur with a few viruses or in some hosts, particularly those that live on land. Asian lineage H5N1 HPAI viruses, for instance, can be shed mainly in the respiratory secretions even from wild waterfowl. 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. Most chickens usually excrete LPAI viruses for a week, and a minority of the flock for up to two weeks, but some species of birds, including waterfowl, may shed some LPAI or HPAI viruses for a few weeks. HPAI viruses have also been found in the yolk and albumen of eggs from chickens, turkeys and quail. LPAI virus shedding in eggs is either nonexistent or very rare. Fomites can be important in transmission, and flies may act as mechanical vectors. One recent study suggested that, under certain conditions, airborne spread might be possible between farms.

People and other mammals are usually infected with avian influenza viruses during close contact with birds or their tissues, although indirect contact via fomites or other means is also thought to be possible. Most viruses are probably acquired via the respiratory tract, but the eye may also act as an entry point. A few Asian lineage H5N1 HPAI virus infections in animals, and rare cases in humans, were likely acquired by eating raw tissues from infected birds. Housecats in an animal shelter might have become infected by ingesting fecal matter from a sick swan, during grooming. Infected animals and people shed avian influenza viruses mainly in respiratory secretions. Fecal shedding has been reported occasionally, but its significance is still uncertain. Asian lineage H5N1 HPAI viruses were also detected in the urine of some mammals. Transplacental transmission may be possible with certain viruses (e.g., Asian lineage H5N1 HPAI viruses) that can spread beyond the respiratory tract.

Influenza A viruses that infect species other than their usual hosts tend to be transmitted inefficiently, and do not typically continue to circulate in that population. However, on rare occasions in the past, a virus has continued to circulate in the new host, either "whole" or after reassorting with another influenza virus. Limited host-to-host transmission has been reported between mammals infected with some avian influenza viruses, including Asian lineage H5N1 HPAI viruses. These viruses were transmitted between zoo tigers in one outbreak, and experimentally between sick cats; however, there was no evidence of transmission from asymptomatic, naturally infected cats. Pigs might transmit this virus to a limited extent within an infected herd. Person-to-person transmission of these H5N1 viruses seems to be rare, and appears to require close, unprotected contact. Likewise, a few family clusters suggest that the Chinese H7N9 LPAI virus might be transmitted between humans during close contact, but common source exposure is hard to rule out, and most infected people did not seem to transmit this virus to others.

Survival of influenza viruses in the environment

Avian influenza viruses can remain viable for a time in the environment, especially at low temperatures. While they are reported to persist for as long as several months or more in distilled water or sterilized environmental water, some laboratory experiments suggest that the presence of natural microbial flora can greatly reduce their survival period. Repeated freezing and thawing may also speed inactivation. Some anecdotal observations from the field suggested that LPAI viruses could survive in feces for as long as 105 days under unspecified conditions; however, avian influenza viruses remained viable from < 1 day to 7 days at temperatures of 15-35°C (59-95°F) under some controlled laboratory conditions. At colder temperatures (4°C; 39°F), virus survival in feces ranged from less than 4 days to at least 30-40 days in different experiments. When protected from sunlight, virus persistence on various surfaces, or in soil, ranged from less than 2 days to more than 2 weeks (and possibly several months), at temperatures ranging from 4°C to 15-30°C (59-86°F). Two studies suggested that virus survival might be particularly prolonged on feathers. In poultry meat (pH 7), a virus survived for 6 months at 4°C. Environmental sampling in Cambodia suggested that avian influenza viruses might not survive long in tropical environments: although RNA from Asian lineage H5N1 HPAI viruses was found in many environmental samples (e.g., soil, straw), virus isolation was only successful from one water puddle.

Disinfection

Influenza A viruses are susceptible to a wide variety of disinfectants including sodium hypochlorite, 60% to 95% ethanol, quaternary ammonium compounds, aldehydes (glutaraldehyde, formaldehyde), phenols, acids, povidone-iodine and other agents. Influenza A viruses can also be inactivated by heat of 56-60°C (133-140°F) for a minimum of 60 minutes (or higher temperatures for shorter periods), as well as by ionizing radiation or extremes of pH (pH 1-3 or pH 10-14).

