Influenza

Flu, Grippe, Avian Influenza, Grippe Aviaire, Fowl Plague, Swine Influenza, Hog Flu, Pig Flu, Equine Influenza, Canine Influenza

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Influenza

Influenza viruses are RNA viruses in the family Orthomyxoviridae that can affect birds and mammals including humans. Influenza B and C viruses are maintained only in human populations, although they are isolated occasionally from other mammals. Influenza A viruses can affect many species, with the vast majority of these viruses occurring among birds. Waterfowl and shorebirds seem to be the reservoir hosts for avian influenza viruses, which are usually carried asymptomatically in these populations. Avian influenza viruses can also become established among poultry, causing two forms of disease. Low pathogenicity avian influenza (LPAI) viruses, the form usually carried in wild birds, generally cause asymptomatic infections, mild respiratory disease or decreased egg production in poultry. Some LPAI viruses can mutate in poultry populations to become high pathogenicity avian influenza (HPAI) viruses. HPAI viruses cause a severe illness that can kill up to 90-100% of a flock. A few influenza A viruses have become adapted to mammals including humans, swine, horses and dogs, and circulate in these populations. These viruses are called human influenza A viruses, swine influenza viruses, equine influenza viruses and canine influenza viruses, respectively. In the mammalian species to which they are adapted, influenza viruses cause respiratory disease with high morbidity but low mortality rates. More severe cases can occur in conjunction with other diseases or debilitation, as well as in infancy or old age.

Influenza A viruses that circulate in birds and mammals are occasionally transmitted from one species to another. In most cases, these infections do not spread efficiently; they remain limited to an individual or a small group, and soon disappear from the novel host population. However, some of these viruses can become adapted to a new species and cause outbreaks, epidemics or pandemics. One equine influenza virus recently began circulating in dog populations, becoming adapted to a new species and cause outbreaks, epidemics or pandemics.

The effects of avian influenza viruses on people are highly variable. Although many human infections are limited to conjunctivitis or mild respiratory disease, some viruses can cause severe disease and death. Currently, HPAI H5N1 avian influenza viruses seem to be the greatest threat to people, as well as to poultry. These viruses first emerged in the late 1990s. They have since become established among birds in Asia, have spread to other geographic regions, and continue to threaten new areas. As of December 2009, H5N1 viruses have been responsible for approximately 450 human infections, generally as the result of close contact with poultry; about 60% of all laboratory confirmed cases have been fatal. Asian lineage H5N1 viruses have also caused disease in 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, H5N1 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. Unusually, numerous deaths have been reported in wild birds, which are rarely affected by avian influenza viruses. There are fears that an Asian lineage H5N1 strain could eventually become adapted to humans, possibly resulting in a severe human pandemic.

Other avian influenza viruses can also undergo cross-species transmission. H9N2 (LPAI) viruses, which have become endemic in poultry in parts of Asia and the Middle East, may be of particular concern. These viruses have caused outbreaks among poultry in many countries, and it has been recently recognized that some isolates share internal genes with H5N1 viruses. H9N2 viruses have been detected in pigs with respiratory disease and fatal paralysis in China. Antibodies to H9N2 viruses, as well as rare clinical cases, have also been reported in humans. As of December 2009, known human H9N2 infections have been relatively mild, and fatal cases have not been reported.

Swine influenza virus infections also occur sporadically among people. Most of these cases have been relatively mild and some may have been asymptomatic, but...
severe illnesses and a few deaths have been reported.\textsuperscript{1,3,21-24,82-94} Swine influenza viruses are usually not well-adapted to humans, and little or no person-to-person transmission usually occurs.\textsuperscript{1,2,22,24,89} Nevertheless, these viruses appear to have been responsible for the first human pandemic of the 21st century. In April 2009, a novel virus with the subtype H1N1 began circulating in people.\textsuperscript{93,95,96} The genetic analysis of this virus suggests that it originated from North American and Eurasian swine influenza viruses that reassorted.\textsuperscript{97-99} The novel H1N1 virus has also been transmitted from people to animals. Pigs are susceptible to this virus, and sporadic outbreaks have been reported among swine herds in a number of countries.\textsuperscript{100-116} Outbreaks have also been reported in turkey flocks, and a few cases have been recognized in pet ferrets, cats and dogs, as well as in a cheetah in a zoo.\textsuperscript{117-129}

**Etiology**

Viruses in the family Orthomyxoviridae cause influenza. There are three genera of influenza viruses: *influenzavirus A*, *influenzavirus B* and *influenzavirus C*.\textsuperscript{130} Separate viral species are not recognized within these genera; the members of each genus belong to the three species “influenza A virus,” “influenza B virus” or “influenza C virus,” respectively.\textsuperscript{130} These viruses are also called type A, type B and type C influenza viruses.

**Influenza A viruses**

Influenza A viruses include avian, swine, equine and canine influenza viruses, as well as the human influenza A 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).\textsuperscript{11,13,19,23} These two proteins are involved in cell attachment and release from cells, and are also major targets for the immune response.\textsuperscript{2,20,131} Wild birds carry most of the known hemagglutinin and neuraminidase antigens, but some, such as H14 and H15, are uncommon and seem to occur only in limited geographic areas.\textsuperscript{17} Only limited subtypes are found in each species of mammal.\textsuperscript{3} Influenza A viruses are also 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.\textsuperscript{1,3} [e.g., the prototype strain of the H7N7 subtype of equine influenza virus, first isolated in Czechoslovakia in 1956, is A/eq/Prague/56 (H7N7).] For human strains, the host is omitted.

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

Influenza A viruses change frequently. Strains evolve as they accumulate point mutations during virus replication; this process is sometimes called 'antigenic drift.'\textsuperscript{3} A more abrupt change can occur during genetic reassortment. Reassortment is possible whenever two 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.\textsuperscript{20} Reassortment between 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 a 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.\textsuperscript{1,2} For example, human viruses can continue to circulate in pigs and could re-emerge into the human population.\textsuperscript{2} 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 viruses**

Avian influenza viruses circulate in a variety of domesticated and wild birds.\textsuperscript{1,11,14,17,34} They are also isolated occasionally from mammals including humans.\textsuperscript{1,9,11,25,26,35,37,44,53,55-57,132,133} Avian influenza viruses are classified as either high pathogenicity (HPAI) or low pathogenicity (LPAI) viruses, based on the genetic features of the virus and the severity of disease in experimentally inoculated chickens.\textsuperscript{11,13,19} 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 poultry, while LPAI infections are generally much milder. To date, all HPAI viruses have contained the H5 or H7 hemagglutinin; subtypes that contained other hemagglutinins have been found only in the LPAI form.\textsuperscript{12,18,19} H5 and H7 LPAI viruses can evolve into high pathogenicity strains, typically while they are circulating among poultry.\textsuperscript{11,12,15} When a subtype has become established and circulates 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.\textsuperscript{11,40,42,73,134,135}

In wild species, avian influenza viruses are especially common among birds that live in wetlands and other aquatic environments.\textsuperscript{17} Waterfowl (order Anseriformes) and shorebirds (order Charadriiformes) seem to be the natural reservoirs for influenza A viruses, and carry all of the known subtypes, usually in the LPAI form.\textsuperscript{1,12,17,23} Important reservoir hosts include ducks, geese, swans, gulls, terns and waders.\textsuperscript{17} The LPAI viruses found in wild birds can be divided into Eurasian and American lineages.\textsuperscript{17} Although viruses occasionally cross between these two geographic regions, this is uncommon.\textsuperscript{17} The predominant subtypes in wild ducks change periodically.\textsuperscript{1} H3, H4 and H6 are detected most often in North
American and northern European wild ducks, but nearly all hemagglutinin and neuraminidase antigens can be found.\(^{13}\) 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.\(^{17}\) Gulls are often infected with H13 LPAI viruses, which are rare in other avian species.\(^{17}\) They can also carry H16 viruses.\(^{15}\) Most, though not all, infections in wild waterfowl and shorebirds are asymptomatic.\(^{1,2,11,12,136,137}\)

Limited information is available on the subtypes found in other species of birds. Subtypes that have been detected in raites include H3N2, H4N2, H4N6, H5N1, H5N2, H5N9, H7N1, H7N3, H9N2, H10N1, H10N4 and H10N7.\(^{18,51,138-140}\) Isolates from cage birds usually contain H3 or H4; however, infections with high pathogenicity subtypes containing H7 or H5 can also occur.\(^{19,51,60,71,141,142}\) Very few avian influenza viruses were found in wild passerine birds, pigeons and doves in one survey.\(^{143}\)

**Swine influenza viruses**

Swine influenza viruses mainly affect pigs, but they can cause disease in turkeys.\(^{1,3}\) Outbreaks have also been described recently in ferrets and mink.\(^{91,144}\) Other species may also be infected, although this seems to be rare. One H1N1 swine influenza virus, which was avirulent for both poultry and pigs, was isolated from a duck in Hong Kong, and experimental infections have been reported in calves.\(^{145,146}\)

The most common subtypes currently found in pigs are H1N1, H1N2 and H3N2; however, the situation is complex, as two or more viruses of each subtype are circulating in swine populations.\(^{2,16,20,147}\) One H1N1 virus found in North America is the ‘classical’ H1N1 swine influenza virus. This virus, the first influenza virus known to have infected pigs, was first detected in swine populations in 1918.\(^{2,12,16,20}\) Reassortant H1N1 viruses, which contain the same neuraminidase and hemagglutinin as the classical H1N1 virus, but have internal proteins from triple reassortant H3N2 viruses (see below), have recently become prominent among pigs in North America.\(^{148-150}\) An ‘avian-like’ H1N1 virus circulates mainly in European pigs.\(^{2,16,20}\) This virus seems to be an avian influenza virus that was transmitted whole to pigs.\(^{16,20,151}\) It has, in some locations, replaced the classical H1N1 virus.\(^{16,20}\) A different ‘avian-like’ H1N1 virus has been detected, together with the classical H1N1 virus, among pigs in Asia.\(^{5,16}\) Other variants have also been found. For example, H1N1 reassortant viruses consisting of classical swine influenza virus genes and a human PB1 polymerase gene have been detected in pigs in Canada\(^{152}\) and a wholly human lineage H1N1 virus was reported from pigs in China in 2007.\(^{153}\)

In North America, some of the most important swine influenza viruses are the triple reassortant H3N2 viruses. These viruses first emerged in U.S. pigs in the late 1990s, mainly in the Midwest,\(^ {20,34,152,154,155}\) and they have been detected in Canada since 2005.\(^ {59,144,156}\) The North American H3N2 triple reassortant viruses contain hemagglutinin and neuraminidase proteins from a human influenza virus, and internal proteins from the classical swine influenza virus, an avian influenza virus and a human influenza virus.\(^ {154}\) The particular combination of internal genes carried by these viruses is known as the triple reassortant internal gene (TRIG) cassette. This cassette seems to be especially efficient in generating swine influenza virus recombinants with new hemagglutinin and neuraminidase genes, including some from human influenza viruses.\(^ {149,150}\) Viruses with this cassette have had increased antigenic drift compared to other swine influenza viruses.\(^ {149}\)

H3N2 viruses also occur in Europe and Asia, but these viruses seem to be the result of reassortment between a human H3N2 virus, circulating there in pigs since the 1970s, and the H1N1 ‘avian-like’ virus.\(^ {2}\) The European H3N2 viruses contain human H3 and N2 proteins, and internal proteins from the avian virus.\(^ {2}\) In China, H3N2 viruses that have been detected include double reassortants that contain human H3 and N2 and internal genes from avian influenza viruses, and triple reassortants with human H3 and N2 and internal gene segments from both swine and avian influenza viruses.\(^ {157}\) Some wholly human-like H3N2 viruses have also been found among pigs in China.\(^ {157}\)

The H1N2 virus in the U.S. is a reassortant of the classical H1N1 swine influenza virus and the North American triple reassortant H3N2 virus.\(^ {2}\) Other variants have also been detected. Some H1N2 viruses isolated from Canadian pigs contained neuraminidase and hemagglutinin genes from two different human influenza viruses, the polymerase gene from human H1N2 viruses, and other internal genes from classical H1N1 swine influenza viruses.\(^ {152}\) The H1N2 virus in Europe is a reassortant of a human H1N1 virus and the ‘human-like’ European H3N2 virus.\(^ {2,16}\) In China, both the H1N2 swine influenza virus from North America, and apparent reassortants between the H1N1 classical swine influenza virus and North American H3N2 human influenza viruses have been reported.\(^ {158}\) Other novel reassortants of swine influenza viruses continue to be discovered.\(^ {159,160}\)

New subtypes have also been found in some swine populations. The novel subtype H3N1 has recently been isolated from pigs in the U.S.\(^ {161,162}\) This subtype appears to contain genes from human, swine and avian influenza viruses.\(^ {161,162}\) A different H3N1 influenza virus, containing human and swine influenza virus genes, has been found in Korea\(^ {163}\) and an H3N1 virus which may be a novel reassortant between H3N2 and H1N1 swine influenza viruses has been reported in Italy.\(^ {164}\) An H2N3 virus isolated from pigs with respiratory disease in the U.S. contained genes from avian and swine influenza viruses.\(^ {165}\) An avian H9N2 virus has been reported from
outbreaks of respiratory disease and paralysis in pigs in southeastern China, and may circulate in swine populations there. This subtype appears to contain neuraminidase and hemagglutinin genes from avian H9N2 viruses and internal genes from an H5N1 virus (Sw/SD/2/03) that also infects pig populations in the area. Avian (LPAI) H5N2 and avian/swine H5N2 reassortant viruses have been isolated from pigs in Korea. The avian H5N2 virus appears to have been circulating among pigs since 2006.

The novel H1N1 virus of swine origin

Swine influenza viruses are occasionally found in humans. In most cases, these viruses are poorly adapted to humans, and little or no person-to-person transmission occurs. In 2009, a novel H1N1 virus, which seems to have originated from one or more swine influenza viruses, emerged in human populations.

