Influenza

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Importance

Influenza viruses are highly variable RNA viruses that can affect birds and mammals including humans. There are currently three species of these viruses, designated influenza A, B and C. Influenza A viruses are widespread and diverse in wild aquatic birds, which are thought to be their natural hosts, but poultry are readily infected, and a limited number of viruses have adapted to circulate in people, pigs, horses and dogs. Two types of influenza viruses are maintained in birds. Most of these viruses, which are known as low pathogenic avian influenza (LPAI) viruses, infect birds asymptomatically or cause relatively mild clinical signs.[1-11] However, some viruses circulating in poultry can mutate to become highly pathogenic avian influenza (HPAI) viruses, which cause devastating outbreaks of systemic disease in chickens and turkeys, with morbidity and mortality rates as high as 90-100%.[3,4,6] In the mammalian species to which they are adapted, influenza A viruses usually cause respiratory illnesses with high morbidity but low mortality rates.[5,12-33] More severe or fatal cases tend to occur mainly in conjunction with other diseases, debilitation or immunosuppression, as well as during infancy, pregnancy or old age; however, the risk of severe illness in healthy humans can increase significantly during pandemics.[5,7,9,13,15,16,18,21,24,34-50]

While influenza A viruses are host-adapted, there is increasing evidence of sporadic transmission to members of other species, as well as occasions when these viruses cause limited outbreaks or become adapted to a new host. Influenza is now known to be an uncommon cause of respiratory illness in species not previously considered susceptible, such as cats, ranched mink and various captive wild mammals, which have been infected by viruses from humans, pigs, birds and other species.[51-70;70a] Two influenza viruses, one from horses and another from birds, began to circulate in some canine populations during the last 20 years, and sporadic illnesses in dogs have been caused by other viruses.[31,57,60,71-83] New viruses have emerged in pigs, especially in North America, where swine influenza viruses have become very diverse.[44,84-88] Some of these viruses have caused outbreaks in people exposed to pigs at fairs.[89-92] Many influenza A virus infections in novel mammalian hosts have been mild, but some viruses can cause life-threatening illnesses in humans and animals.[7,51-59,90-115] Two particularly virulent viruses affecting people are the Asian lineage of H5N1 HPAI viruses and an H7N9 LPAI virus that has caused serious outbreaks in China. Avian influenza viruses also caused or contributed to at least three past pandemics in humans, [5,12,18,116-119] while the 2009-2010 pandemic resulted from the acquisition of a virus from pigs.[118,120,121]

Influenza B and C viruses primarily affect humans, and seem to be less likely to cross species barriers.[5,15,16,35,122-134] However, infections have occasionally been reported in animals, and seals might act as maintenance hosts for some influenza B isolates.[5,20,135-141;142 cited in 139] Novel influenza viruses may also exist. A new influenza C-related virus was recently identified among swine and cattle in North America, and may cause respiratory disease in animals.[143-145]

Etiology

Influenza viruses belong to the genera *influenzavirus A*, *influenzavirus B* and *influenzavirus C* in the family Orthomyxoviridae.[146]. There are no separate viral species within these genera; all the members of each genus belong to the species *influenza A virus*, *influenza B virus* or *influenza C virus*, respectively.[146] These viruses are also called type A, type B and type C influenza viruses. A newly recognized livestock influenza virus, originally thought to be an influenza C virus, might represent a fourth genus.[144,145]

Influenza A viruses

Influenza A viruses are the most widely distributed influenza viruses in birds and mammals. They are classified into subtypes based on two surface antigens, the hemagglutinin (HA) and neuraminidase (NA) proteins. At least 18 hemagglutinins (H1 to H18) and 11 neuraminidases (N1 to N11) have been recognized.[3,4,7,147-149] As of 2014, H1-H16 and N1-N9 have been found in birds; H17, H18, N10 and N11 have been detected only in bats; and other mammals maintain a limited subset of the

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subtypes found in birds.[10,19,148,149] The subtype designation consists of the HA and NA found in that virus (e.g., H1N2). The HA, and to a lesser extent the NA, are major targets for the immune response, and there is ordinarily little or no cross-protection between different HA or NA types.[13,150-158] Influenza viruses are extremely variable, and two viruses that share a subtype may be only distantly related.

The names of influenza A viruses reflect the hosts to which they are adapted. Influenza A viruses are currently maintained in birds (avian influenza viruses), pigs (swine influenza viruses), horses (equine influenza viruses), dogs (canine influenza viruses) and humans. The viruses adapted to people are called human influenza A viruses, to distinguish them from influenza B and C viruses, which are also maintained in human populations. Together, the influenza A, B and C viruses circulating in people are called 'seasonal influenza viruses.'

Strains of influenza viruses are described by their type, host, place of first isolation, strain number (if any), year of isolation and subtype.[5,19] For example, 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. When an influenza virus lineage has circulated for a time in a population, numerous variants may develop. These variants are sometimes classified into clades and subclades (e.g., clade 2.2 of the Asian lineage H5N1 HPAI virus).

Antigenic shift and drift in influenza A viruses

Influenza A viruses are very diverse and change frequently as the result of two processes, mutation and genetic reassortment. Genetic reassortment is facilitated by the nature of the influenza A genome, which consists of 8 individual gene segments.[157,158] Reassortment is essentially a reshuffling of gene segments from two influenza viruses, resulting in genes from both viruses being packaged into a single, novel virion during virus assembly.[12] It can occur whenever two influenza viruses replicate in the same cell, whether the viruses are adapted to the same host species (e.g., two different human influenza viruses) or originally came from different hosts, such as an avian influenza virus and a swine influenza virus.

An important aspect of reassortment is that it can generate viruses containing either a new HA, a new NA, or both. Such abrupt changes, called 'antigenic shifts,' may be sufficient for the novel virus to completely evade the existing immunity in its host species. Antigenic shifts can also occur if one species acquires an influenza virus "whole" from another, or if a virus disappears from a time and is maintained in another host species, then re-emerges in the original host.[5,18] For example, human influenza A viruses can enter and circulate in swine populations, and could later be re-acquired by humans. In addition to major antigenic shifts, reassortment can result in smaller changes, such as the acquisition of a slightly different HA or NA from another virus circulating on the same species, or a different internal protein.

Mutations cause more gradual changes in the HA and NA of the virus, a process called 'antigenic drift.' .[19] Antigenic drift can also reduce the effectiveness of the immune response, although this usually occurs more slowly that with antigenic shifts.