Infections in Animals

Incubation Period

The incubation period in poultry can be a few hours to a few days in individual birds, and up to 2 weeks in the

flock. The incubation period for avian influenza viruses in mammals is also thought to be short, and might be as little as 1-2 days in some cases.

Clinical Signs

Low pathogenic avian influenza

LPAI viruses usually cause subclinical infections or mild illnesses in poultry and other birds. Decreased egg production and quality, respiratory signs (sneezing, coughing, ocular and nasal discharge, swollen infraorbital sinuses), lethargy, decreased feed and water consumption, or somewhat increased flock mortality rates may be seen in chickens and turkeys. Illnesses exacerbated by factors such as concurrent infections or young age can be more severe. Some gallinaceous game birds (e.g., pheasants, quail) infected with LPAI viruses have been asymptomatic, while others had clinical signs including lethargy, respiratory signs, conjunctivitis, decreased egg production and/or diarrhea. One study reported neurological signs and elevated mortality in guinea fowl infected with an H7N1 virus. Some Eurasian H9N2 viruses appear to be more virulent than most LPAI viruses in chickens and quail.

High mortality has been seen in young ostriches during some LPAI outbreaks; however, one outbreak virus caused only green diarrhea in experimentally infected young birds. Domesticated waterfowl are often infected subclinically, although there may be mild signs such as sinusitis. Wild birds infected with LPAI viruses usually have few or no obvious clinical signs, although subtle physiological or behavioral effects have been described.

HPAI viruses in birds

HPAI viruses usually cause severe illness in chickens and turkeys, and few birds in infected flocks survive. Decreased feed and water intake, with other nonspecific systemic, respiratory and/ or neurological signs (e.g., depression, edema and cyanosis of the unfeathered skin, diarrhea, ecchymoses on the shanks and feet, coughing) are common, but no signs are pathognomonic, and sudden death can also be seen. In rare cases, an H5 or H7 virus causes only mild illness in chickens and turkeys, although it has a genetic signature that classifies it as an HPAI virus. Such viruses may have been isolated when they were evolving to become more virulent.

HPAI virus infections may be asymptomatic, mild or severe in other birds, including gallinaceous birds other than chickens and turkeys. Anorexia, lethargy, neurological signs, diarrhea and sudden death have been reported in some gallinaceous game birds, but milder or minimal signs were reported in some flocks. Domesticated waterfowl tend to be mildly affected, but respiratory signs (e.g., sinusitis), diarrhea, occasional cases with neurological signs, and increased mortality may be seen, and some Asian lineage H5N1 HPAI viruses can cause severe acute disease with neurological signs and high mortality rates. Pigeons are also thought to be relatively resistant to disease, although there have been reports of sporadic deaths and rare outbreaks. Young ostriches less than 6 months of age are usually much more severely affected than adults, and can have nonspecific signs, dyspnea; green urine, diarrhea or hemorrhagic diarrhea, with increased mortality. Some evidence suggests that HPAI viruses might not be more virulent than LPAI viruses in this species.

Wild birds or captive wild species can be affected by some HPAI viruses, although susceptibility to infection and the occurrence of clinical signs can differ between species. The clinical signs caused by Asian lineage H5N1 HPAI viruses ranged from nonspecific signs alone (sometimes with high mortality) to diarrhea, respiratory distress and/or neurological signs.

Mammals infected with Asian lineage H5N1 viruses

Asian lineage H5N1 HPAI viruses have caused fatal disease, as well as milder illnesses or asymptomatic infections, in mammals. One group of infected housecats remained asymptomatic, but a few other cats were found dead. One cat developed fever, dyspnea and neurological signs before it died. Conjunctivitis and fatal respiratory signs were described in experimentally infected cats. Some captive tigers and leopards exhibited high fever, respiratory distress and neurological signs before death, while a non-fatal outbreak among captive large felids was characterized by lethargy and inappetence without respiratory signs. Fever, respiratory and/or neurological signs were also reported in a handful of cases in other species, including a dog, captive raccoon dogs, captive palm civets and a wild stone marten. Infected donkeys had moderately severe respiratory signs, but responded well to antibiotics, suggesting that their illness may have been caused or exacerbated by bacterial pathogens. Experimental infections in pigs, as well as reports of infected herds, suggest that H5N1 HPAI virus-infected swine usually remain asymptomatic or have only mild signs.