This virus appears to be a reassortant between North American and Eurasian swine influenza viruses; it contains a hemagglutinin gene that is most closely related to swine influenza viruses in North America, a neuraminidase gene that is related to swine influenza viruses in Eurasia, and internal genes from two or more swine influenza viruses including the North American triple reassortant H3N2 viruses and a Eurasian virus. Similarly to some of the swine influenza viruses described above, the parental swine influenza viruses include some gene segments that originally came from avian and human influenza viruses. In 2009, the novel H1N1 virus was the dominant influenza virus being transmitted in human populations in most parts of the world. It has also been transmitted to animals, including pigs, apparently from infected humans.

Equine influenza viruses

Equine influenza viruses mainly infect horses and other Equidae (i.e., donkeys, mules and zebras). The two subtypes known to circulate in equine populations and cause disease are H7N7 (equine virus 1) and H3N8 (equine virus 2). There is less antigenic drift in these viruses than human influenza A viruses. H7N7 equine influenza viruses have become extinct or are present at only very low levels in most parts of the world where surveillance is conducted. In contrast, H3N8 viruses circulate widely. H3N8 viruses have diverged into distinct Eurasian and American evolutionary lineages. The American lineage contains the classical American lineage (also called the Kentucky lineage), the Florida sublineage (originally called the Florida lineage) and the South American lineage. Some viruses of the American lineage (Florida sublineage) have also become established in Europe and Asia.

In 1989, a novel strain of equine influenza [A/eq/Jilin/89 (H3N8)] caused a serious epidemic, with high morbidity and mortality rates, in Chinese horses. This virus appears to be an avian influenza virus. A related virus caused influenza in a few hundred horses the following year but there were no deaths. The avian-like virus continued to circulate in horses in China for at least five years without further fatalities.

One equine H3N8 virus recently jumped into dogs in North America. Equine influenza viruses can also infect dogs without becoming established in canine populations. A limited outbreak with an equine H3N8 (American lineage) virus was reported among foxhounds in the U.K. in 2002, and equine H3N8 viruses were shown to infect dogs asymptotically during close contact with horses in an experimental study. Infections with equine H3N8 viruses have been reported among pigs in China.

Canine influenza viruses

An H3N8 canine influenza virus has been reported in canine populations in a number of U.S. states. This virus appears to be an equine influenza virus (Florida sublineage) that recently jumped species, and it bears a close resemblance to an isolate seen in horses in Wisconsin in 2004; however, the canine influenza virus has diverged genetically from equine influenza viruses.

An H3N2 virus, isolated during an outbreak of canine respiratory disease in Korea in 2007, has the potential to become a second canine influenza virus. There is evidence that this virus may have been transmitted between dogs during the outbreak, and dog-to-dog transmission occurs readily in experimentally infected dogs. The H3N2 virus seems to have originated in birds. It contains gene segments that may have come from several different avian viruses. At least three different isolates of this virus have been recovered.

Human influenza A viruses

Human influenza A viruses are mainly found in people, but they can also infect ferrets and sometimes swine. Experimental infections have been reported in raccoons. Human viruses can also replicate, to a limited extent, in the nasal epithelium of experimentally infected horses. H1N1, H1N2 and H3N2 viruses are currently in general circulation in humans. H1N2 viruses were first seen in human populations in 2001, probably as a result of genetic reassortment between the H3N2 and H1N1 viruses. H2N2 viruses circulated in the human population between 1957 and 1968. A novel H1N1 virus (see above) emerged in human populations in 2009.

Human influenza viruses change frequently as the result of antigenic drift, and occasionally as the result of antigenic shift. Epidemics occur every few years, due to small changes in the influenza viruses. Human pandemics, resulting from antigenic shifts, were most recently reported in 1918, 1957, 1968 and 2009.
Influenza A viruses in other species

Influenza A viruses are occasionally isolated from outbreaks or isolated cases in other species of mammals. Avian influenza viruses have infected pinnipeds, cetaceans and mink,1,9 and swine influenza viruses have caused outbreaks in mink and ferrets. Antibodies to influenza viruses have been detected in other species including raccoons, cattle, yak, sheep, goats, reindeer and deer,9,19,93 and a variety of mammals have been infected experimentally.1,9,19,194-196 There are also some indications, including the detection of viral nucleic acids by RT-PCR, that reptiles and amphibians can be infected with influenza viruses.9 The Asian lineage H5N1 avian influenza viruses appear to have an unusually wide host range, and can infect housecats, several species of large felids, dogs, foxes, stone martens, mink, palm civets, raccoon dogs, pigs, ferrets, rodents, pikas, rabbits and macaques.9,31,44,45,57-49,51,58,60-64,67-69,132 Unpublished research suggests that some raccoons in Japan have antibodies to H5N1 viruses.193 With the possible exception of H5N1 viruses in pikas,57 there is currently no evidence that influenza viruses have become adapted to, and are circulating in, any species other than birds, swine, humans, dogs and horses.

Influenza B viruses

Influenza B viruses are known to circulate only in human populations. These viruses can cause epidemics, but they have not, to date, been responsible for pandemics.1 They have also been found occasionally in animals.1,2,4,5,9,197 Influenza B viruses are categorized into lineages rather than subtypes. They are also classified into strains.11 Influenza B viruses undergo antigenic drift, though it occurs more slowly than in influenza A viruses.1,100 Until recently, the B/Victoria/2/87 lineage predominated in human populations, and influenza B viruses were said not to undergo antigenic shifts.11,198 In the 1990s, viruses of the B/Yamagata/16/88 lineage circulated to a very limited extent in Asia.199 This lineage emerged in various parts of the world in 2001, and it is now co-circulating with the B/Victoria/2/87 lineage.198,199 Recent evidence suggests that recombination between these two lineages is resulting in antigenic shifts.199,200

Influenza C viruses

Influenza C viruses circulate in human populations, and are mainly associated with disease in people.1,131,192,201 Until recently, they had never been linked to large-scale epidemics.1,131,192,201 However, a nationwide epidemic of influenza C was reported in Japan between January and July 2004.202 Influenza C viruses have also been found in animals.1,8 Influenza C viruses are not classified into subtypes, but they are classified into strains.11 Each strain is antigenically stable, and accumulates few changes over time.201 Recent evidence suggests that reassortment occurs frequently between different strains of influenza C viruses.203,204

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Geographic Distribution

Human influenza viruses, including the novel H1N1 virus that entered human populations in 2009, are found worldwide.1,10,205,206 Avian influenza (LPAI) viruses also occur worldwide in wild birds and poultry.1,3,10,14 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 2003.12 From 2003 to 2007, HPAI H5N1 viruses spread into domesticated or wild birds in other regions of Asia as well as into parts of Europe, the Pacific, the Middle East and Africa.11 Although some countries (e.g., all countries in Europe) eradicate these viruses whenever they occur in domesticated birds, this epizootic is ongoing and worldwide eradication is not expected in the short term.11 Unusually, some Asian lineage H5N1 HPAI viruses are also circulating in wild bird populations in Eurasia.11,12,71,73,207,208 As of December 2009, wild bird surveillance has not detected these viruses in North America or New Zealand.209,210

Swine influenza viruses are enzootic in most areas that have dense populations of pigs.211 This disease is common in North and South America, Europe and parts of Asia, and it has been reported from Africa.4,16 Although the subtypes of the swine influenza viruses found in the U.S. and Europe are the same, they are actually different viruses (see ‘Etiology’).

Equine influenza occurs in nearly all countries with substantial numbers of horses.169 Only a few countries such as New Zealand and Iceland are known to be free from this disease.168-170,212 The H3N8 subtype is widespread in horse populations.25,170 The H7N7 subtype is either extinct or present at very low levels.1,25,168,170

The H3N8 canine influenza virus has been reported in the U.S. In 2004-2006, infections were seen in racing greyhounds in a number of states including Florida, Texas, Arkansas, Alabama, Arizona, West Virginia, Kansas, Iowa, Colorado, Rhode Island and Massachusetts.177,180 Infections were first reported in the general canine population in Florida, but the virus later spread to other states.177,178,181-183,213 The distribution of this virus in the U.S. is patchy; in some cases, it caused an outbreak or was detected serologically in an area, but later disappeared from that region.213 There is no evidence that the canine influenza virus is currently circulating outside the U.S. However, infections with equine influenza viruses are occasionally reported among dogs in other regions. In the U.K., an equine H3N8 virus was responsible for an outbreak of respiratory disease in a foxhound kennel in 2002.32,214 Limited serological evidence also suggests that some U.K. foxhounds were exposed to an H3N8 virus in 2003.215 These cases appear to have been caused by H3N8 equine influenza viruses that did not become established in the canine population.32,213,214 H3N8 infections were reported from dogs in Australia during an equine influenza outbreak in 2007; these were also equine viruses that did not become
adapted to dogs. As of December 2009, the H3N2 influenza virus has been reported only from dogs in Korea.

Transmission

Transmission of mammalian influenza viruses

In mammals, influenza viruses are transmitted in aerosols created by coughing and sneezing, and by contact with nasal discharges, either directly or on fomites. Close contact and closed environments favor transmission. In ferrets, in utero transmission can occur with high viremia after experimental infection.

Transmission of avian influenza viruses among birds

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 the predominant means of spread for LPAI viruses in wild bird populations. 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. Avian influenza viruses have also been found in the yolk and albumen of eggs from hens infected with HPAI viruses. Although infected eggs are unlikely to hatch, broken eggs could transmit the virus to other chicks in the incubator. It might also be possible for LPAI viruses to be shed in eggs, but the current evidence suggests this is very rare, if it occurs at all.

In countries where HPAI has been eradicated from domesticated poultry, the disease could be introduced into flocks by migratory waterfowl or shorebirds, as well as infected poultry 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 26-30 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.

Mammalian influenza viruses (which are shed in respiratory secretions) are relatively labile, but can persist for several hours in dried mucus. There is little information on the survival of mammalian influenza viruses in water or organic material. In one study, swine influenza viruses were inactivated in untreated pig slurry in 1-2.5 hours at 50-55°C (122-131°F), two weeks at 20°C (68°F), and 9 weeks at 5°C (41°F).

Routes of 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
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as some housecats, were apparently infected when they ate raw birds.45,46,48,50,53,63 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.152 Infected raccoon dogs in China were fed chicken carcasses, and might have acquired the H5N1 virus from this source.55 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.11,229 There are other human cases where ingestion probably occurred, but additional routes of exposure also existed.240

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.63,65 Cats appear to shed these viruses from the intestinal tract as well as the respiratory tract.53,65 Pigs and foxes can also be infected by feeding them H5N1-infected poultry, as well as by intranasal or intratracheal inoculation.58,66,69 Infected foxes can excrete this virus in both respiratory secretions and feces, but pigs are known to shed it only from the respiratory tract.58,66,69 In experimentally infected dogs, Asian lineage H5N1 viruses have been found in respiratory secretions, but fecal shedding has not been reported.67,68 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.70 Fecal shedding of Asian lineage H5N1 virus may also be possible in humans; this virus has been recovered from a child with diarrhea.229 In addition, it may be found in the urine of some mammals.9

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.196,232,233 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.234

There are few detailed reports of mammalian infections with avian LPAI viruses. Raccoons that were intranasally inoculated with LPAI H4N8 viruses shed virus from the respiratory but not the digestive tract.189 These raccoons could transmit this virus to uninfected raccoons.189

Transmission of influenza viruses between species – sporadic cases, limited transmission and cross-species jumps

Ordinarily, swine influenza viruses circulate only among pigs, equine influenza viruses among the Equidae, avian influenza viruses among birds, and human influenza viruses among people. Although these viruses occasionally infect species other than their normal host, the virus is usually poorly adapted to the new host population and often affects only one or a few individuals.1,3,4,11,20 Occasionally, one of these viruses may cause an outbreak. For example, avian influenza viruses have affected mink, horses, seals and pigs, swine influenza viruses have caused outbreaks in ferrets, mink and turkeys, and equine influenza viruses have infected dogs.1,3,9,16,25,26,28,32,91,133,144 Generally, efficient transmission requires a novel hemagglutinin and/or neuraminidase protein to evade the immune response, together with viral proteins that are well adapted to the new host’s cells.20 Many outbreaks end without permanent adaptation of the virus to the species. In most of the cases mentioned above, the virus eventually disappeared from the novel host population.

It is, however, possible for a virus to become established in the new species. This has happened occasionally with whole viruses that jump to new hosts. The canine influenza virus, which jumped from horses to dogs, is a good example. Some evidence also suggests that the H1N1 virus, which caused the deadly 1918 ‘Spanish flu’ pandemic, was probably an intact avian virus that became adapted to humans.20,27,31 Dissemination is more likely if the new virus reassorts with a virus that is already adapted to the species.11 Reassortment can occur in the new host’s own cells.11,12,20 It could also occur in an intermediate host, particularly a pig,2,11,12,20 Pigs have receptors that can bind swine, human and avian influenza viruses.2,16,23,147 For this reason, they have been called ‘mixing vessels’ for the formation of new viruses. Repeated reassortment between human, avian and swine influenza viruses has resulted in a wide variety of novel swine influenza viruses that contain segments originating from two or more species. (See ‘Etiology’ for a description of some of these viruses.) Recently, quail cells have also been shown to bind both human and avian influenza viruses.235 Although reassortment can occur anywhere, many new viruses originate in Asia. In rural China and other regions, a variety of species including ducks are kept in close proximity to each other and to humans.1,2,34 This results in an increased opportunity for virus reassortment.

Transmission of Asian lineage H5N1 viruses between mammals

Because Asian lineage H5N1 avian influenza viruses can cause fatal disease in humans and other mammals, there are grave concerns about the possibility that these viruses might become adapted to these species. Over the decade that H5N1 viruses have been circulating among birds, these viruses have changed and differentiated into a number of strains and clades.11,40,42,134,135 An early study showed that, from 1999 to 2002, H5N1 avian influenza viruses isolated from healthy ducks in southern China acquired the ability to replicate and cause lethal disease in
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Asian lineage H5N1 avian influenza viruses have been responsible for nearly 450 confirmed clinical cases in humans, after contact with infected poultry. Because exposure to these viruses can be high in some human populations, and clinical illness is typically severe (thus more likely to be diagnosed), it is difficult to determine whether these viruses are more likely to infect humans than other subtypes.