Antigenic drift and shifts result in the periodic emergence of viruses with new or altered HA and NA proteins in a host species. By evading the immune response, these viruses can cause influenza epidemics and pandemics.

Acquisition and loss of influenza viruses in a species

Although influenza A viruses are adapted to circulate in a particular host, they can occasionally infect other species. In most cases, the virus cannot be transmitted efficiently between members of that species, and soon disappears.[5,7,9,12,19,31,59,68,69,74,82,159-161] On rare occasions, however, a virus continues to circulate in the new host. Complex molecular adaptations, which are still not well understood, are likely to be required for a successful species jump.[162] The viral surface proteins (HA and NA) and internal proteins both seem to play a role in adaptation. Viruses generally undergo a period of adaptation after the transfer, during which time they become more efficient at replicating in the new host.

In some cases, whole viruses have jumped successfully to new hosts.[31,71,72] At other times, the newly acquired virus reassorted with a virus that is already adapted to its new host.[12,18] This reassortment could occur in the new host's own cells, or in an intermediate host, which then transmits the virus further.[7,12,18] For example, an avian influenza virus could reassort with a human influenza virus in a pig, then be transferred to humans. Acquisition of new influenza viruses is more likely when different species are kept in close proximity.[5,18,101]

As well as appearing in new host populations, influenza A viruses can also disappear from hosts where they previously circulated. Some viruses have vanished from human, equine and swine populations after circulating for years or even decades.[5,17,86-88] For unknown reasons, the establishment of a new influenza virus in a species sometimes leads to the disappearance of an older viral lineage.[43]

Avian influenza viruses

Avian influenza viruses are extremely diverse, especially the viruses found in wild birds. These viruses may contain H1 through H16, and N1 through N9. However, some hemagglutinins, such as H14 and H15, seem to be uncommon, or perhaps are maintained in wild bird species or locations that are not usually sampled.[10] Whether all HA and NA combinations can occur in nature is uncertain, but more than 100 subtypes of avian influenza viruses have been detected.[43]

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LPAI and HPAI viruses

The viruses maintained in birds are classified as either low pathogenic (also called low pathogenicity) avian influenza viruses or highly pathogenic (high pathogenicity) avian influenza viruses. A virus is defined as HPAI by its ability to cause severe disease in intravenously inoculated young chickens in the laboratory, or by its possession of certain genetic features that have been associated with high virulence in HPAI viruses (i.e., the sequence at the HA cleavage site).[3,4] HPAI viruses almost always cause severe disease when they infect chickens and turkeys in the field, while LPAI infections are generally much milder.

With rare exceptions, the HPAI viruses found in nature have always contained the H5 or H7 hemagglutinin.[163-166] Two exceptions were H10 viruses that technically fit the HPAI definition if they were injected directly into the bloodstream of chickens, but caused only mild illness in birds that became infected by a more natural respiratory (intranasal) route.[165] Another H10 virus also fit the HPAI definition; however, this virus affected the kidneys and had a high mortality rate in intranasally inoculated young chickens.[167] Non-H7, non-H5 viruses that are pathogenic only after intravenous inoculation have been created in the laboratory by inserting genetic sequences from HPAI viruses.[168] Other viruses created this way (containing H2, H4, H8 or H14) were highly virulent after both intravenous and intranasal inoculation.[168] Whether such viruses could evolve naturally from LPAI viruses is still uncertain.

In rare cases, an H5 or H7 virus has a genetic signature that classifies it as an HPAI virus, but causes only mild illness in poultry.[169,170] These viruses may have been isolated when they were evolving to become more virulent. Their presence triggers the same regulatory responses as fully virulent HPAI viruses.

Avian influenza virus lineages

There are two well-recognized lineages of avian influenza viruses, Eurasian and North American.[10] As implied by the names, Eurasian lineage viruses primarily circulate among birds in Eurasia, and North American lineage viruses in the Americas. The amount of reassortment between these lineages seems to differ between regions, with very few reassortant viruses in some areas or wild bird populations, but significant reassortment where there is overlap between migratory flyways, such as in Alaska and Iceland.[10,171-181] If viruses from Eurasiawere to enter North America in wild birds, it could take place at such 'hot spots' for reassortment. Avian influenza virus surveillance in Central and South America has been limited, but the viruses detected include a unique South American sublineage (or lineage) as well as viruses closely related to the North American lineage.[182] An analysis of a limited number of H7 avian influenza viruses suggests that the viruses in New Zealand and Australia might be geographically isolated.[183]

Important virus lineages circulating among poultry: H5N1 and H5N8 HPAI viruses and H7N9 and H9N2 LPAI viruses

Many different LPAI and HPAI viruses, belonging to multiple subtypes, can infect poultry, but three lineages of H5N1, H7N9 and H9N2 viruses are currently of particular concern.

The A/goose/Guangdong/1996 lineage ('Asian lineage') of H5N1 HPAI viruses first emerged among poultry in China in the late 1990s, and has become widespread and diverse.[7,184,185] These H5N1 viruses have evolved into multiple genotypes, clades and subclades, and new variants are continuing to emerge as they circulate.[7,185-190] The primary reasons for concern, in addition to the severe outbreaks HPAI viruses cause in some poultry, are the serious illnesses this lineage causes in humans, the wide variety of mammalian species it can infect, and the periodic (and unusual) detection of this virus in wild birds, including migratory waterfowl.[7,51-59,93-114,191] Some clades or subclades of Asian lineage H5N1 HPAI viruses differ in their virulence for mammals and/or birds.[103,114,189] HPAI H5N2, H5N5 and H5N8 viruses, resulting from reassortment between the Asian lineage H5N1 viruses and other avian influenza viruses, have also been reported among poultry in Asia.[192-197] Some of these viruses may also cause illness in mammals.[60,198,199] HPAI H5N8 viruses became widespread among birds in Asia and Europe in 2014.[199a] These viruses have been isolated from wild birds, and they have caused outbreaks in domesticated poultry in a number of countries.[199a-199c] They reached North America (the Pacific Northwest) in late 2014, and have reassorted with North American lineage viruses to produce unique variants of various subtypes such as H5N1 and H5N2.[199b-199c] (whether any of these variants will persist is uncertain) No illnesses caused by these viruses in mammals have been reported, as of February 2015, and their zoonotic potential is currently unknown.