Mammals infected with other subtypes

Infections with influenza A viruses, apparently of avian origin, have been associated with outbreaks of pneumonia in seals. An influenza virus was also isolated from a diseased pilot whale with nonspecific signs, although whether is caused the illness is uncertain. Mink infected with an H10N4 virus had respiratory signs and elevated mortality. Respiratory signs, but no deaths, were seen in an H5N2 HPAI-virus infected dog, dogs and cats inoculated with this virus, and dogs inoculated with an H9N2 virus. Few or no clinical signs were noted in cats inoculated with several LPAI viruses from waterfowl or an H7N7 HPAI virus isolated from a fatal human case. Miniature pigs infected with the zoonotic H7N9 LPAI viruses from humans in China did not become ill.

Post Mortem Lesions

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Low pathogenic avian influenza in birds

Poultry infected with LPAI viruses may exhibit rhinitis, sinusitis, congestion and inflammation in the trachea, but lower respiratory tract lesions such as pneumonia usually occur only in birds with secondary bacterial infections. Lesions (e.g., hemorrhagic ovary, involuted and degenerated ova) may also be observed in the reproductive tract of laying hens, and the presence of yolk in the abdominal cavity can cause air sacculitis and peritonitis. A small number of birds may have signs of acute renal failure and visceral urate deposition.

Highly pathogenic avian influenza in birds

The lesions in chickens and turkeys are highly variable and resemble those found in other systemic avian diseases. Classically, they include edema and cyanosis of the head, wattle and comb; excess fluid (which may be blood-stained) in the nares and oral cavity; edema and diffuse subcutaneous hemorrhages on the feet and shanks; and petechiae on the viscera and sometimes in the muscles. There may also be other abnormalities, including hemorrhages and/or congestion in various internal organs including the lungs, as well as severe airsacculitis and peritonitis (caused by yolk from ruptured ova). However, the gross lesions in some outbreaks may not fit the classical pattern, and birds that die peracutely may have few or no lesions.

The reported lesions in other gallinaceous birds include necrotic lesions in the pancreas, splenomegaly with parenchymal mottling, renal lesions, hemorrhages in internal organs and skeletal muscles, and pulmonary lesions. However, some lesions seen in chickens and turkeys, such as cyanosis and hemorrhagic lesions in unfeathered skin, may not be as prominent. Gross lesions of hepatitis and peritonitis, with other secondary lesions, have been seen in ostriches infected with avian influenza viruses. Petechial hemorrhages, pancreatic lesions, pulmonary congestion and edema, and other lesions have been reported in other species of birds infected with HPAI viruses.

Avian H5N1 influenza viruses in mammals

Asian lineage H5N1 HPAI viruses can cause systemic lesions as well as pulmonary lesions in some animals. Gross lesions reported in some cats and other felids included pulmonary consolidation and/or edema, pneumonia; hemorrhagic lesions in various internal organs; and in some cases, other lesions such as multifocal hepatic necrosis, hemorrhagic pancreatitis, or cerebral, renal and splenic congestion. Severe pulmonary congestion and edema were reported in a naturally infected dog. Pulmonary lesions including interstitial pneumonia have been noted in some experimentally infected pigs, while other pigs had mild to minimal gross lesions.

Diagnostic Tests

Avian influenza viruses can be detected in oropharyngeal, tracheal and/or cloacal swabs from live birds, with differing recovery rates from each site depending on the virus, species of bird and other factors. Samples from internal organs are also tested in dead birds. Diagnostic tests should be validated for the species of bird, and some tests that are useful in chickens and turkeys may be less reliable in other avian species.

Avian influenza viruses can be isolated in embryonated eggs, and they can be subtyped with specific antisera in hemagglutination and neuraminidase inhibition tests, by RT-PCR, or by sequence analysis of the viral HA and NA genes. RT-PCR assays can detect influenza viruses directly in clinical samples, and real-time RT-PCR is the diagnostic method of choice in many laboratories. Viral antigens can be detected with ELISAs including rapid tests, but these tests are more reliable as flock tests than in individual birds.