Some currently circulating H9N2 viruses might undergo relatively frequent cross-species transmission. H9N2 (LPAI) viruses, which circulate among poultry in parts of Asia and the Middle East, have been associated with disease in Chinese pigs. Humans can also be infected with H9N2 viruses. Surveys in China report that from 0% to 4.5% of the human populations studied have antibodies to H9 viruses. In one study, the overall seroprevalence was 4.5%; 15.5% of poultry retailers, 2.6-5.7% of farmers and other poultry workers, and 1.3% of the general population were seropositive. Another survey reported seroprevalences of 0% to 1.7% in poultry workers, depending on the geographic area. Symptomatic infections have occasionally been reported in H9N2-virus infected humans. In general, these cases appear to be clinically indistinguishable from human influenza virus infections.

Some serological evidence suggests that poultry workers, veterinarians and hunters may be regularly exposed to avian influenza viruses of various subtypes; antibodies to H4, H5, H6, H7, H9, H10 and H11 viruses have been found in healthy people. These antibodies may be more common among people who are exposed to free-range or backyard poultry than workers in poultry confinement facilities. Experimental infections, accompanied in some cases by mild respiratory signs and other influenza symptoms, have been established in human volunteers inoculated with some subtypes including H4N8, H10N7 and H6N1.

Swine influenza viruses in humans

Infections with swine influenza viruses are reported sporadically in humans. Most of these infections occur after direct contact with pigs, but viruses may also spread to people through another host. For example, an H1N1 swine influenza virus, which had infected a turkey herd, was then transmitted to a laboratory technician who developed respiratory signs. How often swine influenza viruses infect people is unknown. If most infections resemble human influenza, they may not be

Zoonotic influenza viruses reported in humans

Infections with avian or swine influenza viruses are reported periodically in humans. With rare exceptions, these viruses have not become adapted to people.

Avian influenza viruses in humans

- Two of the last four human pandemics appear to have been the result of reassortment between avian and human influenza viruses. The 1957 H2N2 (‘Asian flu’) virus contained avian hemagglutinin, neuraminidase and an internal protein, and five other proteins from a human H1N1 strain. The H3N2 ‘Hong Kong flu’ virus of 1968 had two new proteins from an avian virus – the new hemagglutinin and an internal protein – but kept the neuraminidase and remaining proteins from the H2N2 virus.

- Illnesses caused by H5, H7 and H9 avian influenza viruses are documented occasionally in people. Most of these infections have resulted from direct contact with infected poultry or fomites; however, during a 2003 outbreak in the Netherlands, three family members of poultry workers were also infected. The virus subtype was H7N7. No sustained person-to-person transmission has been reported, to date, with any of the viruses currently circulating in bird populations.

- Asian lineage H5N1 avian influenza viruses have been reported among zoo tigers and experimentally infected housecats. No animal-to-animal transmission was reported in asymptomatic cats infected by exposure to a sick swan, or in experimentally infected pigs. In one study, an 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 Asian lineage H5N1 viruses might have become established among some pika populations in China; these viruses do not seem to cause severe clinical signs in these animals.

In humans, only rare cases of limited person-to-person spread have been documented, and these cases occurred after close, prolonged contact. In 2007, an Asian lineage H5N1 virus with the ability to bind human receptors was isolated from a person in Thailand. Whether this modification would allow the virus to be transmitted more efficiently from person to person is unknown. This particular isolate was found only once, to date, and may have been eliminated by infection control measures.

Sustained person-to-person transmission has never been reported, as of December 2009.© 2009

Swine influenza viruses in humans

Infections with swine influenza viruses are reported sporadically in humans. Most of these infections occur after direct contact with pigs, but viruses may also spread to people through another host. For example, an H1N1 swine influenza virus, which had infected a turkey herd, was then transmitted to a laboratory technician who developed respiratory signs. How often swine influenza viruses infect people is unknown. If most infections resemble human influenza, they may not be
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Incubation Period

The incubation period for seasonal human influenza is short; most infections appear after one to four days. Infections with the novel H1N1 virus circulating in humans usually become apparent in two to seven days.

The incubation period for avian influenza in humans is difficult to determine. Limited data from Asian lineage H5N1 infections suggest that, for this virus, it may range from two to eight days and could be as long as 17 days. In most cases, the first symptoms occur 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

Seasonal human influenza

Uncomplicated infections with human influenza A or B viruses are usually characterized by upper respiratory symptoms, which may include fever, chills, anorexia, headache, myalgia, weakness, sneezing, rhinitis, sore throat and a nonproductive cough. Diarrhea, abdominal pain and photophobia are also possible. Nausea, vomiting and otitis media are common in children, and febrile seizures can occur in severe cases. In young children, the initial signs may mimic bacterial sepsis. Most people recover in one to seven days, but in some cases, the symptoms may last up to two weeks or longer.

More severe syndromes, including pneumonia, can be seen in some individuals, especially those with chronic respiratory or heart disease. Secondary bacterial or viral infections may also occur. In addition, influenza A has been associated with encephalopathy, transverse myelitis, Reye syndrome, myocarditis, pericarditis and myositis.

Because influenza C viruses are difficult to isolate, there are few reports on their clinical features. These viruses are mainly thought to cause mild upper respiratory disease in children and young adults, but more severe cases with lower respiratory signs including bronchitis or pneumonia can also occur; some recent descriptions suggest that clinical cases may be indistinguishable from influenza A or B. In one recent study, the...
most common clinical signs were fever, cough and rhinorrhea, but 29 of 179 children were hospitalized with more serious illnesses such as pneumonia, bronchitis or bronchiolitis.259 Serious disease was most common in children less than two years of age.259 Fever and cough were the most common signs in 14 patients from France, with rhinitis, pharyngitis, wheezing and/or otitis in some individuals.257 This study also documented lower respiratory tract signs including pneumonia and bronchiolitis in a few patients.256 Fever, cough, arthralgia, headache, sore throat and rhinorrhea were reported in four infected children in Cuba.258 A study from Spain reported high fever and lower respiratory tract illness, severe enough to require hospitalization, in a few infants.256 Gastrointestinal symptoms including diarrhea and vomiting have been reported in some patients; co-infections with gastrointestinal pathogens were present in some but not all cases.256,257 Some influenza C infections may be asymptomatic.

**Novel H1N1 virus of swine origin**

In most people, the novel H1N1 virus causes a relatively mild illness, which resembles the disease caused by other human influenza viruses.167,167,205,205,255,255,260-262 Vomiting and diarrhea have been reported in a significant number of cases.205,255,255,260-262 Most people have a self-limiting illness, and recover within a week.205,255,255,260-262 Severe primary viral pneumonia and/or acute respiratory distress syndrome occur in a small percentage of cases, and may be fatal.167,255,262-265 Patients who become severely ill usually begin to deteriorate 3-5 days after the onset of the symptoms, and their condition rapidly becomes serious, often progressing to respiratory failure within 24 hours.260,265 Multiple organ failure may be seen.260,265 Like other influenza viruses, the novel H1N1 virus can also exacerbate chronic medical conditions, especially respiratory diseases such as asthma or chronic obstructive pulmonary disease, and some cases may be complicated by secondary bacterial infections.205,205,255,255,260-262 Underlying health conditions, very young age or pregnancy increase the risk of severe disease.167,255,264,267-270 A significant number of serious or fatal cases have been reported in healthy children or young adults, who would not be expected to have a high risk of complications.167,260,264,267,268

**Avian influenza infections in humans**

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.12 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.2,11,12,15,33-35,38

**Asian lineage H5N1 viruses**

The Asian lineage H5N1 HPAI viruses appear to cause more severe disease than other HPAI viruses or LPAI viruses.38 High fever and upper respiratory symptoms resembling human seasonal influenza tend to be the initial signs.12,30,271 In some patients, there may also be mucosal bleeding, or gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain.12,40,271 Respiratory signs are not always present at diagnosis; two patients from southern Vietnam had acute encephalitis without symptoms to indicate respiratory involvement.12 Similarly, a patient from Thailand exhibited only fever and diarrhea.12 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 crumbliness during inspiration.12,40 The respiratory secretions and sputum are sometimes bloodstream.12 Most patients deteriorate rapidly.12,40 Heart failure, kidney disease, encephalitis and multiorgan dysfunction are common in the later stages, and disseminated intravascular coagulation can occur.12,40,271 Milder cases have been reported occasionally, particularly among children.38,39 One H5N1 infection in a child with upper respiratory signs and an uncomplicated recovery after antibiotic treatment was recognized only by routine virus surveillance.39 Asymptomatic infections with Asian lineage H5N1 viruses seem to be rare.38,41

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

- In 1997, the first eighteen H5N1 infections in people were reported during an HPAI outbreak among poultry in Hong Kong.2,11,12,15,34 The symptoms included fever, sore throat and cough and, in some cases, severe respiratory distress and viral pneumonia.12 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.11,12,34,38 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.11,34,38
- In 2002, antibodies to an avian H7N2 virus were found in one person after an LPAI outbreak among poultry in Virginia.11
- In 2003, two HPAI H5N1 infections were reported in a Hong Kong family that had traveled to China.11,12,34 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.11,35,35 Most cases occurred in
poultry workers, but three family members also became ill.\textsuperscript{11,33} In 78 of the confirmed cases, conjunctivitis was the only sign of infection.\textsuperscript{35} 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.\textsuperscript{35} 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.\textsuperscript{35} 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.\textsuperscript{196}

- Cases of conjunctivitis have been reported after contact with HPAI H7N7 avian viruses in infected seals.\textsuperscript{26,35}
- In 2003, an H9N2 LPAI infection was confirmed in a child in Hong Kong.\textsuperscript{11,12,36} The symptoms included mild fever, mild dehydration and cough.\textsuperscript{36} The child was hospitalized but recovered.
- In 2003, an LPAI H7N2 infection with respiratory signs was reported in a patient in New York.\textsuperscript{17} 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.\textsuperscript{11} 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 11 2009, 445 confirmed human cases had been reported to WHO; 263 cases were fatal.\textsuperscript{43}
- In 2007, a mild LPAI H9N2 virus infection was reported in a 9-month-old child in Hong Kong.\textsuperscript{11}
- In 2008, an H9N2 virus was found in a 2-month-old infant in China.\textsuperscript{37}
- In 2009, an H9N2 virus infection was reported in a 3-year-old child with a fever, cough and rhinorrhea in Hong Kong.\textsuperscript{37} She was hospitalized but recovered. There is no indication in the report that this case was more severe than the previously reported infections.

**Swine influenza virus infections in humans**

Serological evidence suggests that swine influenza virus infections might occur regularly among people who are occupationally exposed.\textsuperscript{1,2,21,22} Serological evidence suggests that approximately 500 people on the fort had been infected by person-to-person spread. (This virus is not the same virus involved in the swine-origin H1N1 pandemic of 2009.)

- A localized outbreak was reported at Fort Dix, New Jersey in 1976. An H1N1 swine influenza virus was isolated from five recruits with respiratory disease, including one who died of pneumonia.\textsuperscript{1,2,23} Other people on the base may also have been ill with the same infection.\textsuperscript{21,24} Serological evidence suggests that approximately 500 people on the fort had been infected by person-to-person spread. (This virus is not the same virus involved in the swine-origin H1N1 pandemic of 2009.)
- A self-limiting illness with influenza symptoms was reported in a college student infected with an H1N1 virus in 1979.\textsuperscript{22} There was evidence that his roommate had been infected but remained asymptomatic.
- In 1980, an H1N1 virus infection with influenza symptoms including diarrhea occurred in a young boy, who recovered.\textsuperscript{22} There was no evidence of spread to his family.
- Swine influenza virus (H1N1) was isolated from an immunocompromised child with fulminant pneumonia who died in 1982.\textsuperscript{82} Serological evidence of possible infection was found in five contacts, but the infection did not spread further.
- In 1986, an H1N1 virus caused severe viral pneumonia in a 29-year-old swine farmer in the Netherlands.\textsuperscript{85} The farmer had been in contact with pigs showing signs of respiratory disease.
- In 1988, an H1N1 swine influenza virus was isolated from a pregnant woman with viral pneumonia in Wisconsin.\textsuperscript{86} She apparently became infected while attending an agricultural fair, and died shortly after giving birth. Several health care workers developed influenza-symptoms after exposure.\textsuperscript{21}
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- In 1991, a healthy young laboratory animal caretaker in Maryland died of pneumonia caused by an H1N1 influenza virus. He had close contact with pigs in a research facility. The virus appeared to be a reassortant, but all of the gene segments were of swine influenza virus origin. No one who had been in contact with the caretaker became ill, and only one person was seropositive.

- In 1993, an H1N1 swine influenza virus caused severe viral pneumonia in a 5-year-old child who lived on a pig farm in the Netherlands. The virus, which was also found in sick pigs on the farm, was a triple reassortant H3N2 virus with genes from swine, human and avian influenza viruses. The infected individual was given antiviral drugs, and recovered uneventfully. Other workers on the farm were treated prophylactically and did not become ill.

- In 2004, an Asian H1N2 swine influenza virus was isolated in the Philippines from a 25-year-old man with symptoms of influenza including high fever, dizziness and occasional vomiting. He recovered without complications. There was no evidence of person-to-person transmission.

- In 2005, an Asian H1N1 swine influenza virus was isolated from a 4-year-old boy in Thailand with rhinorrhea, fever and myalgia. The child recovered without complications, and there was no evidence that the virus had infected others.

- In 2005, a recombinant swine influenza virus was recovered from a farm worker with influenza symptoms in Canada. The virus, which was also found in sick pigs on the farm, was a triple reassortant H3N2 virus with genes from swine, human and avian influenza viruses. The infected individual was given antiviral drugs, and recovered uneventfully. Other workers on the farm were treated prophylactically and did not become ill.