H9N2 (LPAI) viruses are of concern because they are currently widespread among poultry in parts of Asia and the Middle East, they have caused clinical cases (mostly mild) in people, and they can infect other mammals.[87,88,200-216] These H9N2 viruses have become very diverse, and they have reassorted with the Asian lineage H5N1 HPAI viruses and other viruses.[201,210,217-221] H9N2 variants may differ in their ability to replicate in mammals and/or cause disease.[219,220]

Another avian influenza virus of concern is an H7N9 LPAI virus, which causes little or no disease in poultry, but has been responsible for serious human outbreaks in China.[222-228] This virus appears to be the result of reassortment between H7, N9 and H9N2 viruses.[223,229] Some evidence suggests that the H7N9 virus may have circulated subclinically for a long time among poultry before emerging in people.[230] H7N7 viruses with similar internal H9N2 genes as the H7N9 virus have been identified among poultry in China, and might have the potential to infect mammals.[229]

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Human influenza A viruses

In people, influenza A viruses tend to form a single global population.[213] H1N1, H1N2, N2N2 and H3N2 human influenza viruses have been widely distributed at times during the last century, but only H1N1 and H3N2 viruses are currently in general circulation.[5,34,35,231,232]

Human influenza viruses are under considerable selection pressure from immunity (acquired after an infection or by vaccination) in a long-lived species. As a result, the predominant viruses circulating in human populations change constantly, resulting in epidemics and pandemics. Pandemics were most recently reported in 1918, 1957, 1968 and 2009. The 1918 'Spanish flu' pandemic was caused by an H1N1 virus whose origins remain controversial. Some evidence suggests that it was probably an avian virus that became adapted to humans,[12,116] while other studies indicate that it may have been a reassortant,[118,119] and it is possible that it adapted to another host, such as a pig, before becoming established in people.[118,233] H1N1 viruses gradually changed as they circulated in the human population, then apparently disappeared in 1957 when an H2N2 virus emerged.[12,18,117,234] The next two pandemics seem to have been caused by reassortment between avian and human influenza viruses.[12] The 1957 H2N2 ('Asian flu') virus consisted of the HA, NA and an internal protein from an avian influenza virus, and five other proteins from a human H1N1 strain.[12,18] These H2N2 viruses circulated in people between 1957 and 1968.[5,232] The H3N2 'Hong Kong flu' virus, which appeared in 1968, had two new proteins from avian viruses - the new HA and an internal protein - but kept the NA and remaining proteins from the H2N2 virus.[12,18] H1N1 viruses re-emerged into human populations in 1977, and then co-circulated with the H3N2 viruses.[5,117] (While this event is also technically a pandemic, these viruses were not new, but descendants of the H1N1 viruses that first entered human populations in 1918.) H1N2 viruses did not cause a pandemic, but viruses with this subtype been found at times in limited locations, and one H1N2 virus (which probably resulted from genetic reassortment between H3N2 and H1N1 viruses) circulated globally between 2001 and 2003.[34,232,235,236]

2009 pandemic H1N1 virus

A novel H1N1 virus emerged in human populations in 2009 and caused a pandemic.[118,120,121,237] This virus is thought to be a reassortant between North American H1N2 and Eurasian H1N1 swine influenza viruses.[118,120,121] Its HA is most closely related to swine influenza viruses in North America, and the NA to swine influenza viruses in Eurasia, while the internal proteins came from two or more swine influenza viruses including the North American triple reassortant H3N2 viruses (see swine influenza, next section) and a Eurasian virus. Before being acquired by swine influenza viruses, some of these gene segments had belonged to avian and human influenza viruses.[118,121] How humans acquired pandemic H1N1 is not known, but genetic analysis suggested that this virus was probably transmitted to people shortly before the pandemic began, most likely from pigs, and that it might have previously circulated among swine in an unknown location for years.[118,121] After the 2009-2010 pandemic, this virus became established as a seasonal influenza virus, and it continues to circulate throughout the world. It has had several names (e.g., swine influenza virus, swine-origin influenza virus, novel H1N1) but, at present, the most commonly used name is 2009 pandemic influenza A (H1N1) virus or 2009 pandemic H1N1 virus.

Swine influenza viruses

At present, diverse viruses of the subtypes H1N1, H1N2 and H3N2 circulate in swine populations, although other subtypes have transiently infected pigs in limited locations.[9,12,18,44,84,86-88,213,238-243] Different sets of viruses circulate on each continent, and sometimes in different countries or regions within a continent.[9,12,18,44,86-88,213,243]

The first influenza virus to be recognized in pigs was an H1N1 virus known as the 'classical' swine influenza virus.[244-246] Pigs are thought to have acquired this virus during the 1918 Spanish flu pandemic, possibly from infected people.[5,9,12,18,245-248] H1N1 viruses circulated in both species after this time, but diverged genetically in the two host populations.[234,249]

The classical H1N1 swine influenza virus was the major virus among swine populations in North America for approximately 70 years.[44] Some H3 viruses from humans were also found in pigs at low levels during this time, but they did not become established as stable lineages.[44] Triple reassortant H3N2 viruses first emerged in North American pigs in the late 1990s, mainly in the U.S. Midwest, and spread to other regions.[12,68,101,238,250-253] These viruses contain HA and NA derived from human influenza viruses, and internal proteins from the classical swine influenza virus, an avian influenza virus and a human influenza virus.[252] The particular combination of internal genes carried by these viruses is known as the triple reassortant internal gene (TRIG) cassette. Viruses that contain TRIG seem to be prone to increased antigenic drift.[85] They also seem to readily acquire new HA and NA genes; there are now additional TRIG-containing swine influenza viruses with various combinations of H1, H3, N1 or N2 from additional human influenza viruses, and/or H1 and N1 from the classical swine influenza virus.[44,84,85,237,254,255] Some herds have been infected with the 2009 pandemic H1N1 virus from humans, which has reassorted with other viruses circulating in pigs.[69,256-261] As a result of all these factors, North American H1N1, H1N2 and H3N2 swine influenza viruses have become very diverse, and are continuing to change.[44,84,85,254,255,261,262] Other influenza variants and subtypes, such as H2N3 and H3N1 viruses, have been detected occasionally in North American herds, but do not seem to have become established in swine populations.[238-242]

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Different swine influenza viruses circulate in Europe. The classical H1N1 swine influenza virus was found in Europe at one time (although records of its isolation and times of circulation are scarce), but a wholly avian-origin H1N1 virus entered European swine populations in the late 1970s and circulated after this time.[9,12,18,43,86,87,243,263-265] Various human-origin H3N2 viruses were also found in pigs between the mid-1970s and mid-1980s, and were eventually replaced in some areas by a reassortant that has human-origin H3 and N2, but contains internal gene segments from the avian-origin H1N1 virus.[18,43,86,263] Several H1N2 viruses have also been found, either transiently or long-term, although they are overall less common than other subtypes.[18,43,86,243,263,266,267] Pandemic H1N1 virus and its reassortants have been detected,[86,267] and additional subtypes (e.g., H3N1 viruses) have been found occasionally, but do not seem to have persisted.[43,86,243,268] One unique variant was an H1N7 virus, which was apparently a reassortant between swine and equine influenza viruses.[43,86]