Serology can be valuable for surveillance and demonstrating freedom from infection, but it is not very useful in diagnosing HPAI infections in highly susceptible birds, as they usually die before developing antibodies. Agar gel immunodiffusion (AGID) tests and ELISAs to detect conserved influenza virus proteins can recognize all avian influenza subtypes, but hemagglutination inhibition (HI) tests are subtype specific and may miss some infections. Cross-reactivity between influenza viruses can be an issue. Tests that can distinguish infected from vaccinated birds (DIVA tests) should be used in surveillance when vaccination is part of a control program.

Treatment

There is no specific treatment for influenza virus infections in animals. Poultry flocks infected with HPAI viruses are depopulated (this is generally mandatory in HPAI-free countries). The disposition of infected LPAI flocks may vary with the virus and the country.

Control

Disease reporting

A quick response is vital for containing avian influenza outbreaks. In addition to national notification requirements, HPAI viruses and LPAI viruses that contain H5 or H7 must be reported to the World Organization for Animal Health (OIE) by member nations. Veterinarians who encounter or suspect a reportable disease should follow their country-specific guidelines for informing the proper authorities (state or federal veterinary authorities in the U.S. for diseases in animals). Unusual mortality among wild birds should also be reported to the appropriate agency.

Prevention

The risk of introducing a virus to poultry or other birds can be reduced by good biosecurity and hygiene, which includes preventing any contact with other domesticated or wild birds, mechanical vectors and fomites including water

sources. All-in/ all-out flock management is helpful in poultry flocks, and birds should not be returned to the farm from live bird markets or other slaughter channels. To help prevent reassortment between human and avian influenza viruses, people are encouraged to avoid contact with birds while suffering flu symptoms.

In different countries, vaccines may be used routinely to protect poultry flocks, as an adjunct control measure during an outbreak, or to protect valuable species such as zoo birds from highly virulent viruses such as H5N1. Although some vaccines can increase resistance to infection and/or decrease virus shedding, birds that are clinically protected may still become infected and shed these viruses. Thus, vaccination can mask infections if good surveillance programs (e.g., regular flock testing, the use of DIVA tests, and/or sentinel birds) are not used simultaneously. Vaccine-resistant isolates can also emerge.

During outbreaks, HPAI viruses are normally eradicated by depopulation of infected flocks, combined with other measures such as movement controls, quarantines and perhaps vaccination. Insect and rodent control, disposal of contaminated material, and thorough cleaning and disinfection are also important.

For mammals, prevention involves avoiding close contact with infected birds or their tissues. Keeping susceptible animals indoors may be helpful in areas where outbreaks are occurring.

Morbidity and Mortality

The prevalence of influenza viruses in poultry differs between nations, but commercial poultry in developed countries are generally free of LPAI and HPAI viruses. Even in these regions, LPAI viruses may be present in backyard flocks, live poultry markets and similar sources. HPAI outbreaks are uncommon under ordinary conditions, while LPAI outbreaks tend to occur more often. However, the continued presence of Asian lineage H5N1 HPAI viruses in poultry elevates the risk of outbreaks throughout the world, and especially in the Eastern Hemisphere.

LPAI viruses usually cause mild illnesses or asymptomatic infections in birds, including chickens and ducks, but outbreaks can be more severe when there are concurrent infections or other exacerbating factors. HPAI viruses usually cause high and rapidly escalating mortality in chicken and turkey flocks, with cumulative morbidity and mortality rates that may approach 90-100%. While similar high morbidity and mortality rates can sometimes be seen in other birds, susceptibility may vary greatly, and certain species such as waterfowl tend not to be severely affected. Some Asian lineage H5N1 viruses cause severe illness even in waterfowl, and the introduction of these viruses may be heralded by unusual deaths among wild birds (e.g., swans in Europe and recently crows in Pakistan). Currently, surveillance suggests that carriage of H5N1 HPAI viruses in wild bird populations without unusual mortality events is rare.

Asian lineage H5N1 HPAI virus infections in mammals have ranged from asymptomatic or relatively mild to fatal, sometimes in the same species. Overall susceptibility to illness may differ between species. Infections with this lineage in pigs seem to be mild or subclinical. Experimentally infected cats became severely ill, but dogs had only mild signs except when the inoculation method bypassed normal upper respiratory defense mechanisms. There is also serological evidence of infection with H5N1 viruses in apparently healthy dogs, cats, pigs, horses, donkeys and other species from endemic areas. Reports of antibodies to other subtypes (e.g., H9N2, H10N8) and the isolation of H9N2 viruses from both sick and healthy dogs in China raise questions about the effects and prevalence of avian influenza viruses in some species.