- In 2007, an H3N2 swine influenza virus was isolated from an infant with respiratory disease in Canada. The child was hospitalized but recovered. He had no direct contact with animals, but lived on a communal farm. Four of 7 household members and 4 of 46 other people on the farm had antibodies to this virus.

- In November 2008, a mild, self-limited case of H1N1 swine influenza was reported from a 50-year-old woman who worked on a swine farm in Spain. This case was diagnosed only because the physician participated in an influenza surveillance program and collected a laboratory sample for virus identification. The physician who treated her reported an influenza-like illness shortly afterward, but was not tested for the virus. No other potential cases were associated with this infection.

- Between 2005 and February 2009, 11 human infections with triple reassortant H1N1 swine influenza viruses were reported to the U.S. Centers for Disease Control and Prevention (CDC). The symptoms included fever, coughing, sore throat, headache, diarrhea, vomiting, myalgia, shortness of breath and conjunctivitis. Two children were hospitalized for dehydration, but recovered without other complications. Two patients, a 26-year-old previously healthy woman and a 48-year-old woman with asthma and a history of smoking, experienced severe illness with pneumonia and respiratory failure, but recovered. Nine of the patients had a history of contact with pigs, and one case was thought to have been transmitted from person to person. One patient had three family members with suspected but unconfirmed swine influenza virus infections.

- A recent literature review summarized 49 cases of swine influenza that had been documented in scientific journals as of April 2006 (including many of the cases described above), and one additional case identified in an ongoing survey of swine influenza among farmers. Thirteen of the cases were from the outbreak at Fort Dix; the other 37 were described as ‘cases in civilians.’ Twenty of the 37 civilian patients were previously healthy; others had immunosuppressive conditions including cancer and pregnancy. Four cases involved H3N2 viruses; the remainder were H1N1. All cases were described in the literature as upper respiratory disease, acute respiratory disease or pneumonia. Most patients recovered, but seven deaths were reported.

Equine and canine influenza virus infections in humans

Antibodies to equine H3N8 viruses have been reported in humans. Human volunteers inoculated with an equine virus became ill, and virus could be isolated for up to 10 days. There are no reports of clinical cases caused by natural exposure to equine influenza viruses or canine influenza viruses.

Communicability

Human influenza viruses are readily transmitted from person to person. Infected adults usually begin to shed influenza A viruses the day before the symptoms appear, and are infectious for 3-5 days after the initial signs. Young children can shed virus for up to six days before, and 10 or more days after they become ill. Severely immunocompromised individuals may remain infectious for weeks to months. Humans have transmitted influenza viruses to ferrets and occasionally to swine.

For the novel (2009 pandemic) H1N1 virus, the estimated period of communicability is from 1 day before the symptoms appear, to as long as 7 days after their
onset. People may shed this virus for as long as they are ill, and in some cases, for 2-3 days after the fever has resolved. Children and people who are immunocompromised might be infectious for longer. One study presented at a recent conference found that viral nucleic acids could be detected by reverse transcription polymerase chain reaction (RT-PCR) assays in children for 1 to 13 days after they became febrile, and virus could be isolated for 1 to 7 days. Atypical prolonged shedding up to 28 days (by PCR) has been reported in healthy adults with severe or relatively severe cases. Humans can transmit the novel H1N1 virus to animals as well as people. Swine herds, turkeys, ferrets, felids and dogs have apparently been infected from human contacts.

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 the Asian lineage H5N1 virus has been documented in a child with diarrhea. Transmission of this virus across the placenta may also be possible.

Swine influenza viruses have typically been transmitted only to a few close contacts, at most. There are two known outbreaks with more extensive spread. One was a localized outbreak among recruits infected with an H1N1 virus at a military base in Fort Dix, New Jersey. Approximately 500 people on the base, which contained 12,000 people, were infected or exposed; however, the virus did not spread to the surrounding community. The other is the 2009 H1N1 pandemic in humans.

**Diagnostic Tests**

Human influenza A and influenza B infections can be diagnosed by virus isolation or by the detection of antigens or nucleic acids. The viruses can be isolated in cell lines or chicken embryos, with identification by hemagglutination and neuraminidase inhibition tests or by RT-PCR. Antigens can be detected in respiratory secretions by immunofluorescence or enzyme-linked immunosorbent assays (ELISAs). Commercial rapid diagnostic test kits can provide a diagnosis within 30 minutes. RT-PCR techniques are also available. Infections can also be diagnosed by serology; a rising titer must be seen. Serological tests include complement fixation, hemagglutination inhibition and immunodiffusion. RT-PCR or culture can be used for the diagnosis of influenza C.

Infections with the novel H1N1 virus can be confirmed by RT-PCR or virus isolation from respiratory secretions. Samples should be collected as soon as possible after the onset of illness. The current immunofluorescence or rapid antigen tests for human influenza cannot distinguish other human influenza viruses from the novel H1N1 virus. Serology is currently used mainly in epidemiology and research.

Avian influenza viruses can be identified by RT-PCR, antigen detection or virus isolation from respiratory and throat swab samples. 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 PCR or antigen tests are confirmed by the 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 needed 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**

Supportive care for uncomplicated influenza in humans includes fluids and rest. More severe cases, or infections that have an elevated risk of complications, may be treated with antiviral drugs. Four drugs - amantadine, rimantadine, zanamivir and oseltamivir - are used to treat influenza. Amantadine and rimantadine ( adamantanes) are active against human influenza A viruses, if treatment is begun within the first 48 hours. Zanamivir and oseltamivir are effective for both influenza A and influenza B. Treatment usually results in milder symptoms and recovery, on average, one day sooner. Side effects, including neuropsychiatric events, may occur. Testing must be done to determine each individual virus’s drug susceptibility. Drug resistance develops rapidly in viruses exposed to amantadine or rimantadine, and may emerge during treatment. During the 2006-2008 flu seasons, human influenza viruses circulating in the U.S. and Canada exhibited high resistance to amantadine and rimantadine. The CDC recommends that these two drugs be avoided until the circulating strains become susceptible again. Laboratory studies have shown that influenza viruses can also become resistant to zanamivir and oseltamivir; however, this appears to be less common than resistance to adamantanes. The novel (swine origin) H1N1 virus circulating among humans in 2009 is resistant to amantadine and rimantadine ( adamantanes), but it is usually sensitive to oseltamivir and zanamivir. Oseltamivir-resistant isolates of this virus have been reported sporadically, but they are currently uncommon. Current recommendations for the treatment of infections with the novel H1N1 virus, including the use of antiviral drugs, are available on the CDC and WHO Web sites (see Internet Resources).
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 on the optimum dose and duration of treatment, is still needed. These viruses are resistant to amantadine and rimantadine. Although resistance to zanamivir and oseltamivir has also been reported in H5N1 viruses, it is currently uncommon.

**Prevention**

*Preventative measures for seasonal human influenza viruses*

An annual vaccine is available for influenza A and B. The vaccine is given in the fall before the flu season. It contains the viral strains that are most likely to produce epidemics during the following winter, and it is updated annually. Details on vaccine efficacy, vaccine types, and recommendations for vaccination in specific population groups are available from the CDC.

Three antiviral drugs - amantadine, rimantadine and oseltamivir - can be used for prophylaxis in high-risk populations such as the elderly or immunocompromised. Due to the high resistance of currently circulating viruses to amantadine and rimantadine, the CDC recommends that these two drugs be avoided in the U.S. until the influenza strains become susceptible again. Other preventative measures include the avoidance of contact with people with symptomatic disease, as well as hand washing and other hygiene measures.

To protect ferrets from infection with human influenza, people who are ill should avoid contact with these animals. If contact is unavoidable, good hygiene and the use of face masks and/or other measures that prevent accidental droplet transmission from coughs and sneezes may be helpful. Avoidance of contact with swine should also be considered, as influenza viruses have been transmitted occasionally to or from this species, and recombination can occur between human and swine influenza viruses. Because infections with seasonal human influenza viruses cannot be distinguished clinically from infections with the novel (pandemic) H1N1 virus, anyone with an undiagnosed flu-like illness should also avoid unnecessary close contact with species susceptible to the latter virus.

*Preventative measures for the novel H1N1 virus circulating in humans*

Preventative measures are similar to those for seasonal human influenza, and include the avoidance of close contact (approximately 6 feet) with people who have flu-like illnesses, as well as frequent hand washing, the avoidance of unnecessary hand contact with the eyes, nose or mouth, and other common sense hygiene measures. To protect others, the mouth and nose should be covered when coughing or sneezing.

There appears to be little or no cross-reactivity with the H1N1 strains in the current seasonal human influenza vaccine, but vaccines for the novel H1N1 virus became available in Fall 2009. Where limited quantities of these vaccines are available, specific risk groups may be targeted first for vaccination. Antiviral drugs may be used for prophylaxis in some high risk populations after exposure. In other cases, people may be monitored, and treated at the first sign of disease. The CDC Web site has detailed information on the current recommendations.

In areas where infections with the novel H1N1 virus are common, people at an increased risk for complications should consider avoiding crowded conditions or close contact with others. The CDC currently recommends that anyone infected with the novel H1N1 virus and anyone who has an undiagnosed flu-like illness limit contact with others, and stay home except for necessities (for instance, seeking medical care). The CDC has published specific guidelines for self-isolation and treatment, as well as recommendations for infection control measures in health care settings. People who remain home should minimize contact with others in the household during their illness. Face masks and respirators are no longer recommended in homes, communities or non-healthcare occupational settings, but they may be used voluntarily by individuals at risk for complications. To prevent virus transmission to pigs, anyone who has a flu-like illness should avoid contact with this species. Care should also be taken to avoid spreading the virus to other animals, particularly turkeys, ferrets, cats (both housecats and other felines) and dogs.

*Preventative measures for swine influenza viruses occurring in pigs*

Good hygiene and sanitation, including frequent hand washing, can help prevent human infections with swine influenza viruses. Protective clothing, gloves and other personal protective equipment also reduce exposure.

There is no indication that any swine influenza virus can be acquired by eating well-cooked pork. In pigs, swine influenza viruses replicate in the lungs and upper respiratory tract, and they are not ordinarily expected to occur outside these tissues (e.g., in meat). Ordinary food safety precautions including hand washing before and after handling raw meat, the prevention of cross-contamination of foods or surfaces used for food preparation, and the use of hot soapy water to wash contaminated surfaces would be protective if any viruses survived long enough to reach consumers. Influenza viruses are also killed by sanitizing cutting boards with 1 tbsp bleach in a gallon of water, and by cooking pork to an internal temperature of 160°F (71.1°C).
Influenza

Preventative measures for avian influenza viruses

Controlling avian influenza 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 and respirators. In addition, the World Health Organization recommends prophylaxis with antiviral drugs in people who cull birds infected with Asian lineage 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. 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.

In areas where H5N1 viruses might 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. 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 poultry products. 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 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 they 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 an avian influenza pandemic occurs in humans, 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 quarantines of infected individuals can limit the spread of disease.

Morbidity and Mortality

Seasonal human influenza

Although the morbidity rate for seasonal influenza is high, uncomplicated infections with human influenza viruses are rarely fatal in healthy individuals. Infections are more severe in the elderly, young children (particularly infants), people with respiratory or cardiac disease, and those who are immunosuppressed. Influenza-related deaths are usually the result of pneumonia or the exacerbation of a cardiopulmonary condition or other chronic disease. Over 90% of these deaths occur in the elderly. The estimated mortality rate from seasonal influenza is 0.0004 - 0.0006% in persons under 50 years old, 0.0075% between the ages of 50 and 64, and 0.1% in those over 65. Deaths are rare in children, but can occur. Immunity to the viral surface antigens (the hemagglutinin and neuraminidase) reduces the risk of infection and severity of disease. Antibodies offer limited or no protection against other virus types or subtypes.

Human influenza can occur as a localized outbreak, an epidemic, a pandemic or as sporadic cases. Although a new virus may spread among a population before the “flu season,” epidemics in temperate regions usually do not begin until after school starts in the fall. During a typical epidemic, influenza appears first among school-aged children, then spreads to preschool children and adults. During epidemics, 15% to 40% of the population may be infected. The outbreak usually lasts for three to six weeks. Epidemics in tropical regions are not usually seasonal. Antigenic drift is usually responsible for small-scale epidemics and localized outbreaks. In North America, an epidemic of influenza A usually occurs every 1 - 3 years, and an epidemic of influenza B every 3-4 years. Since 1968, the type A (H3N2) viruses have caused the most serious outbreaks with the highest mortality rates. Pandemics, which last occurred in 1918, 1957, 1968 and 2009, are caused by antigenic shifts in influenza A viruses. During influenza pandemics, the morbidity and mortality rates may increase dramatically in all age groups. In the most severe pandemic, in 1918, the morbidity rate was 25-40% and the case fatality rate 2-5%. Approximately 500,000 deaths were reported in the U.S. and an estimated 20-50 million deaths worldwide. It should be noted that antiviral drugs and antibiotics were not available at the time, and intensive care procedures were less effective. After a pandemic, an influenza virus usually becomes established in the population and circulates for years.