Information about swine influenza viruses in Asia is limited, especially for some regions, but H1N1, H3N2 and H1N2 viruses are known to circulate. Various North American and European lineage viruses belonging to these three subtypes have been reported, as well as reassortants between North American and Eurasian lineages, and viruses unique to Asia.[9,59,87,88,213,269-273] Some of these viruses infected Asian pigs only transiently, and different swine influenza viruses may predominate in different regions.[87,88] The pandemic H1N1 virus, as well as its reassortants, have also been found, and novel subtypes (e.g., H3N1 viruses) have been isolated occasionally.[87,88,274,275]

At present, there is little information about swine influenza viruses in some other regions, including Mexico, Central and South America. H3N2 and H1N1 viruses are known to circulate in Latin America, but genetic characterization has rarely been reported.[276] One H3N2 virus isolated from an outbreak of respiratory disease in Argentina was of wholly human influenza virus origin, although it was highly transmissible in pigs.[276] Whether this was a limited outbreak, or the virus circulates there in swine populations is not known. Pandemic H1N1 and/or its reassortants with human-like H1N1 swine influenza viruses, were reported from outbreaks among pigs in Argentina and Brazil.[277,278] H1 viruses were documented in one report from Africa, and a recent study from Cameroon found pandemic H1N1 viruses in free-range swine.[279,280]

Whether a virus is circulating in pigs or represents a one-time event can sometimes be difficult to determine without long-term surveillance, which is not always available.[87] A long-term analysis conducted in Hong Kong abattoirs, where the majority of the pigs originate from China, suggests that swine influenza viruses reassort frequently, but only a few of these viruses persist, and that the population of viruses gradually changes.[213] This is also likely to be true of other regions and continents.

Equine influenza viruses

Two subtypes of influenza viruses circulated widely in equine populations during the last century, H7N7 (equine virus 1) and H3N8 (equine virus 2).[5,17,19] H7N7 equine influenza viruses were last isolated in 1979, and most authors believe they are likely to be extinct, although anecdotal reports or serology has occasionally suggested that they might persist in some areas where surveillance is limited.[5,17,23,281-283;284 cited in 285]

In the 1980s, the equine influenza H3N8 viruses diverged into distinct Eurasian and American evolutionary lineages.[286-288] The American lineage divided further into 3 sublineages: the classical American lineage, the Florida sublineage and the South American sublineage.[287,288] The Florida sublineage has become widespread, while the Eurasian lineage is now uncommon, and the classical American lineage is found occasionally in some areas.[286-288] There are currently 2 clades of the Florida sublineage, with clade 1 predominating in North America and clade 2 viruses in Europe.[288] Equine influenza viruses appear to change more slowly than human influenza A viruses or swine influenza viruses.[17,19,283]

A novel H3N8 virus (A/eq/Jilin/89) caused two outbreaks in China in the late 1980s/ early 1990s, with serological evidence indicating continued exposure of horse populations for a few years longer.[17,23,59] This virus appeared to be of avian origin. It did not persist long-term and is not known to have spread outside China.[17]

Canine influenza viruses

The first canine influenza virus to be recognized was an H3N8 virus acquired from horses in North America in the late 1990s or early 2000s.[73] This virus seems to have originated from a Florida sublineage equine influenza virus.[31,72] It has diverged genetically from equine influenza viruses, and adapted to circulate in dogs.[31,72,289-291]

An H3N2 virus, apparently of avian origin, also seems to be adapted to dogs. This virus was first recognized in 2007, and appears to circulate among dogs (and possibly cats) in several Asian countries.[70,74-81] Dog-to-dog transmission occurs readily under experimental conditions.[74-77] An H3N1 virus, which appears to be a reassortant between the Asian canine H3N2 virus and the human pandemic H1N1 virus, was recently isolated from a dog with respiratory signs in Korea.[292] No other infections with the H3N1 virus have been published at present, and it may have been a transient isolate.

Bat influenza viruses

Two new subtypes of influenza viruses were identified recently in South American bats.[148,149] These viruses have distinct hemagglutinins, which have provisionally been designated H17 and H18, unique neuraminidases, and distinctive internal genes. and could not be isolated in the cell lines and chicken embryos where other influenza A viruses are grown.[148,149] Nevertheless, gene expression studies suggest that they might be able to reassort with other influenza A viruses in mammalian cells.[148]

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Influenza B viruses

Influenza B viruses are categorized into lineages (and strains) rather than subtypes. Currently, the two important lineages in people are B/Victoria/2/87 and B/Yamagata/16/88.[293] Both lineages are widespread and co-circulate, although this was not always the case in the past.[293-295] Recombination between the two lineages can result in antigenic shifts.[294,296] Influenza B viruses also undergo antigenic drift, though it occurs more slowly than in influenza A viruses.[5,231]

Influenza C viruses

Influenza C viruses, are not classified into subtypes. Each strain of influenza C is antigenically more stable than influenza A, and accumulates fewer changes over time.[123,297] At least six lineages (Taylor/1233/47-, Sao Paolo/378/82-, Kanagawa/1/76-, Aichi/1/81-, Yamagata/26/81- and Mississippi/80-related lineages) have been identified.[297] Reassortment can occur between different strains or lineages.[123,124,297]

Influenza C-related livestock virus

A new livestock-associated influenza virus, which shares 50% amino acid identity with human influenza C viruses, was recently isolated from pigs and cattle in North America.[143,144] Initially, this virus was thought to be a new subtype of influenza C, but subsequent experiments suggest that it might represent a new genus of influenza viruses.[144,145]

Species Affected

Influenza A viruses

Avian influenza viruses

Wild birds

Birds are thought to be the natural reservoir hosts from which all influenza A viruses originated.[2,4,5,8-10,101] The vast majority of LPAI viruses are maintained in asymptomatic wild birds, particularly birds found in wetlands and other aquatic habitats.[2,4,5,8-11,147,298] Infections are especially common in members of the order Anseriformes (waterfowl, such as ducks, geese and swans) and two families within the order Charadriiformes, the Laridae (gulls and terns) and Scolopacidae (shorebirds).[2,4,5,9-11,18,147,175,180,298-303] Within the Laridae, viruses tend to occur more often in gulls than terns.[11] Aquatic species belonging to other orders occasionally have high infection rates, and might also be involved in the epidemiology of this disease.[11,304,305; 306 cited in 305] While LPAI viruses can infect birds that live on land (terrestrial birds), low overall infection rates suggest that these birds are not important reservoir hosts.[11,298,307-316] Higher rates are occasionally reported in individual species, and in a study from Vietnam, viruses were particularly common in some terrestrial birds that forage in flocks.[309,315]