Infections in Humans

Incubation Period

The incubation period for Asian lineage H5N1 HPAI viruses might be as long as 8-17 days, but most cases become apparent within 5 days.[1] Estimates of the mean incubation period for the zoonotic H7N9 viruses have varied from 3 days to 5-6 days, with a range of 1-13 days.

Clinical Signs

Asian lineage H5N1 HPAI viruses

Most clinical cases caused by Asian lineage H5N1 HPAI viruses have been severe. The initial signs are often a high fever and upper respiratory signs resembling human seasonal influenza, but some patients may also have mucosal bleeding, or gastrointestinal signs such as diarrhea, vomiting and abdominal pain. Lower respiratory signs tend to develop soon after the onset of the illness. Respiratory secretions and sputum are sometimes blood-tinged. Most patients deteriorate rapidly, and serious complications including heart failure, kidney disease, encephalitis and multiorgan dysfunction are common in the later stages. Milder cases have been reported occasionally, particularly among children.

H9N2 LPAI viruses

Most illnesses caused by H9N2 viruses have been reported in children and infants. These cases were usually mild and very similar to human influenza, with upper respiratory signs, fever, and in some cases, gastrointestinal signs (mainly vomiting and abdominal pain) and mild dehydration. All of these patients, including a 3-month-old infant with acute lymphoblastic lymphoma, made an uneventful recovery. Acute, influenza-like upper respiratory signs were also reported in two adults, a 35-year-old woman and a 75-year-old man. Severe lower respiratory disease, which developed into respiratory failure, was seen in a 47-year-old woman, who had chronic graft vs. host disease and bronchiolitis obliterans after a bone marrow transplant, and was receiving immunosuppressive therapy.

Although she recovered, she required long term oxygen supplementation.

Zoonotic H7N9 LPAI viruses in China, 2013-2014

Most clinical cases caused by H7N9 viruses in China have been serious, to date. The most common symptoms were fever and coughing, but a significant number of patients also had dyspnea and/or hemoptysis on initial examination, and most cases progressed rapidly to severe pneumonia, frequently complicated by acute respiratory distress syndrome and multiorgan dysfunction. Diarrhea and vomiting were sometimes reported, but conjunctivitis was uncommon, and most patients did not have nasal congestion or rhinorrhea as the initial signs.

A few uncomplicated cases were characterized by mild upper respiratory signs or fever alone, especially in children. At least one asymptomatic infection has been reported in an adult.

Other avian influenza viruses

Mild illnesses, with conjunctivitis and/or upper respiratory signs, have been reported in a number of people infected with various H7 LPAI or HPAI viruses and an H10N7 virus. One H7N7 HPAI virus, which caused only mild illness in most people, resulted in fatal acute respiratory distress syndrome and other complications in one otherwise healthy person. His initial symptoms included a persistent high fever and headache, but no signs of respiratory disease. Severe pneumonia was reported in a person infected with an LPAI H7N2 virus who had serious underlying medical conditions. He was hospitalized but recovered. A 20-year-old woman infected with an H6N1 virus in China developed a persistent high fever and cough, progressing to shortness of breath, with radiological evidence of lower respiratory tract disease. She made an uneventful recovery after treatment with oseltamivir and antibiotics. Three people with H10N8 infections in China developed severe lower respiratory tract disease, progressing in some cases to multiple organ failure and septic shock. Two cases in elderly patients were fatal. The third patient, who was 55 years of age, was hospitalized but eventually recovered.

Diagnostic Tests

Avian influenza viruses may be found in samples from the upper and/or lower respiratory tract in humans. Infections with these viruses are often diagnosed by RT-PCR, although virus isolation can also be used, and serology is occasionally helpful in retrospective diagnosis. The microneutralization assay is considered to be the most reliable test for detecting antibodies to avian influenza viruses, although other serological tests (e.g. hemagglutination inhibition) are also used. However, serology may not always be reliable. Adults infected with some avian influenza viruses did not seroconvert, even in virologically confirmed cases. Titers were also low or absent in children with mild illnesses caused by the H7N9 virus in China, even when adults with severe illnesses seroconverted. Testing for novel influenza viruses is generally performed by state, regional or national public health laboratories, and in some cases by reference laboratories capable of handing dangerous human pathogens such as H5N1 HPAI viruses.