Less is known about influenza C than influenza A or B. Until recently, these viruses were thought to cause only sporadic cases of influenza and minor localized outbreaks. However, in 2004, a nationwide influenza C epidemic was reported in Japan. Influenza C infections seem to be most serious in very young
children. In one study, 30% of the children hospitalized with severe infections were less than two years old, and an additional 12% were between the ages of two and five.259 Symptomatic influenza C infections are reported less often than illnesses caused by influenza A or B viruses;256,257,259 however, serological studies suggest that a large percentage of the population is exposed to influenza C viruses in childhood.258-301

2009 pandemic: Novel H1N1 virus of swine origin

Morbidity and mortality information for the novel H1N1 virus are still preliminary. The initial outbreak with this virus occurred in Mexico in April.95,96,205,302-304 This was followed by the identification of the virus among travelers in other countries, then by the recognition of sustained person-to-person transmission outside Mexico.95,96,302-304 In June, a human pandemic was declared.250 As of November 27 2009, more than 622,000 cases and 7,800 deaths attributed to this virus had been reported to the World Health Organization.305 Because many countries no longer count or report individual cases, this underestimates the number of cases, particular those that are mild.206,279,305

Cases were reported in both the Northern and Southern Hemispheres during the initial stage of the outbreak. However, like other human influenza viruses, the novel H1N1 virus has been transmitted most widely during the traditional flu season, which begins in the autumn. Because the virus emerged in April, this occurred first in the Southern Hemisphere. During the flu season in the Southern Hemisphere, the reported hospitalization rates from various countries ranged from 2.0 to 31.8 per 100,000 population.269 The mortality rate in the Southern Hemisphere was relatively low, with less than 1 death per 100,000 population in most countries; individual countries reported mortality rates from 0 to 36.1 per million population.269 In Victoria, Australia, approximately 5% of the population is thought to have become ill, and 0.3% of those infected were hospitalized, with 20% of hospitalized patients transferred to an intensive care unit (ICU).265 In Victoria, 85% of these critically ill patients survived.265 In Taiwan, the mortality rate among 91 hospitalized patients was approximately 10%.306 In New South Wales, Australia, the overall mortality rate from influenza was lower than in previous years, but severe illness was seen in some high risk groups.269 Peru reported 8381 confirmed cases and 143 deaths, most (75%) in people who had other health issues.269 A small number of H1N1 infections may be asymptomatic.269 Transmission of the novel H1N1 virus appears to have declined normally after the flu season in the temperate regions of the Southern Hemisphere.279 The autumn flu season in the Northern Hemisphere has been very active in the initial stages.206,279,305,307 The impact of the novel H1N1 virus has been greater among indigenous people in both the Northern and Southern Hemispheres, with hospitalization and mortality rates that were 3-7 times greater than in non-indigenous groups.269

Although the vast majority of cases have been mild and uncomplicated, viral pneumonia has been a significant concern with this virus.167,260,264,306 Secondary bacterial infections have also contributed to some severe cases and deaths.260,266 The risk of severe illness has been greatest in children under the age of 2 years (especially infants under a year of age), pregnant women, people with underlying health conditions such as chronic respiratory disease, some cardiovascular conditions or immunosuppression, and those who are obese.267,260,262,264,265,267-270,279,284,306,307 HIV infection was linked to more severe illness in South Africa,269 but data from other countries suggest that this is not necessarily the case among HIV-infected individuals who are receiving antiretroviral drugs.167 Unusually, severe or fatal cases have also been reported among some young, previously healthy individuals, who are not ordinarily expected to be at high risk.167,265,262,264,265,267,268,279,307 The reported percentage of hospitalized patients who have had no significant pre-existing conditions ranges from approximately 24% to 59%, depending on the country and the conditions that are defined as predisposing.255,307,308 Some older people may have some immunity to the novel H1N1 virus,309,310 and this group has had lower morbidity rates than expected, but they are more likely to have severe symptoms if they become ill.167,249,260,264,269

Zoonotic swine influenza

The overall prevalence of swine influenza virus infections in humans is unknown; however, serological evidence suggests that exposure may be relatively common among people who work with pigs.1,2,21,240,246-248 Swine influenza infections have been reported among farm workers, laboratory workers, visitors at agricultural fairs or livestock shows, and a meat packer.21 Infections not associated with swine contact have included instances of limited person-to-person transmission and some published cases with no known connection to swine.21,22,84 Most sporadic cases of swine influenza have been relatively mild and some may have been asymptomatic, but some severe illnesses and a few deaths have been reported.1,2,21,22,24,82-90 During the outbreak at the Fort Dix military base, one person died of pneumonia, at least twelve additional cases thought to be swine influenza were reported, other probable cases were suspected, and serological evidence of infection was found in approximately 500 of 12,000 people on the base.1,2,21,22,244

One review reported that, of 37 other cases reported in the literature, six cases were fatal.21 Four of these patients had primary viral pneumonia, one had secondary bacterial infection, and one had extensive involvement of the abdominal organs.21 Two patients who died were described as previously healthy, one was pregnant, and two were immunosuppressed by cancer.1,2,21,22,82,83 The health status of one person was not known. In a series of 11 infections with North American triple reassortant
Influenza

H1N1 swine influenza viruses between 2005 and 2009, two children were hospitalized for dehydration, and severe illnesses were reported in a previously healthy 26-year-old woman and a 48-year-old woman with asthma and a history of smoking. All of the patients in this study recovered.

**Zoonotic avian influenza**

The severity of avian influenza varies 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. From 2003 through December 11 2009, 445 laboratory confirmed human H5N1 avian virus infections, 263 of them fatal, were reported to WHO. The overall case fatality rate, as of December 11, was 59%. 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 infection with various H7 viruses and H9N2 viruses. The reported infections with H9N2 viruses have resembled human influenza, and they have not been fatal. Most infections with H7 viruses have been limited to conjunctivitis, but influenza symptoms have also been seen. A single death was reported in an otherwise healthy veterinarian who became infected with an 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**

**Influenza A viruses**

Influenza A viruses can cause disease in birds and many mammals including swine, horses, ferrets, dogs, cats, mink, pinnipeds and cetaceans. Influenza viruses circulate in some of these species; only individual cases or limited outbreaks have been reported in others.

**Avian influenza viruses**

Avian influenza viruses mainly infect birds, but some strains can also infect and/or cause disease in mammals. Waterfowl and shorebirds, which tend to carry these viruses asymptomatically, appear to be the natural reservoir hosts. Poultry can develop serious or mild disease, depending on the subtype and strain of the virus. A few isolates, such as the Asian lineage H5N1 viruses or an H5N3 virus isolated from terns in the 1960s, can also cause serious disease in other avian species including gulls, terns, wood ducks, farmed ostriches, emus and passerine birds.

**Host range of the Asian lineage H5N1 avian influenza viruses**

Asian lineage H5N1 viruses can infect and/or cause disease in many species of birds in addition to poultry. Many H5N1 viruses have been isolated from birds in the order Anseriformes, particularly the families Anatidae (ducks, swans and geese) and Charadriiformes (shore birds, gulls and terns). Symptomatic or fatal 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, krestels, 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). Disease can also occur in passeriform birds; species that can be affected include 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. Asymptomatic infections with 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. Symptomatic infections with Asian lineage H5N1 viruses have also been reported in mammals including 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...
Influenza viruses in other species

In ferrets, clinical cases or outbreaks have been reported in animals infected with human influenza viruses, 185–188 the novel (swine origin) H1N1 virus, 119, 122,262,310,322 and an H1N1 swine influenza virus. 91 Experimental infections with avian, swine and equine influenza viruses have also been established in this species. 165,194,196,232,236,324,327

In 1984, an H10N4 virus was isolated from mink during an epidemic in Sweden. 1,9 This virus is thought to have been of avian origin. An H3N2 swine influenza virus caused a recent outbreak in mink. 144 Experimental infections with H1N1 and H3N2 human influenza viruses, H1N1 swine influenza virus, H3N8 equine influenza virus, and H3N8 and H4N6 avian influenza viruses have been established in mink, but the animals remained asymptomatic despite shedding virus. 9 Mink can also be infected with H5N3, H7N7, H8N4 and H11N4 viruses. 9

Raccoons in the U.S. have serological evidence of infection with H1, H3, H4 and H10 viruses, and they can be infected experimentally with avian LPAI H4N8 viruses and human H3N2 viruses. 189 Unpublished research suggests that some raccoons in Japan have antibodies to H5N1 viruses. 193

Influenza A viruses can infect pinnipeds and cetaceans. H3N3, H7N7, H4N5 and H4N6 viruses, closely related to avian viruses, have been isolated from seals. 1,9 Antibodies to H1, H3, H4, H6, H7, H8 and H12 viruses have also been found in these animals. 9,328 Influenza A infections have been reported sporadically in cetaceans, and H1N3, H13N2 and H13N9 viruses have been isolated from whales. 1,9 Antibodies to influenza A viruses have been reported in sea lions and porpoises. 9

Serological evidence of infection with influenza A viruses has also been reported from some other mammals including cattle, yak, sheep, goats, reindeer and deer. 9 Human influenza viruses have been isolated from some of these species, and an H3N2 virus isolated from cattle caused an illness resembling influenza in calves. 9 Antibodies to influenza A viruses have been reported in reptiles and amphibians including snakes, crocodiles, alligators, caimans, toads and frogs, and influenza A viruses have been detected by RT-PCR in caimans, alligators and crocodiles. 9 There is evidence that some of these viruses were avian, human and equine influenza viruses. 9

Influenza B viruses

Influenza B viruses can cause disease in humans, ferrets and seals, and these viruses have also been isolated from pigs and a horse. 1,2,4,197 Serological evidence of infection has been found in pigs, dogs, horses and seals. 1,3,28 Serological studies from the U.K. suggest that influenza B infections in swine are sporadic and do not spread to other pigs. 8

Influenza viruses

Equine influenza viruses

Equine influenza viruses mainly affect horses, donkeys and mules, but they can also occur in zebras. 25,168,169 Recently, infections with equine H3N8 viruses were reported among pigs in China. 175 Experimental infections have been established in cattle, dogs and humans, and antibodies to equine H3N8 viruses have been detected in dogs and humans. 1,13,170,174,174,215 Clinical cases have also been reported in dogs exposed to infected horses. 32,213

Recently, an H3N8 equine influenza virus jumped into dogs, becoming the first canine influenza virus. 28,29,173 The new H3N8 canine influenza viruses have diverged genetically from the viruses found among horses, 30 and circulate only in dogs. To date, canine influenza virus infections have not been reported in other species, including humans. 29 An H3N2 virus has been reported in dogs in Korea. 133,184

Swine influenza viruses

Swine influenza viruses mainly affect pigs, but they can also cause disease in turkeys. 13 Outbreaks have been described recently in ferrets and mink. 91,144 One H1N1 swine influenza virus, which was avirulent for both poultry and pigs, was isolated from a duck in Hong Kong. 146 Experimental infections have been reported in calves. 145

Human influenza viruses

Human seasonal influenza A viruses mainly cause disease in people and ferrets. 185–188 They can also infect pigs, and have been reported in dogs, cattle and birds. 1,3,5,122,153 Experimental infections have been established in horses and raccoons. 1,170,189

Novel H1N1 virus of swine origin

The novel (swine origin) H1N1 virus circulating in humans has infected pigs and turkeys. 100-102,125,322,321 A few clinical cases have also been reported in pet ferrets, cats, a cheetah in a zoo, and dogs. 13,3,5,122,153 Experimental infections have been established in ferrets, mice and cynomolagus macaques (Macaca fascicularis). 262,310,322 In one experiment, chickens exposed to infected pigs did not become infected. 323

Housecats, and Asian lineage H5N1 viruses have been recovered from populations of apparently healthy wild pikas. 57,132 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. 9,56,58,59 Unpublished research suggests that some raccoons in Japan also have antibodies to H5N1 viruses. 193 Experimental infections have been established in housecats, dogs, foxes, pigs, ferrets, rodents, cynomolagus macaques and rabbits. 34,51,58,60–70

Cattle can be experimentally infected with viruses isolated from cats. 70 The currently circulating H5N1 strains are continuing to evolve, and other species may also be susceptible to infection and/or disease.

Influenza B viruses

Influenza B viruses can cause disease in humans, ferrets and seals, and these viruses have also been isolated from pigs and a horse. 1,2,4,197 Serological evidence of infection has been found in pigs, dogs, horses and seals. 1,3,28 Serological studies from the U.K. suggest that influenza B infections in swine are sporadic and do not spread to other pigs. 8

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Influenza C viruses

Influenza C viruses have been isolated from humans and swine.1,4,6,201 These viruses can cause disease in experimentally infected dogs.1 Serological evidence of infection has been found in pigs, dogs and horses.1,3,7,8

Incubation Period

In poultry, the incubation period can be a few hours to a week.3,13,14 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.13 The incubation period for mammalian influenza viruses is also short. The clinical signs usually appear within 1-3 days in horses, pigs or seals,1,3,4,25,147,168,170,255,323,329 although incubation periods up to 5 days have been reported in some horses.330 The incubation period for H3N8 canine influenza can be two to five days, but most cases appear in 2-3 days.178,213 Little is known about H3N2 influenza virus in dogs; however, fever first appeared at 24 hours in experimentally infected dogs, and other clinical signs began 2-8 days after inoculation.184

Clinical Signs

Avian influenza

HPAI viruses usually cause severe disease in poultry. These viruses can cause serious infections in some species of birds on a farm while leaving others unaffected.1,13 The clinical signs are variable.3,13,18,19 Sudden death of large numbers of birds is a common presentation.13 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.13 Sinusitis, lacrimation, edema of the head, cyanosis of the head, comb and wattle, and green to white diarrhea may also be seen.3,13,15-19 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.13,13-15 However, none of these signs is pathognomonic, and sudden death may occur with few other signs.19 Most of the flock usually dies.13 Because a virus can be defined as HPAI based on its genetic composition, it is also possible for an HPAI virus to be isolated from gallinaceous birds showing mild signs consistent with LPAI.331

LPAI viruses usually cause subclinical infections or mild illness in poultry.13,18 Decreased egg production, misshapen eggs, decreased fertility or hatchability of the eggs, respiratory signs, lethargy, decreased feed and water consumption, or somewhat increased flock mortality rates may be seen.11,13,14,332,342 More severe disease, mimicking high pathogenicity avian influenza, can occur if the birds are concurrently infected with other viruses or there are other exacerabating factors.18,19

Clinical signs tend to be minimal in ducks and geese infected with avian influenza viruses, including most HPAI viruses. In ducks, the most common signs are sinusitis, diarrhea and increased mortality.3,10,72 However, some recent H5N1 isolates have caused severe acute disease with neurological signs and high mortality rates in domesticated ducks.11,60,71,73,136,219,345 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.140 Green diarrhea was the only sign of illness in ostriches inoculated with an LPAI virus of the same subtype.140 High mortality is occasionally seen in young ostriches infected with either LPAI or HPAI viruses.140