The most common influenza subtypes in wild birds may differ between species and regions, and can change over time.[10,301,302,305,317-319] Some birds may maintain viruses long-term, while others might be spillover hosts. Migrating birds, which can fly long distances, may exchange viruses with other populations at staging, stopover or wintering sites.[10] A few avian influenza subtypes seem to have a limited host range, and may rarely (or never) be transferred to poultry.[10,171,175,302,320-325]

HPAI viruses are not usually found in wild birds, although they may be isolated transiently near outbreaks in poultry.[311] Exceptions include the Asian lineage H5N1 viruses, which have been found repeatedly in wild birds, an H5N3 virus isolated from an outbreak among terns in the 1960s, an H7N1 virus that was isolated from a sick wild siskin, *Carduelis spinus*, and an H5N2 virus found in a few asymptomatic wild ducks and geese in Africa.[56,94,101,102,112-114,326-338]

Domesticated birds

Poultry and game birds, including gallinaceous birds and domesticated waterfowl, are readily infected by LPAI and HPAI viruses.[4,102,112-114,153,333,339-353] When LPAI viruses from wild birds are transferred to poultry, the viruses may circulate inefficiently and die out; become adapted to the new host and continue to circulate as LPAI viruses; or if they contain H5 or H7, they may evolve into HPAI viruses.[7,8,163] Once a virus has adapted to poultry, it rarely re-establishes itself in wild birds.[163] Infections also occur in other domesticated birds, although they do not appear to be very common in either cage birds or pigeons.[1,94,102,112,312,328,334,354-358]

Host range of the Asian lineage H5N1 HPAI avian influenza viruses and reassortants

Asian lineage H5N1 HPAI viruses have an unusually wide host range. These viruses can infect domesticated and wild birds belonging to many different orders.[56,94,101,102,112-114,329-338] Although many recognized infections have been symptomatic (and in some cases, fatal), subclinical infections can occur in some species.[94,334,337,359] Wild migratory birds can introduce Asian lineage H5N1 HPAI viruses to uninfected regions, but whether they can maintain these viruses for long periods (or indefinitely), or are repeatedly infected from poultry, is still controversial.[329,332,337,360-362]

Asian lineage H5N1 HPAI viruses can infect many species of mammals, and their full host range is probably not yet known. They have been found in pigs, cats, dogs, donkeys, tigers (*Panthera tigris*), leopards (*Panthera pardus*), clouded leopards (*Neofelis nebulos*), lions (*Panthera leo*), Asiatic golden cats (*Catopuma temminckii*), stone martens (*Mustela foina*), raccoon dogs (*Nyctereutes procyonoides*), palm civets (*Chrotogale owstoni*), plateau pikas (*Ochotona curzoniae*) and a wild mink (*Mustela vison*).[7,51-59,93-97,99,100,115,211,363,364] Antibodies to these viruses were detected in horses and raccoons.[59,97,99,100,115,211,364-367] Experimental infections have been established in housecats, dogs, foxes, pigs, ferrets, laboratory rodents, cynomolgus

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macaques (*Macaca fascicularis*) and rabbits.[59,94,99,101-111,363,368,369] Cattle were infected in the laboratory with viruses isolated from cats,[111] but serological studies in Egypt suggest that cattle, buffalo, sheep and goats are not normally infected.[365]

One reassortant H5N2 virus, recovered from a dog with respiratory signs in China, could be transmitted from experimentally infected dogs to dogs, chickens and cats.[60,198,199] This virus mainly contained gene segments from Asian lineage HPAI H5N1 viruses, but had a neuraminidase related to North American lineage avian influenza viruses.[60] At present, there are no reports of illnesses in mammals caused by the currently circulating HPAI H5N8 viruses.

Host range of H9N2 (LPAI) avian influenza viruses

H9N2 viruses and/or antibodies to these viruses have been found occasionally among pigs in endemic areas.[87,88,201,214,215] These viruses have also been detected in dogs,[211,212] and infections can be reproduced experimentally in this species.[370] Serological evidence of infection with H9 viruses was detected in performing macaques in Bangladesh, and in wild plateau pikas in China.[216,371] Pikas could be infected experimentally.[371]

Host range of the zoonotic H7N9 avian influenza viruses

Among birds, infections with the zoonotic H7N9 LPAI virus in China have mainly been found in poultry (and in environmental samples from poultry markets, farms and similar sites), although this virus or its nucleic acids were also detected in two pigeons, an asymptomatic tree sparrow, and wild waterfowl.[228,372,373] Based on experimental infections, chickens and quail are most likely to maintain this virus, but several species of ducks, geese, pigeons, parakeets (*Melopsittacus undulates*) and various passerine birds could also be infected.[358,374] There have been no reports of illnesses in mammals, as of June 2014, and no evidence of H7N9 infections was found among stray dogs living near live poultry markets.[211,228] In experimental studies, isolates from humans could infect miniature pigs, ferrets, laboratory mice and cynomolgus macaques.[375-377]

Other avian influenza viruses in mammals

Infections caused by other avian influenza viruses are reported sporadically in mammals. Diverse subtypes (e.g., H4, H5N2, H6N6, H7, H10N5 and H11N2) have been isolated occasionally from pigs, especially in Asia.[87,88,159,201,378-382] An H10N4 virus was responsible for an epidemic in farmed mink, and experimental infections with H3N8, H4N6, H5N3, H7N7, H8N4 and H11N4 avian influenza viruses have been established in this species.[5,59] Cats have been infected experimentally with H1N9, H6N4, and H7N3 LPAI viruses, as well as with an H7N7 HPAI virus isolated from a fatal human case,[383-385] and dogs have been infected with an H6N1 virus.[386] Serological evidence of infection with H10N8 viruses was reported in some dogs in China,[387] and domesticated guinea pigs in South America had antibodies to H5 influenza viruses.[388] Few studies have investigated wild animals; however, antibodies to H4 and H10 viruses were found in raccoons in the U.S. (in addition to antibodies to H1 and H3 viruses, which could also originate from mammals), and antibodies to H3N8 viruses, possibly of avian origin, were reported in Japan.[389-391] Raccoons could be infected experimentally with an avian H4N8 virus,[390] and striped skunks (*Mephitis mephitis*) with H4N6 and H3N8 viruses.[392; 393 cited in 392].