During routine influenza diagnosis, testing that identifies the presence of influenza A, but does not detect the hemagglutinins in common human influenza viruses, might indicate a novel, possibly zoonotic, virus. Commercial rapid diagnostic test kits used to detect seasonal human influenza virus infections may not recognize avian influenza viruses.

Treatment

Treatment for avian influenza may vary, depending on the severity of the case, and can include various drugs, including antibiotics to treat or prevent secondary bacterial pneumonia, and antivirals. Antiviral drugs are most effective if they are started within the first 48 hours after the onset of clinical signs, although they may also be used in severe or high risk cases first seen after this time. The most commonly used antiviral, the neuraminidase inhibitor oseltamivir, is thought to increase the chance of survival in patients infected with Asian lineage H5N1 HPAI viruses or the H7N9 viruses, particularly if it is given early. Both of these viruses are usually sensitive to oseltamivir, although resistant isolates have been reported. Most (though not all) of the H5N1 viruses and possibly all of the H7N9 viruses are resistant to adamantanes, the other class of antiviral drug used to treat some influenza A infections. Antiviral resistance can develop rapidly, and may even emerge during treatment.

Prevention

Protective measures for zoonotic avian influenza viruses include controlling the source of the virus (e.g., eradicating HPAI viruses, closing infected poultry markets); avoiding contact with sick animals, animals known to be infected, and their environments; employing good sanitation and hygiene (e.g., hand washing); and using personal protective equipment (PPE) where appropriate. While the recommended PPE can vary with the situation and risk of illness, it may include respiratory and eye protection such as respirators and goggles, as well as protective clothing including gloves. The hands should be washed with soap and water before eating, drinking, smoking, or rubbing the eyes.

Because HPAI viruses have been found in meat and/or eggs from several avian species, careful food handling practices are important when working with poultry or wild game bird products in endemic areas, and all poultry products including meat and eggs should be completely cooked before eating. Wild birds should be observed from a distance. H5N1 vaccines for humans have been developed in the event of an epidemic, but are not in routine use. More

detailed recommendations for specific groups at risk of exposure (e.g., people who cull infected birds, field biologists, and hunters) have been published by some national and international agencies. In some cases, recommendations may include antiviral prophylaxis (e.g., for people who cull birds infected with Asian lineage H5N1 HPAI viruses) and/or vaccination for human influenza to reduce the risk of reassortment between human and animal influenza viruses. People who become ill should inform their physician of any exposure to avian influenza viruses.

Morbidity and Mortality

Asian lineage H5N1 avian influenza viruses

Illnesses caused by Asian lineage H5N1 HPAI viruses are, overall, rare; however, these viruses have been found in poultry (including small backyard flocks) for over a decade, resulting in high levels of human exposure. More than 650 laboratory-confirmed human infections were reported between 1997 and September 2014. Most patients were young and had no predisposing conditions. The case fatality rate for all laboratory confirmed cases reported to WHO has consistently been about 59-60% in the last few years. however, it differs between countries, and is particularly low in Egypt, where 28% of confirmed, suspect and probable cases between 2006 and 2010 were fatal. A high proportion of these cases occurred in young children, and their young age, early diagnosis and, treatment-related factors, and possibly the virulence of the circulating viruses, might improve survival. Antibodies to H5 viruses have been reported in a small percentage (typically <5%) of poultry-exposed populations, fueling speculation on the likelihood of asymptomatic or mild infections. Laboratory confirmed, asymptomatic or mild cases have been recognized, but only rarely.

H7N9 avian influenza viruses

Approximately 450 clinical cases have been caused by LPAI H7N9 viruses in China, as of September 2014. They mainly occurred in two waves, the first between February and May 2013, and the second from October 2013 to May 2014, with sporadic cases reported between the two outbreaks. Although the second wave has subsided, the virus has not been eradicated and further cases can be expected. Human illnesses have mainly been associated with live bird poultry markets, although the source of the virus was uncertain in some cases, and exposure to backyard poultry or poultry farms was an additional risk factor in rural patients.