Avian influenza is often subclinical in wild birds, but some strains can cause illness and death.9,11,14-17,54,136,137,319 Strains known to cause fatal illness include some of the currently circulating Asian lineage H5N1 viruses.12,54,72,73,136,137 Some captive wild birds infected with these viruses have died suddenly, within a few hours, without apparent clinical signs.144 In other cases, anorexia, extreme lethargy, dark green diarrhea, respiratory distress and/or neurological signs were seen, with death within 1-2 days.54 Swans have been severely affected by H5N1 viruses; these birds are generally found dead.137,319 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.344 Diving ducks, grebes and mergansers also seem to be highly susceptible to these viruses.143 Experimental infections with H5N1 viruses in call ducks (Anas platyrhyncha var. domestica; a cross between wild and domesticated ducks) or wood ducks (Aix sponsa) resulted in drowsiness, severe weakness and neurological signs, but some 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 one of these strains.136,345

Symptomatic infections with H5N1 viruses have also been reported in experimentally infected gulls and passerine or psittacine birds.60,142,317 Laughing gulls (Larus atricilla) developed severe neurological disease; the clinical signs included weakness, cloudy eyes, ruffled feathers, incoordination and torticolis.136 Most infected gulls died. One gull that recovered had a persistent head tilt; another recovered completely. Anorexia and depression occurred in experimentally infected zebra finches, and all of the birds died within five days of inoculation.142 House finches and budgerigars developed anorexia, depression and neurological signs, and died rapidly.142 In one study, H5N1 infections were mild in house sparrows, which experienced only mild depression and survived, and starlings, which remained asymptomatic.142 In another study, house sparrows but not starlings had severe, often fatal infections.137
Other subtypes can also be pathogenic to some wild birds. An H7N1 (HPAI) virus caused conjunctivitis, apathy and anorexia, with a high mortality rate, in canaries and a siskin\textsuperscript{141} and an H5N3 HPAI virus caused an outbreak with a high mortality rate among South African terns in the 1960s.\textsuperscript{318}

**Other influenza viruses in birds**

Turkeys infected with swine influenza viruses may develop respiratory disease, have decreased egg production, or produce abnormal eggs.\textsuperscript{3}

**Avian H5N1 influenza in mammals**

Both symptomatic and subclinical Asian lineage H5N1 virus infections have been seen in felids. Although fatal infections have been reported in some housecats,\textsuperscript{47,48,53} little is known about the clinical signs after natural exposure in this species. One cat had fever, depression, dyspnea, convulsions and ataxia,\textsuperscript{48} and a few infected housecats were found dead.\textsuperscript{53} One of the latter cats was apparently well up to 24 hours before its death.\textsuperscript{57} In contrast, asymptomatic infections were reported in housecats that had been accidentally exposed to a sick, H5N1-infected swan.\textsuperscript{132} In experimentally infected housecats, the clinical signs included fever, lethargy, conjunctivitis, protrusion of the third eyelid, dyspnea and death.\textsuperscript{63,65,67} Fatal infections have also been reported in some captive tigers and leopards.\textsuperscript{45,46,50} Some of these animals exhibited respiratory distress, serosanguineous nasal discharge, high fever and neurological signs before death.\textsuperscript{47,48} 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.\textsuperscript{54}

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.\textsuperscript{49} Experimentally infected dogs have been asymptomatic or developed only transient fever and conjunctivitis.\textsuperscript{11,67,68} Fatal respiratory disease was reported in infected raccoon dogs.\textsuperscript{55} Other raccoon dogs on the same farm had died with respiratory signs and/or diarrhea before the virus was found.\textsuperscript{55} Captive palm civets had neurological signs, with evidence of interstitial pneumonia, encephalitis and hepatitis at necropsy.\textsuperscript{9} Some infections in palm civets were fatal.\textsuperscript{9} A wild stone marten was also found with neurological signs.\textsuperscript{9} HPAI H5N1 viruses have been isolated from wild pikas; however, there was no evidence that the pika population was seriously affected.\textsuperscript{57}

Asian lineage H5N1 infections in pigs appear to be mild or asymptomatic. Mild respiratory signs including cough, fever and transient anorexia were observed in some experimentally infected pigs.\textsuperscript{58} 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.\textsuperscript{66} One group reported that miniature pigs were resistant to infection.\textsuperscript{60,61}

Experimental infections have been established in foxes, ferrets, mice and cattle, although no naturally infected animals have been reported. Some infected foxes developed fever but no other clinical signs; however, lung lesions were reported at necropsy.\textsuperscript{66} 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).\textsuperscript{61,66} The clinical signs in severe cases included high fever, extreme lethargy, anorexia, weight loss, respiratory disease, diarrhea and neurological signs.\textsuperscript{61,66} Similarly, infections in mice varied with the isolate and the route of inoculation (respiratory or intragastric).\textsuperscript{229} Cattle inoculated with high titers of H5N1 viruses isolated from infected cats remained asymptomatic but could transiently shed virus.\textsuperscript{70}

**Equine influenza**

Equine influenza usually spreads rapidly in a group of animals. In naïve horses, the first sign is usually a high fever, followed by a deep, dry cough.\textsuperscript{1,2} In experimentally infected horses, the first sign is usually a high fever, extreme lethargy, anorexia, weight loss, respiratory disease, diarrhea and neurological signs before death.\textsuperscript{1,2} 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.\textsuperscript{54}

Healthy adult horses usually recover within 1-3 weeks, but the cough may persist longer.\textsuperscript{1,2,25,168,253} In severely affected animals, convalescence can take up to six months.\textsuperscript{168} Secondary bacterial infections prolong recovery.\textsuperscript{2,25,168} Death in adult horses usually results from bacterial pneumonia, pleuritis or purpura hemorrhagica.\textsuperscript{25} Sequelae may include chronic pharyngitis, chronic bronchiolitis and emphysema.\textsuperscript{25,168,253} Interstitial myocardiitis may occur during or after the infection.\textsuperscript{1,25,253} Loss of eyesight has also been reported.\textsuperscript{25,3} Young foals without maternal antibodies can develop rapidly fatal viral pneumonia.\textsuperscript{1,25,253,330} Postinfection encephalopathy has also been reported in foals.\textsuperscript{25,3}

**Other influenza viruses in horses**

Horses experimentally infected with human influenza virus (H3N2 ‘Hong Kong’) developed a mild febrile illness.\textsuperscript{1} The virus could be isolated for up to five days.

**Canine influenza (H3N8)**

Canine influenza is an emerging disease in dogs. The most common presentation seen with H3N8 viruses is relatively mild and resembles kennel cough.\textsuperscript{28,176,177,179,213} In this form, an initial (usually low grade) fever is followed by a persistent cough and sometimes a purulent
The clinical signs can last for up to a month regardless of treatment. The nasal discharge appears to resolve with antibiotics, suggesting that secondary bacterial infections may be important in this disease. More severely affected dogs exhibit a high fever with an increased respiratory rate and other signs of pneumonia or bronchopneumonia. Lethargy and anorexia are common. Some dogs have been found dead peracutely with evidence of hemorrhages in the respiratory tract; this syndrome has been seen in greyhounds, but does not seem to be prominent in pets. Asymptomatic seroconversion also occurs.

**Other influenza viruses in dogs**

In the U.K., an H3N8 equine influenza (American lineage) virus caused a limited outbreak among foxhounds in 2002. The disease, which was diagnosed as bronchointerstitial pneumonia, was characterized by coughing, lethargy and weakness, sometimes progressing to loss of consciousness. One dog died and several were euthanized. Asymptomatic infections were reported in an experimental study with a Japanese H3N8 (Florida sublineage) isolate, which was used to infect dogs via close contact with horses.

The only known outbreak of H3N2 canine influenza was characterized by severe respiratory disease with fever, nasal discharge, sneezing, coughing and anorexia. Four of five pet dogs seen at veterinary clinics died. Fever, sneezing, coughing and nasal discharges occurred in experimentally inoculated dogs, and severe pathological changes were seen in the lungs.

The clinical signs in dogs experimentally infected with influenza C virus included nasal discharge and conjunctivitis, which persisted for 10 days.

**Swine influenza**

Swine influenza is an acute upper respiratory disease characterized by a variety of clinical signs, which may include fever, lethargy, anorexia, weight loss and labored breathing. Coughing can occur in the later stages of the disease. Sneezing, nasal discharge, conjunctivitis and/or abortions may also be seen. Some outbreaks are more severe than others, and swine influenza viruses can circulate in pigs with few or no clinical signs. Complications may include secondary bacterial or viral infections. Severe, potentially fatal bronchopneumonia is occasionally seen.

**H9N2 influenza viruses in pigs**

An avian H9N2 virus caused respiratory disease and paralysis in pigs in southeastern China.

**Novel H1N1 virus of swine origin in mammals**

A number of swine herds have been infected with the novel H1N1 virus circulating in humans. The illness has been mild, with little or no mortality, and the clinical signs have resembled those caused by other swine influenza viruses. Coughing, nasal discharge, fever, weakness and decreased appetite have been reported. Abortions or diarrhea have also been seen in some herds. Experimentally infected pigs developed mild disease, with nasal discharge, sneezing and fever as the most prominent signs. Diarrhea was reported in some experimentally infected animals. In one study, miniature pigs remained asymptomatic although they shed the virus.

Infected turkey flocks reported in Chile and Canada experienced only decreased egg production and reduced quality of the eggs, with no mortality or other clinical signs. Decreased egg production was also reported in a turkey flock in the U.S.

Upper or lower respiratory signs including sneezing and coughing in some cases, and pneumonia in others, have been described in cats. Some cats with respiratory disease did not have a fever. Although some animals apparently had milder cases, one cat became dyspneic and severely ill but recovered with medical care, and two cats died. The illness lasted for several weeks in some animals. An infected cheetah developed lethargy, anorexia and a cough, but recovered. There is little information on cases in dogs, but the novel H1N1 virus was isolated from sick animals in China, and a dog in the U.S. was ill with clinical signs of lethargy, anorexia, fever and coughing, and radiological evidence of pneumonia. The dog in the U.S. was hospitalized and treated with supportive care including antibiotics, and recovered.

Respiratory disease has been reported in naturally infected ferrets; the clinical signs included fever, coughing, sneezing, nasal discharge and weakness. Several ferrets recovered, but one died. In experimentally infected ferrets, lethargy, decreased appetite, sneezing, nasal discharge and ruffled fur were reported in one study, and lethargy and weight loss, with little sneezing, in another.

**Influenza viruses in ferrets**

Ferrets are susceptible to human influenza viruses. The clinical signs may include fever, anorexia, depression, listlessness, sneezing, purulent nasal discharge and coughing. The infection is not usually fatal in adult animals, which generally recover in five to two weeks. More severe or fatal disease can be seen in neonates. Infections with the novel 2009 H1N1 (swine origin) virus have also been reported after contact with humans. The clinical signs (see previous section) appeared to be similar to those caused by human seasonal influenza viruses, but one death was reported.

A single outbreak caused by a swine influenza virus has been reported in ferrets. The virus was a triple reassortant H1N1 swine influenza virus, and the clinical signs included sneezing, coughing, crustng of the nose and eyes, and severe dyspnea. Some severely affected animals died.
Influenza

Influenza viruses are readily transmitted between animals in the species to which they are adapted. Chickens can begin shedding avian influenza viruses as soon as 1-2 days after infection. Most chickens shed LPAI influenza viruses for only a week, but a minority of the flock can excrete the virus in 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. Pigs may begin excreting swine influenza viruses within 24 hours of infection, and typically shed the viruses for 7-10 days. Shedding up to four months has been documented in one pig. Horses begin excreting equine influenza viruses during the incubation period, and usually shed these viruses for 4-5 days or less after the onset of clinical signs.

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Influenza in mink

In 1984, an H10N4 avian influenza virus caused an epidemic on 33 mink farms in Sweden. The clinical signs included anorexia, sneezing, coughing, and nasal and ocular discharges, and many mink died. Mink naturally infected with a Canadian H3N2 swine influenza virus had respiratory signs including pneumonia, with increased mortality particularly on ranches where the mink were co-infected with other pathogens.

Influenza in raccoons

Serological evidence of infection with H1, H3, H4 and H10 viruses has been reported in wild raccoons, but whether clinical signs occur is unknown. Raccoons that were experimentally infected with avian LPAI H4N8 or human H3N2 viruses shed these viruses but remained asymptomatic. According to yet unpublished research, antibodies to H5N1 viruses have also been found among raccoons in Japan.

Influenza in marine mammals

Influenza A viruses have been associated with outbreaks of pneumonia in seals and disease in a pilot whale. The viruses appeared to be of avian origin. 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 signs were nonspecific and included extreme emaciation, difficulty maneuvering and sloughing skin. Influenza B infections have been reported in some stranded seals.