Laboratory mice (*Mus musculus*) and ferrets serve as models for mammalian infections with influenza viruses, including avian influenza viruses.[394-402] Most laboratory mice have a defective gene (Mx1), which increases their susceptibility to influenza viruses compared to their wild-type progenitors.[403-405] However, one recent study suggested that wild *Mus musculus* mice may also be susceptible to experimental inoculation with certain LPAI viruses.[403]

Human influenza viruses

Human influenza A viruses mainly cause disease in people, but pet ferrets can become ill, and nonhuman primates can also be infected.[14,216,406-410] Most primate studies have been done in captive animals, but there was also evidence of infection in pet, performing and wild macaques in Asia.[216] Infections are reported occasionally in pigs, and human or part-human viruses can become established in these animals.[12,18,43,44,86-88,213,238,243,252,270,271,276] Serological and/or virological evidence of infection has sometimes been reported in other animals such as dogs, cats, cattle and even birds (including poultry),[5,19,135,216,238,270,282,409,411,412] and experimental infections have been established in cats, dogs, mink, raccoons and ducks.[5,23,390,410,412-416] Some domesticated guinea pigs in South America have antibodies to H1 and H3 viruses that might be of human origin.[388] Human influenza A viruses can replicate, to a limited extent, in the nasal epithelium of experimentally infected horses,[23] and there was some evidence for inapparent infections in horses at the time of the human 'Asian flu' epidemic.[417]

The 2009 pandemic H1N1 virus (now a seasonal human influenza virus) is often found in pigs.[86,88,256-258,267,278,280,418-421] It has also caused outbreaks in turkeys,[411,422-426] and a few clinical cases have been reported in pet ferrets, cats and dogs; captive wild species including cheetahs, a black-footed ferret (Mustela nigripes), an American badger (Taxidea taxus taxus), a Bornean binturong (Arctictis binturong penicillatus), captive giant pandas (Ailuropoda melanoleuca); and possibly wild striped skunks.[61-67,427-443] This virus was reported in healthy wild northern elephant seals (Mirounga angustirostris) off the coast of North America in 2010, but there was no evidence of infection in other marine mammals tested.[444] Experimental infections have been established in cats, dogs, ferrets, mice, cynomolgus macaques, turkeys and quail.[440-443,445-447] Chickens do not seem to be susceptible to this virus.[446,448,449]

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Swine influenza viruses

Swine influenza viruses mainly affect pigs, but some viruses can also cause disease in turkeys, ferrets and mink.[5,19,59,68,69,159,161,239,249,450-453] Some swine influenza viruses found in turkeys, but not others, can be transmitted back to pigs.[159] Chicken flocks infected with swine influenza viruses have not been reported, and chickens do not seem to be very susceptible to these viruses after experimental inoculation.[159] One H1N1 swine influenza virus, which was avirulent for both poultry and pigs, was isolated from a duck in Hong Kong,[454] and ducks can be infected experimentally.[416] Experimental infections have also been reported in calves.[454,455] Antibodies to H3 viruses found recently in cattle might have been caused by exposure to swine influenza viruses, but definitive identification of the virus source was not possible.[456]

Equine influenza viruses

Equine influenza viruses mainly affect horses and other Equidae (e.g., donkeys, mules and zebras).[5,17,22,457] Several instances of horse to dog transmission of H3N8 viruses have been reported, without the virus becoming established in canine populations.[28,82,83,458,459] Dogs have also been infected experimentally with these viruses.[460,461] Few infections have been reported in other species; however, an equine H3N8 virus caused an outbreak among pigs in China,[462] and a reassortant (H1N7) between swine and equine influenza viruses was detected in pigs in Europe.[43,86] Mink, ferrets and cats can be infected experimentally with some viruses from equids.[59,70a,399] Cattle could be infected with an equine influenza virus in an older experiment,[5,23] but in a recent study, there was no evidence of infection when they were exposed to aerosolized H3N8 equine influenza virus.[456]

Canine influenza viruses

The H3N8 canine influenza virus has only been reported in dogs,[26,27,29,31,32,72] Although this virus can still infect horses under some experimental conditions, its ability to infect horses and replicate in equine populations appears to be significantly reduced.[290,291] One study reported that horses were not infected when kept in close contact with experimentally infected dogs.[463] In laboratory studies, the canine H3N8 virus was not transmitted readily to chickens, turkeys or ducks.[464]

The H3N2 canine influenza virus has caused clinical cases in dogs and cats.[70,74,79,80] Antibodies to this virus have been found in both species, dogs and cats are susceptible to experimental infection by contact with infected dogs, and cats can transmit the virus to other cats.[70,74-81,211,465-468] Ferrets seem to be less susceptible, although they could be infected by direct inoculation of the virus, and limited ferret-to-ferret transmission was reported from these animals.[466,469] Attempts to transmit the H3N2 canine influenza virus to chickens and ducks were unsuccessful.[76]

Influenza viruses in marine mammals

H3N3, H3N8, H7N7, H4N5 and H4N6 viruses, closely related to avian viruses, have been isolated from seals, and pandemic H1N1 was found in northern elephant seals in 2010.[5,59,444,470,471] An avian-origin H3N8 virus isolated from an outbreak among seals in 2011 appeared to have adaptations that would increase its transmissibility in mammals.[471] Antibodies to H1, H2, H3, H4, H6, H7, H8, H10 and H12 viruses have been found in seals, and in some cases, in sea lions and/or walruses (*Odobenus rosmarus*).[59,140,141,470,472]

Influenza A infections have been reported sporadically in cetaceans, and H1N3, H13N2 and H13N9 viruses have been isolated from whales.[5,59] Sequence analysis of the limited isolates available from whales suggests that they do not maintain influenza viruses, but are infected from other species (birds).[473] Antibodies to influenza A viruses have been reported in porpoises.[59]

Influenza A viruses of uncertain origin in other species

Serological evidence of infection with influenza A viruses has been reported occasionally from other mammals not normally thought to be hosts for these viruses, such as yak, sheep, goats, reindeer and deer.[59,456] Definitive identification of the virus source can be difficult, but some viruses might have come from humans.[59] Antibodies to influenza A viruses have also 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.[59] There is evidence that some of these viruses might have been avian, human and equine influenza viruses.[59]