Many clinical cases have occurred in older people; 55% of the patients in the first wave were at least 60 years of age. Most reported cases in adults (including young and middle-aged adults) have been serious, while many cases in children were mild. Oseltamivir treatment may have mitigated the severity in some mild cases, but other mildly affected patients had not received antivirals. The reported case fatality rate in hospitalized, laboratory confirmed patients was approximately 36% during both waves, and the risk of death among hospitalized patients increased significantly with age. Concurrent diseases or predisposing causes were reported in a significant number of patients.

The likelihood of additional, undiagnosed mild or asymptomatic infections is still being assessed, although few cases were found during national virological sampling of people with influenza-like illnesses who visit clinics. Some serological studies found no H7N9 reactivity among poultry market workers, healthcare staff, patient contacts and other populations. However, recent surveys detected antibodies to these viruses in up to 14% of poultry workers.

H9N2 avian influenza viruses

Clinical cases caused by H9N2 viruses have mainly been reported in children. Most cases, including an infection in an immunocompromised infant, have been mild, and were followed by uneventful recovery. Severe illness was reported in an adult with serious underlying medical conditions. Serological studies have found antibodies to H9N2 viruses in poultry-exposed groups in endemic regions, generally at low prevalence (<5%). A prospective study of adults reported that two people seroconverted, but did not report being ill.

Other avian influenza viruses

Most reported infections with H7 viruses other than the H7N9 virus in China have been mild in healthy people, whether they were caused by an LPAI or HPAI virus; however, one H7N7 HPAI virus caused a fatal illness in a healthy person, while affecting others only mildly. Mild signs were reported in poultry workers infected with an H10N7 virus in Australia, but H10N8 viruses caused fatal infections in two elderly patients in China and a serious illness in a 55-year-old. A young woman infected with an H6N1 virus in China had evidence of lower respiratory tract complications, but recovered with treatment. Antibodies to various subtypes have been found occasionally in people with poultry exposure. A few people seroconverted to H6, H7 and H12 viruses in prospective studies of adults, but no clinical cases were identified.

Internet Resources

Canadian Food Inspection Agency [CFIA]. Fact Sheet - Avian Influenza
http://www.inspection.gc.ca/animals/terrestrial-animals/diseases/reportable/ai/eng/1323990856863/1323991018946

CFIA Notifiable Avian Influenza Hazard Specific Plan
http://www.inspection.gc.ca/english/anima/disemala/avflu/man/avflue.shtml

Centers for Disease Control and Prevention. Avian Influenza
http://www.cdc.gov/flu/avianflu/

Department of the Interior. Appendix H: Employee Health and Safety Guidance for Avian Influenza Surveillance and Control Activities in Wild Bird Populations http://www.doi.gov/emergency/pandemicflu/appendix-h.cfm

European Food Safety Authority. Highly pathogenic avian influenza A subtype H5N81 http://www.efsa.europa.eu/en/efsajournal/pub/3941.htm

Public Health Agency of Canada (PHAC). Influenza http://www.phac-aspc.gc.ca/influenza/index-eng.php

Public Health Agency of Canada (PHAC). Influenza http://www.phac-aspc.gc.ca/influenza/index-eng.php

PHAC. Pathogen Safety Data Sheets http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/index-eng.php

The Merck Manual http://www.merckmanuals.com/professional/index.html

The Merck Veterinary Manual http://www.merckmanuals.com/vet/index.html

United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS). http://www.aphis.usda.gov/wps/portal/aphis/home/

USDA APHIS. Biosecurity for the Birds 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

USGS National Wildlife Health Center. Wildlife Health Bulletin #05-03 (with recommendations for field biologists, hunters and others regarding contact with wild birds http://www.nwhc.usgs.gov/publications/wildlife_health_bulletins/WHB_05_03.jsp

World Health Organization. Zoonotic Influenza http://www.who.int/influenza/human_animal_interface/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/international-standard-setting/terrestrial-manual/access-online/

OIE Terrestrial Animal Health Code http://www.oie.int/international-standard-setting/terrestrial-code/access-online/

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