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Post Mortem Lesions

High pathogenicity avian influenza

The lesions in chickens and turkeys are highly variable and resemble those found in other systemic avian diseases.\textsuperscript{10,347} Birds that die peracutely and young birds may have few or no lesions.\textsuperscript{13,14,347} In other cases, the sinus may be swollen, and the comb and wattle are often edematous, hemorrhagic, congested and/or cyanotic.\textsuperscript{13,14,347} 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.\textsuperscript{13,14} Hemorrhagic tracheitis can be seen in some birds; in others, the tracheal lesions may be limited to excess mucoid exudate.\textsuperscript{13} The lungs may be reddened from hemorrhages and congestion, and they may exude fluid when cut.\textsuperscript{13} Petechiae may be noted throughout the abdominal fat, on serosal surfaces and on the peritoneum, and they can sometimes be found in the muscles.\textsuperscript{13,14,347} 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.\textsuperscript{13} The kidneys can be severely congested and are sometimes plugged with urate deposits.\textsuperscript{13} 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.\textsuperscript{13} 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.\textsuperscript{237}

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.\textsuperscript{136} 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.\textsuperscript{136} 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.\textsuperscript{319} Pancreatic lesions alone or no gross lesions have also been seen in some swans.\textsuperscript{348} Mild or absent gross lesions were reported in experimentally infected zebra finches, house finches and budgerigars despite high mortality rates in these species.\textsuperscript{142}

Low pathogenicity avian influenza

Rhinitis and catarrhal to purulent sinusitis are often seen in young birds infected with LPAI viruses.\textsuperscript{13} Congestion and inflammation may also occur in the trachea, and less frequently, the lungs.\textsuperscript{13,14} Lower respiratory tract lesions such as pneumonia are usually seen only in birds with secondary bacterial infections.\textsuperscript{13} The ovary can be hemorrhagic in laying hens, with involuted and degenerated ova.\textsuperscript{13} Yolk may be present in the abdominal cavity, and can cause severe air sacculitis and peritonitis.\textsuperscript{13} The oviduct may also be edematous, with exudates in the lumen.\textsuperscript{13,14} Some birds may have signs of acute renal failure and visceral urate deposition.\textsuperscript{14}

Avian H5N1 influenza viruses in mammals

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.\textsuperscript{47,48,53} The lungs were also affected in experimentally infected cats, with multiple to coalescing foci of pulmonary consolidation.\textsuperscript{53,65} 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.\textsuperscript{65} Petechial hemorrhages occurred in the liver of some cats, and in one cat, the liver lesions were accompanied by generalized icterus.\textsuperscript{65} 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.\textsuperscript{46}

Bloody nasal discharge, severe pulmonary congestion and edema, and congestion of the spleen, kidney and liver were reported in a naturally infected dog.\textsuperscript{49} Pulmonary lesions including interstitial pneumonia have been noted in some experimentally infected pigs.\textsuperscript{58} In one study, Asian lineage H5N1-infected pigs had mild to minimal gross lung lesions, with mild to moderate bronchiolitis and alveolitis detected on histopathologic examination.\textsuperscript{66} Experimentally infected foxes also developed lesions mainly in the lung.\textsuperscript{69} More severe lesions were seen in foxes inoculated intratracheally than in animals fed infected birds, and some of these animals also had histopathologic evidence of encephalitis and myocarditis.\textsuperscript{69}

Swine influenza

In uncomplicated infections, the gross lesions are mainly those of a viral pneumonia.\textsuperscript{2} Affected parts of the lungs are depressed and consolidated, dark red to purple-red, and sharply demarcated.\textsuperscript{2,4} Lesions may be found throughout the lungs, but they are usually more extensive in the ventral regions.\textsuperscript{2,4} Other parts of the lungs may be pale and emphysematous.\textsuperscript{4} The airways are often dilated and filled with mucopurulent exudate.\textsuperscript{4} The bronchial and mediastinal lymph nodes are typically edematous but not congested.\textsuperscript{2,4} Severe pulmonary edema, as well as serous or serofibrinous pleuritis, may also be seen.\textsuperscript{4} Some strains of swine influenza viruses produce more marked lesions
Influenza

**Novel H1N1 virus of swine origin**

Typical swine influenza lesions in the lungs, including a diffusely non-collapsed parenchyma, rubbery texture and areas of bronchiopneumonia were reported in pigs experimentally infected with the novel H1N1 virus.19 Salpingitis, peritonitis and interrupted follicular development were the only lesions reported in turkeys.19

**Equine influenza**

The gross lesions are typically those of an upper respiratory infection (including nasal discharge), and are often accompanied by enlargement of the lymph nodes of the head.25 Interstitial pneumonia, bronchitis and bronchiolitis have been reported in fatal cases, which are most often seen in young foals.25,170,253,330 Ventral edema of the trunk and lower limbs can also occur.253 Severe necrotizing myocarditis, as well as catarrhal or hemorrhagic enteritis, have been reported with some strains.170,253

**Canine influenza**

In dogs that die of canine influenza (H3N8), hemorrhages may be found in the lungs, mediastinum and pleural cavity.28,173 The lungs may exhibit signs of severe pneumonia, and can be dark red to black.173 Hemorrhagic lesions are not always present in fatal cases; in some cases, suppurrative secondary bacterial pneumonia may be seen alone.30 Fibrinous pleuritis may also be noted.173,213 On histological examination, there may be tracheitis, bronchitis, bronchiolitis, and severe interstitial or bronchointerstitial pneumonia.28,173,213 There is limited information on the lesions found in mild cases. In experimentally infected puppies with this form, the bronchial lymph nodes were edematous, and cranioventral lymph node was greatly enlarged.213

**Influenza in other mammals**

In seals infected with avian influenza viruses, pneumonia with necrotizing bronchitis, bronchiolitis and hemorrhagic alveolitis has been reported.28,173,253 In a single case in a whale, the lungs were hemorrhagic and a hilar lymph node was greatly enlarged.229 Acute interstitial pneumonia was seen in mink infected with a swine influenza virus.9

The gross lesions in ferrets inoculated with zoonotic avian H7 viruses ranged from mild pulmonary lesions to widespread hemorrhages, focal areas of pulmonary discoloration and pervasive discoloration of the liver.96 The extent of the lesions varied with the isolate.

**Diagnostic Tests**

**Avian influenza**

Avian influenza can be diagnosed by a variety of techniques including virus isolation.13,14,19 These viruses 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).19 Oropharyngeal, tracheal and cloacal swabs (or intestinal contents), and organ samples (trachea, lungs, air sacs, intestine, spleen, kidney, brain, liver and heart) are tested in dead birds.13,19 Virus isolation is performed in embryonated eggs; hemagglutinating activity indicates the presence of influenza virus.14,19 The virus can be identified as an influenza A virus with agar gel immunodiffusion (AGID) or ELISAs. Avian influenza viruses are subtyped with specific antisera in AGID or hemagglutination and neuraminidase inhibition tests.19 Virulence tests in susceptible birds, together with genetic tests to identify characteristic patterns in the hemagglutinin, are used to differentiate LPAI from HPAI viruses.13,19

RT-PCR assays can identify avian influenza viruses in clinical samples, and can replace virus isolation in some cases.13,14,19,349 These tests can also distinguish some subtypes.13,19 Real-time RT-PCR is the method of choice for diagnosis in many laboratories.13,19

Viral antigens can be detected with ELISAs including rapid tests.19,349 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.19 Some rapid tests, including various PCR assays, were evaluated and compared in a recent review.349

Serological tests including agar gel immunodiffusion, hemagglutination, hemagglutination inhibition and ELISAs are useful as supplemental tests.19 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.13 In wild birds, some serological tests may underestimate the prevalence of H5N1 infections.136

**Swine influenza**

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Swine influenza can be diagnosed by virus isolation, the detection of viral antigens or nucleic acids, and serology. Mammalian influenza viruses can be isolated in embryonated chicken eggs or cell cultures.\textsuperscript{2,147} Swine influenza viruses are often recovered in Madin–Darby canine kidney cells, but other cell types can also be used.\textsuperscript{147} These viruses can be isolated from lung tissues at necropsy, and from nasal or pharyngeal swabs taken from acutely ill pigs.\textsuperscript{3,4,147} Recovery is best from an animal with a fever, 24-48 hours after the onset of illness.\textsuperscript{147} Isolated viruses can be subtyped with hemagglutination inhibition and neuraminidase inhibition tests or RT-PCR.\textsuperscript{2,147}

Immunofluorescent techniques can detect antigens in fresh lung tissue, nasal epithelial cells or bronchoalveolar lavage.\textsuperscript{2,13} Other antigen detection tests include immunohistochemistry on fixed tissue samples, and ELISAs.\textsuperscript{2,147} RT-PCR assays are used to detect viral RNA.\textsuperscript{2,147}

Serology on paired samples can diagnose swine influenza retrospectively.\textsuperscript{2} The hemagglutination inhibition test, which is subtype specific, is most often used.\textsuperscript{2,4,147} It may not detect new viruses.\textsuperscript{2} ELISA kits are available. Uncommonly used serological tests in swine include agar gel immunodiffusion, the indirect fluorescent antibody test and virus neutralization.\textsuperscript{147}

Equine influenza

Equine influenza may tentatively be diagnosed based on the clinical signs.\textsuperscript{165} As in swine, the disease is confirmed by virus isolation, the detection of viral antigens (e.g., by ELISA), or the detection of nucleic acids by RT-PCR.\textsuperscript{2,3,25,168,169} Equine influenza viruses can be isolated from nasopharyngeal swabs or nasal and tracheal washes. In horses, peak virus shedding is thought to occur during the first 24 to 48 hours of fever; whenever possible, samples should be collected within the first 3-5 days after the onset of clinical signs.\textsuperscript{25,169} Ideally, virus recovery should be attempted in both embryonated eggs and cell cultures.\textsuperscript{169} Equine influenza can also be diagnosed retrospectively by serology, using paired serum samples.\textsuperscript{25,168,169} The most commonly used serological tests in horses are the hemagglutination inhibition test and a single-radial hemolysis (SRH) test.\textsuperscript{25,169}

Canine influenza

At this time, serology and RT-PCR are the most reliable methods for detecting H3N8 canine influenza.\textsuperscript{177,213,350} Hemagglutination inhibition is the most commonly used serological test.\textsuperscript{213} Virus neutralization (microneutralization test) can also be done, but this test is usually too cumbersome for routine use.\textsuperscript{213} Acute and convalescent titers should be submitted if possible.\textsuperscript{213,350} Because canine influenza is an emerging disease, most dogs are not expected to have pre-existing titers to the canine influenza virus; however, single titers are still considered to be less useful.\textsuperscript{213,350}

RT-PCR is the most reliable method to detect the virus directly.\textsuperscript{213} This test can be used on nasal swabs from live animals or lung tissue samples at necropsy.\textsuperscript{213,350} Virus isolation may also be successful in some dogs, but only during the early stages of disease before antibodies develop.\textsuperscript{213} The H3N8 canine influenza virus can be found in lung tissue samples taken post-mortem, but virus isolation fails to detect the virus in many infected dogs that do not die of the disease.\textsuperscript{28,177,213,350} In experimental infections, nasal swabs have been more likely to yield virus than nasopharyngeal swabs.\textsuperscript{213,350} The H3N8 canine influenza virus has been isolated in both embryonated eggs and cell cultures (MDCK cells)\textsuperscript{213}. Antigen-capture ELISA tests do not seem to be reliable in individual dogs, probably because the amount of virus shed is low.\textsuperscript{213} However, these tests may be able to detect H3N8 canine influenza during outbreaks at kennels or other large facilities.\textsuperscript{213}

Little is known about testing for Korean H3N2 viruses in dogs. Some H3N2 viruses were isolated from nasal swabs taken from dogs during an outbreak.\textsuperscript{133} In experimentally infected dogs, these viruses were shed in nasal secretions from one to six days after inoculation.\textsuperscript{133} RT-PCR can also detect this virus.\textsuperscript{133} Serology is expected to be useful.

Treatment

Animals with influenza are usually treated with supportive care and rest.\textsuperscript{4,14,25,168} In horses, prolonged recovery and more severe disease have been associated with increased stress.\textsuperscript{23} Antibiotics may be used to control secondary bacterial infections; they seem to be particularly important in the treatment of canine influenza.\textsuperscript{4,14,25,168,179} Antiviral drugs are not generally given to most animals; however, ferrets have been treated with amantadine as well as antihistamines, antibiotics and other supportive therapy.\textsuperscript{185} Antiviral drugs could also be of use in valuable horses.\textsuperscript{185}

Poultry flocks infected with HPAI viruses are depopulated and are not treated.\textsuperscript{3,11}

Prevention

Vaccines

Influenza vaccines are available for pigs, horses, dogs and, in some countries, birds.\textsuperscript{1,3,4,13,25,147,168,169,352} The vaccines do not always prevent infection or virus shedding, but the disease is usually milder if it occurs. Influenza vaccines may change periodically to reflect the current subtypes and strains in a geographic area. In general, swine and equine viruses display less antigenic drift than human viruses, and these vaccines are changed less often.\textsuperscript{2,3,25}

In the U.S., avian influenza vaccines are used most often in turkeys and are intended only to prevent infection by LPAI viruses.\textsuperscript{19} HPAI 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.\textsuperscript{19,353} 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 may 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 “DIVA” (differentiating vaccinated from infected animals) strategies, 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.

Other preventative measures

Poultry can be infected by contact with newly introduced birds or fomites, as well as by contact with wild birds, particularly waterfowl and shorebirds. Illegal poultry movements may be of primary importance in transmission in some regions. 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. Keeping flocks indoors is often recommended in areas where the H5N1 virus has been isolated from wild birds. Poultry 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. Mammals should not be fed poultry or other birds that may be infected with the avian influenza viruses. They should also keep from contact with potentially infected flocks and wild birds. During outbreaks of H5N1 avian influenza, cats and dogs should be kept indoors whenever possible.

In pigs and horses, influenza is usually introduced into a facility in a new animal. Isolation of newly acquired animals can decrease the risk of transmission to the rest of the herd. Similarly to birds, good biosecurity is important. Pigs should also be protected from the influenza viruses found in other species, particularly birds and humans. To prevent human influenza viruses from entering a herd, swine workers who are ill should avoid contact with pigs, and the public should be restricted from entering swine operations. Once a herd of swine has been infected with a swine influenza virus, the virus usually persists in the herd and causes periodic outbreaks; however, good management can decrease the severity of disease. Infected swine herds can be cleared of influenza viruses by depopulation.

Ferrets can be infected by human influenza viruses (including the novel H1N1 virus), and people with influenza should avoid contact with this species. If contact is unavoidable, good hygiene, as well as the use of face masks and/or other measures to prevent droplet transmission from coughs and sneezes, may be helpful. Felids (including housecats and a cheetah) and dogs have also been infected with the novel H1N1 virus from humans.

Eradication and prevention of virus transmission during outbreaks

During an outbreak of influenza among mammals, quarantines and isolation of infected animals help prevent virus dissemination. Good hygiene can keep the virus from spreading on fomites. Rest decreases virus shedding in horses. Infected facilities should be cleaned and disinfected after the outbreak.

In poultry, outbreaks of high pathogenicity avian influenza are controlled by eradication. The outbreak is managed by quarantine, depopulation, cleaning and disinfection, and surveillance around the affected flocks. Strict hygiene is necessary to prevent virus transmission on fomites. Because H5 and H7 LPAI viruses can mutate to become HPAI viruses, these infections are reportable to the OIE, and are being controlled similarly in many countries.