Influenza B viruses

Influenza B viruses are proven to circulate only in human populations, although they have also been found in animals, and might have other maintenance hosts.[5,18,20,59,135,138-141,474;142 cited in 139] In particular, virus isolation and serological studies suggest that either seals or an unknown marine host might maintain viruses distinct from those circulating concurrently among humans.[138-141;142 cited in 139] Influenza B viruses have been associated with illnesses in ferrets and seals, and were also isolated from pigs and a horse.[5,10,18,20,138,474;142 cited in 139] Serological evidence of infection has been found in captive nonhuman primates, pigs, dogs and horses, as well as in guinea pigs raised for food in South America.[5,135,388,409] Experimental infections can be established in guinea pigs, which can transmit the virus to co-housed guinea pigs.[475] Serological studies from the U.K. suggest that influenza B infections in swine are acquired sporadically from humans and do not spread in swine populations.[135]

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Influenza C viruses

Influenza C viruses are maintained in people, but these viruses have been also been isolated (rarely) from pigs.[5,13,16,18-20,122,476,477] Influenza C viruses can cause disease in experimentally infected dogs,[5] and serological evidence of infection has been found in pigs, dogs and horses.[5,135-137]

Influenza C-related livestock virus

The newly characterized livestock-associated influenza C-related virus (C/Oklahoma/1334/2011) was first isolated from an outbreak in pigs, but cattle might be the primary hosts.[143,144] Experimental infections have been established in pigs and ferrets.[143]

Zoonotic potential of influenza viruses

Zoonotic infections have mainly been caused by swine and avian influenza viruses. Infections with H1N1, H3N2 and H1N2 swine influenza viruses are reported sporadically in humans,[5,18,90-92,147,245,246,251,478-490] and serological evidence suggests that mild or asymptomatic infections might occur occasionally in people exposed to pigs.[5,18,147,267,289,491-500] Certain viral genotypes may be more likely to infect humans. Many recent infections in the U.S. were caused by triple reassortant H3N2 viruses that contained the 'M' gene from 2009 pandemic H1N1 virus.[89,91,92]

The two avian influenza viruses reported most often in human clinical cases are the Asian lineage H5N1 HPAI viruses and recently, H7N9 LPAI viruses in China.[8,18,101,222-228,501] Illnesses caused by H5N1 viruses are, overall, rare; however, these viruses have been found in poultry (including small backyard flocks) for over a decade, resulting in high levels of human exposure. The H7N9 virus in China might be transmitted more readily transmitted to people.[375,502] These two viruses could also be identified more often because they tend to cause serious, life-threatening illnesses, which are more likely to trigger laboratory testing than mild flu symptoms.[184,202,222-228,503] Illnesses caused by other subtypes, including H6N1, H9N2 and multiple H7 and H10 avian influenza viruses, have been reported sporadically in people,[7,8,18,101,147,200,202,203,206-209,501,504-507] and other subtypes are also likely to cause disease. Serological surveys in some highly exposed populations suggests the possibility of low level exposure to HA types found in birds including H4, H5, H6, H7, H9, H10, H11 and H12.[201,202,204,205,492,497,508-518] Experimental infections with some subtypes (e.g., H4N8, H10N7 and H6N1), have been established in human volunteers, and some of these viruses caused mild influenza symptoms.[202]

Very few human infections have been linked to species other than birds and swine. One person acquired an H7N7 (avian origin) virus from a seal,[470] and an H1N1 swine influenza virus, which had infected a turkey herd, was transmitted to a laboratory technician.[246,519] Serological evidence and one experiment in volunteers suggest that humans might be susceptible to equine viruses,[5] but there is no evidence of recent natural infections.[17] A survey from Mongolia found that very few people had antibodies to H3N8 equine influenza viruses, despite high levels of exposure to horses.[520] A preliminary analysis suggest that there may be little or no seroreactivity to the livestock-associated influenza C-related virus (C/Oklahoma/1334/2011).[143] Likewise, no infections with either canine influenza virus have been reported.

Geographic Distribution

Human influenza viruses, including 2009 pandemic H1N1 virus, occur worldwide.[5,6,521,522] Avian influenza (LPAI) viruses are cosmopolitan in wild birds, although the specific viruses differ between regions.[5,10,182,183] The influenza viruses of domesticated birds, pigs and horses also tend to occur wherever their maintenance hosts are found, unless there are good control programs that exclude them.[9,20,44,86-88,523] LPAI and HPAI viruses are usually absent from commercial poultry in developed nations, although LPAI viruses may be present in backyard flocks, live poultry markets and similar sources.[2] The H9N2 viruses and Asian lineage HPAI H5N1 viruses are currently limited to parts of Eurasia, and do not occur in the Americas, Australia or New Zealand, even in wild birds,[7,94,171-177,524-529] Asian lineage HPAI H5N8 viruses were widely detected in Asia and Europe in 2014, and reached North America (the Pacific Northwest region) in late 2014.[199a-199c] In North America, these viruses reassorted with North American lineage viruses to generate unique viruses of other subtypes such as H5N1 and H5N2, but whether any of these reassortants will persist is uncertain.[199a-199b] The zoonotic H7N9 LPAI viruses causing outbreaks in mainland China have not been reported from other regions, with the exception of a few imported cases in travelers.[226,227,530,531] A few countries such as New Zealand, Iceland and Australia are known to be free from all equine influenza viruses.[22,23,46,457,532]

The H3N8 canine influenza virus has been found, at least sporadically, in most states in the U.S., although its distribution appears to be uneven.[26,29,30,73,533-536] There is no evidence that this virus is currently circulating outside the U.S. As of 2014, the H3N2 canine influenza virus appears to be limited to Southeast Asia; it has been reported from dogs and/or cats in South Korea, China and Thailand.[70,74,76,78-81] Bat-adapted influenza viruses appear to be common in South America.[149] There is currently no information about these viruses in other areas.