Morbidity and Mortality

The severity of an influenza virus infection varies with the dose and strain of virus and the host’s immunity. In mammals, uncomplicated infections are usually associated with high morbidity rates, low mortality rates and rapid recovery. Secondary bacterial infections can exacerbate the clinical signs, prolong recovery and result in complications such as pneumonia.

Avian influenza

Avian influenza outbreaks occur in most countries including the U.S. Low pathogenicity forms occur most often, but outbreaks with high pathogenicity H5 and H7 viruses are also seen occasionally. Seasonality has been reported in the current H5N1 epidemic; this virus has tended to reemerge during colder temperatures in the Northern Hemisphere. The reason for the seasonality is unknown, but it may be the result of multiple factors such as increased virus survival in the cold, increased poultry trade during winter festivals, and wild bird movements. In domesticated poultry (particularly chickens), high pathogenicity avian influenza has very high morbidity and mortality rates, up to 90-100%. Any surviving birds are usually in poor condition. LPAI viruses usually result in mild or asymptomatic infections, but may also mimic HPAI viruses.

High mortality is occasionally seen in young ostriches infected with either LPAI or HPAI viruses.

Symptomatic infections are unusual in wild birds; however, some of the Asian lineage H5N1 viruses have caused outbreaks with high mortality rates. In April 2005, an outbreak that began at Qinghai Lake in central China resulted in the death of more than 6000 migratory wild birds. Asian lineage H5N1 viruses have also been isolated sporadically from other dead birds, including waterfowl, in a number of countries. High mortality rates have been reported in some but not all cases.
all experimentally infected wild birds. In one study, all six laughing gulls infected with recent strains of H5N1 became severely ill, and four died.\textsuperscript{136} Four of six infected wood ducks also became severely ill while two others remained asymptomatic.\textsuperscript{136} 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.\textsuperscript{136} Morbidity and mortality rates in passerine and psittacine birds have varied with the species. In one study, mortality rates approached 100% in zebra finches, house finches and budgerigars, but all house sparrows experienced mild disease and survived, and all starlings remained asymptomatic.\textsuperscript{142} In a study with a different Asian lineage H5N1 virus, the mortality rate was 66-100% in house sparrows, but no deaths were seen in starlings.\textsuperscript{317}

**Avian H5N1 influenza in mammals**

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.\textsuperscript{59} In contrast, no antibodies were detected in 171 cats from areas of Austria and Germany where infections had been reported in wild birds.\textsuperscript{361} Some infections with Asian lineage H5N1 viruses have been fatal; deaths have been reported in housecats, some large felids, a dog, raccoon dogs, palm civets and experimentally infected ferrets.\textsuperscript{4,16,53,55,61,66} However, both mild and severe cases have been reported in several of these species. Fatal cases were reported in some naturally infected housecats, and some experimentally infected cats exhibited severe disease and high mortality rates.\textsuperscript{47,48,53,63,65} In contrast, asymptomatic infections were reported in cats exposed to an infected swan in an animal shelter.\textsuperscript{132} Few of these cats shed virus, and none became ill despite the presence of other viral and bacterial infections, and high stress levels in this population.\textsuperscript{132} 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.\textsuperscript{4,46,50,54} Asymptomatic or mild infections have been reported in experimentally infected dogs, but one death was reported in a naturally infected dog.\textsuperscript{49,67,68} 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).\textsuperscript{61,66} Interestingly, there is no evidence that HPAI H5N1 viruses are causing significant illness among infected pikas in China,\textsuperscript{57} and Asian lineage H5N1 viruses isolated from Indonesian pigs were less virulent in mice than isolates from poultry.\textsuperscript{56}

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.\textsuperscript{58} Asian lineage H5N1 viruses have also been detected in swine in Indonesia,\textsuperscript{56} and these viruses have been isolated rarely from pigs in China.\textsuperscript{5,58} However, there are no reports of severe illness among swine. Experimental infections also suggest that the clinical signs may be mild in this species,\textsuperscript{58,66} and miniature pigs were resistant to infection in one study.\textsuperscript{60}

**Swine influenza**

Influenza is a major cause of acute respiratory disease in finishing pigs. Approximately 25-33% of 6-7 month-old finishing pigs and 45% of breeding pigs have antibodies to the classical swine H1N1 virus in the U.S.\textsuperscript{1,16} High seroprevalence rates to swine influenza viruses have also been reported in other countries.\textsuperscript{1,2,5,16} In addition, pigs can be infected with human influenza A, B and C viruses.\textsuperscript{1,6,8,201} In the U.K., a study found antibodies to both swine and human influenza viruses in 14% of all pigs.\textsuperscript{16} Approximately 10% of the pigs were seropositive for influenza C viruses, but only sporadic infections with the human influenza B viruses were found.\textsuperscript{28} In Japan, a similar study found antibodies to the type C viruses in 19% of pigs.\textsuperscript{8}

Swine influenza viruses are usually introduced into a herd in an infected animal, and can survive in a few carrier animals for up to four months.\textsuperscript{3,4,16,94} In a newly infected herd, up to 100% of the animals may become ill but most animals recover within 3-7 days if there are no secondary bacterial infections or other complications.\textsuperscript{2,4,147} In uncomplicated cases, the case fatality rate has ranged from less than 1% to 4%.\textsuperscript{1,3,4}

Once the virus has been introduced, it usually persists in the herd.\textsuperscript{1,2,16,94} Annual outbreaks are often seen, and in temperate regions, occur mainly during the colder months.\textsuperscript{1,2,4,16,94} Many infections in endemically infected herds are subclinical; typical signs of influenza may occur in only 25% to 30% of the pigs.\textsuperscript{2,16,94} Maternal antibodies decrease the severity of disease in young pigs.\textsuperscript{2} Viruses may also infect the herd with few or no clinical signs.\textsuperscript{1,2,16,94}

Influenza epidemics can occur if a virus infects a population without immunity to the virus, or if the infection is exacerbated by factors such as poor husbandry, stress, secondary infections or cold weather.\textsuperscript{1,16} In the epidemic form, the virus spreads rapidly in pigs of all ages.\textsuperscript{147} In the 1918 epizootic, millions of pigs developed influenza, and thousands of the infections were fatal.\textsuperscript{1}

**Novel H1N1 virus of swine origin**

The H1N1 virus circulating in humans appears to cause mild disease in pigs.\textsuperscript{103,107,108,345} Morbidity rates from less than 1% to as high as 90% have been reported, but little or no mortality has been seen.\textsuperscript{102-104,107,108,111-116,252,321} Experimental studies support this view; deaths have not been reported among experimentally infected pigs.\textsuperscript{310,323,346}

Decreased egg production may be the main effect in turkeys. In a turkeys flock in Chile, the morbidity rate was
61%, but no deaths were seen.\textsuperscript{117} Egg production in this flock dropped from 70% to 31%. Similarly, egg production dropped by approximately 80%, in affected turkey flocks in Canada.\textsuperscript{118} Although a slight increase in flock mortality occurred in the latter case, it may have been unrelated to the H1N1 infection.\textsuperscript{162} Decreased egg production and no mortality were reported in a U.S. turkey flock.\textsuperscript{125}

A few cats, pet ferrets and dogs have been infected naturally with the novel H1N1 virus.\textsuperscript{119-124,127-129} Several ferrets recovered, but one died.\textsuperscript{119,120,122} Two infected cats died, another developed severe illness with dyspnea but recovered with medical care, and some cats apparently had milder cases.\textsuperscript{121,123,129} An infected dog in the U.S. was ill with pneumonia, and required hospitalization and supportive care, but recovered.\textsuperscript{128} Experimental studies in mice, ferrets and nonhuman primates suggest that this virus might cause more severe lung pathology and/or clinical signs than seasonal human H1N1 viruses, or that the illness might last longer.\textsuperscript{126,310,322}

**Equine influenza**

In horses, influenza outbreaks are not as seasonal as they are in pigs or humans.\textsuperscript{25} Most outbreaks are associated with sales, races and other events where horses congregate.\textsuperscript{3,25} Close contact with other horses, crowding and transportation are typical risk factors for disease.\textsuperscript{170} Widespread epidemics can be seen, with morbidity rates of 60-90% or greater, in naïve populations.\textsuperscript{1,25,255,330} In 1987, an equine influenza epidemic in India affected more than 27,000 animals and killed several hundred.\textsuperscript{25} In populations that have been previously exposed, cases are seen mainly in young and newly introduced animals.\textsuperscript{1,25}

Unless there are complications, healthy adult horses usually recover within 1-3 weeks, although coughing can persist.\textsuperscript{1,25,168,255} The H3N8 viruses usually cause more severe disease than the H7N7 viruses.\textsuperscript{1,25} Deaths are rare in adult horses, and are usually the result of secondary bacterial infections.\textsuperscript{1,25,168,330} Higher mortality rates have been reported in foals, animals in poor condition, donkeys and zebras.\textsuperscript{25,168,330} In horses, tracheal clearance rates can be depressed for up to a month after infection.\textsuperscript{25}

Avian influenza viruses have rarely been reported in horses. In 1989, a novel strain of equine influenza [A/eq/Jilin/89 (H3N8)] caused a serious epidemic in Chinese horses.\textsuperscript{25,170} The morbidity rate was at least 80% and the mortality rate was 20-35%.\textsuperscript{25,170} The virus appeared to be an avian influenza virus. A related virus caused influenza in a few hundred horses the following year but there were no deaths. The avian-like virus continued to circulate in horses for at least five years without further fatalities.

**Canine influenza**

Canine H3N8 influenza was first reported in racing greyhounds and, at first, appeared to be confined to this breed.\textsuperscript{177,213} Although this disease was first reported in 2004, new evidence suggests that the H3N8 virus may have been circulating in U.S. greyhound populations as early as 1999.\textsuperscript{28,180,263} More recently, H3N8 canine influenza has been seen in a variety of breeds at veterinary clinics and animal shelters in several states.\textsuperscript{28,30,179,181,183,213} All dogs regardless of breed or age are now considered to be susceptible.\textsuperscript{178,179,213} The prevalence of this disease in the U.S. is not yet known. One study suggests that canine influenza is rare, if it exists at all, in Canada. In the province of Ontario, a survey found antibodies to the H3N8 virus in only one of 225 dogs in 2006.\textsuperscript{364} This dog was a greyhound that had come from a racetrack in Florida, and may have been infected there. It had no recent history of respiratory disease.

Because dogs have not been exposed to the canine influenza virus before, most of the population is expected to be fully susceptible.\textsuperscript{177,178} In kennels, the infection rate may reach 100%, and clinical signs can occur in 60-80% of the dogs infected.\textsuperscript{178,213} Most dogs are expected to develop the less severe form of the disease, and recover; however, a more severe form with pneumonia may occur in a minority.\textsuperscript{177,179,213} In dogs with severe disease, the overall mortality rate is thought to be 1-5%.\textsuperscript{28,173,176,179} Higher case fatality rates have been reported in small groups of greyhounds.\textsuperscript{213} At one Florida greyhound racetrack, the case fatality rate was 36%.\textsuperscript{28} High case fatality rates are not expected in most canine populations; however, severe disease is more likely in dogs that are in poor condition or are concurrently exposed to other pathogens.

The H3N2 virus has been reported from outbreaks at three veterinary hospitals and a kennel in South Korea.\textsuperscript{133} Cases were described in a miniature schnauzer, a cocker spaniel, a Yorkshire terrier and two Jindo dogs (a Korean breed of hunting dog), as well as 13 dogs of unknown breed at an animal shelter.\textsuperscript{133} Only one of the five dogs seen at veterinary clinics survived. The fate of the dogs in the animal shelter was not stated.

**Influenza in other mammals**

In 1984, an avian H10N4 virus caused an outbreak on Swedish mink farms. It affected 33 farms and killed 3,000 mink.\textsuperscript{1} The morbidity rate was nearly 100%, with a mortality rate of 3%.\textsuperscript{9} In an outbreak caused by a triple reassortant H1N1 swine influenza virus in ferrets, the morbidity rate was 8% and the mortality rate was 0.6%.\textsuperscript{91} In seals, the case fatality rate was estimated to be 20% in one outbreak with an H7N7 virus, and 4% in an outbreak with an H4N5 virus.\textsuperscript{1} Explosive epidemics in seals are thought to be exacerbated by high population densities and unseasonably warm temperatures,\textsuperscript{329} and they may be more severe if the animals are co-infected with other pathogens.\textsuperscript{9}

**Internet Resources**

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Canadian Food Inspection Agency. H1N1 Flu Virus (Human Swine Influenza) Questions and Answers [includes biosecurity and waiting period recommendations for veterinarians examining potentially infected herds]

Centers for Disease Control and Prevention (CDC). Avian Influenza
http://www.cdc.gov/flu/avian/

CDC. H1N1 Flu (Swine Flu)
http://www.cdc.gov/h1n1flu/

CDC. Seasonal influenza (flu).
http://www.cdc.gov/flu/

Medical Microbiology
http://www.gsbs.utmb.edu/microbook

Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices, 2006
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5510a1.htm

Public Health Agency of Canada (PHAC). H1N1 Flu Virus
http://www.phac-aspc.gc.ca/alert-alerte/h1n1/index-eng.php

PHAC. Material Safety Data Sheets

The Merck Manual
http://www.merck.com/pubs/mmanual/

The Merck Veterinary Manual
http://www.merckvetmanual.com/mvm/index.jsp

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

USDA APHIS. Avian Influenza.

USDA APHIS. Avian Influenza Portal
http://www.usda.gov/wps/portal/!ut/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/

USDA APHIS. H1N1 Flu
http://www.usda.gov/wps/portal/?navid=USDA_H1N1


http://www.nwhc.usgs.gov/disease_information/avian_influenza/affected_species_chart.jsp

World Health Organization
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_summary.htm

OIE Terrestrial Animal Health Code
http://www.oie.int/eng/normes/mcode/A_summary.htm

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