Transmission

Transmission of avian influenza viruses among birds

In birds, avian influenza viruses may occur in both the feces and respiratory secretions.[4,5,19] In aquatic species such as waterfowl, most viruses are predominantly spread by fecal-oral transmission, and possibly also by fecal-cloacal

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transmission.[10,114] Respiratory spread is, overall, thought to play little or no role in these birds,[10] but some Asian lineage H5N1 HPAI viruses are shed mainly in respiratory secretions,[114,347,537] and a few LPAI viruses have been detected only from respiratory and not cloacal samples in wild waterfowl.[538] Respiratory spread might be more important in some wild terrestrial species.[10,313]

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.[4,8,539,540] The possibility of wind-borne transmission of HPAI viruses between farms was suggested by one study,[541] but has not been conclusively demonstrated. Avian influenza viruses have also been found in the yolk and albumen of eggs from chickens, turkeys and quail infected with HPAI viruses.[542-548] Although infected eggs are unlikely to hatch, broken eggs could transmit the virus to other chicks in the incubator. It might be possible for LPAI viruses to be shed in eggs, but the current evidence suggests this is very rare, if it occurs at all.[542,549]

How long birds remain contagious differs between avian species, and with the severity of the infection (chickens and turkeys infected with HPAI viruses die very soon after infection). Most chickens usually excrete LPAI viruses for a week, and a minority of the flock for two weeks, but some species of birds, including waterfowl, may shed some LPAI or HPAI viruses for a few weeks.[18,312,342,550-552]

Transmission of influenza viruses in mammals

In mammals, influenza viruses are transmitted in droplets and aerosols created by coughing and sneezing, and by contact with nasal discharges, either directly or on fomites.[5,9,15,16,19,21,35,258,553] Close contact and closed environments favor transmission.[35,554,555] Influenza viruses enter the body via the respiratory tract, but there is increasing evidence that they may also use the eye as a portal of entry.[376,400,402,556,557] While aerosol transmission is usually thought to occur only during close contact, a recent study suggested that aerosolized viruses can be present in and perhaps near densely populated swine barns.[553,558] The possibility of local airborne spread was also suggested during a recent equine influenza epidemic among naive horses in Australia.[559] Fecal shedding has been reported in both humans and animals, although its significance (if any) is still uncertain. Viral RNA has been detected in the feces of a few human patients infected with seasonal influenza A or influenza B viruses (particularly children with diarrhea, but also hospitalized adults),[560-564] and in severely ill patients infected with pandemic H1N1 virus, Asian lineage H5N1 HPAI viruses, or zoonotic H7N9 LPAI viruses in China.[565-569] In a few cases, the presence of live virus was confirmed by virus isolation. Whether these viruses (or viral RNA) come from swallowed respiratory secretions or other sources is not known.[562,564] However, Asian lineage HPAI H5N1 viruses, which can cause systemic infections, seem to be able to replicate in human intestinal tissues.[570] H5N1 viruses were also found in the feces of experimentally infected cats and foxes (but not some other species, such as pigs),[96,107-110,368] while minimal intestinal shedding of an H3N2 human influenza virus was reported in experimentally infected raccoons.[390]

Mammals often begin shedding influenza viruses before the onset of clinical signs, but the period of virus excretion is usually brief.[15,17,19,21,25,30,34,35,45,246,571,572] However, prolonged shedding is possible in individual cases. Children can sometimes shed human influenza viruses for 10 days or more, and viruses may be detected for weeks in patients who are severely ill or immunocompromised.[15,16,34,35,50,573-579]

Acquisition of influenza viruses during cross-species transmission

People and animals are usually infected with viruses from other species during close contact with the host or its tissues, although indirect contact via fomites or other means is also thought to be possible.[5,7,18,51,53-55,57,58,83,90-92,96,105,227,251,289,460,478,480,489-494,497,499,500,502,580-592] Respiratory transmission is likely to be an important route of exposure, and experimental infections in animals are usually established by inoculation into the respiratory tract.[99,105,107,108,368,383-386,390] The eye might act as an entry point for some viruses: mice and ferrets can develop systemic disease after intraocular inoculation with H7 and H5N1 (HPAI) viruses.[376,400,402,556] A few H5N1 HPAI virus infections in animals, and rare cases in humans, have been linked to the ingestion of raw tissues from infected birds.[51,53-55,57,58,96,105,583,590-592] Feeding experiments provide evidence that H5N1 viruses can enter the body by this route in cats, pigs, ferrets, mice, hamsters and foxes, and transmission has been confirmed in cats by direct inoculation of the virus into the gastrointestinal tract.[53,57,105,107,108,591,593,594] Uncooked meat from pigs or turkeys might have been sources of swine influenza viruses during two outbreaks in mink,[68,450] but whether animals became infected by ingestion or by contamination of the respiratory mucous membranes is uncertain.

Other routes of virus acquisition have been suggested in a few cases. Some experiments suggest that turkeys might be more susceptible to intrauterine inoculation of pandemic H1N1 virus than respiratory transmission,[595-597] and that accidental transmission during artificial insemination may have been responsible for some outbreaks.[411,422] (Turkeys can also be infected experimentally by intranasal inoculation.[446,598]) A ferret model suggested that some viruses might be transmitted to the fetus when there is high viremia during a systemic infection.[14] Viral antigens and nucleic acids were also found in the fetus of a woman who died of an Asian lineage H5N1 infection.[599] However, most influenza viruses replicate only in the respiratory tract, and transplacental transmission seems much less likely in these cases.

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Host-to-host transmission of novel influenza viruses

Animals or humans infected with influenza viruses from other species may or may not transmit the virus to others. Sustained transmission is a rare event, but limited host-to-host transmission can sometimes result in clusters of infections or outbreaks.[5,59,87,88,201,380,444,470,471] Such events may be difficult to distinguish from exposure to a common source of the virus, or transmission on fomites (e.g., exposure to boots worn in a pig barn by the first person who became infected with a swine influenza virus).

Limited host-to-host transmission of Asian lineage H5N1 HPAI viruses has been reported rarely in humans during close, prolonged contact,[586-589] among tigers in one outbreak at a zoo,[55] and experimentally between cats.[105] No experimental transmission of this virus was reported between limited numbers of dogs and cats.[109] or between pigs.[99] However, a recent analysis of H5N1 outbreaks in Indonesia found evidence for limited pig-to-pig transmission within herds, although each introduction of H5N1 viruses appeared to occur independently from poultry.[600] In rare cases, limited transmission to family members was also suspected for some H7 LPAI or HPAI avian influenza viruses in humans,[601-603] including LPAI H7N9 viruses in China.[223,227,502,604,605] There was no evidence for transmission to close contacts in a number of other avian influenza cases investigated,[506,601,606,607] although seroconversion to some of these viruses may be unreliable.[504,603]

Person-to-person transmission of swine influenza viruses has been reported to family members or other close contacts ,and a limited outbreak occurred on a military base in the 1970s; however, most cases seem to be acquired by direct contact with swine, and were not transmitted to other people.[5,18,90-92,245,251,478,480,486,489,580,584,585] In contrast, swine influenza viruses transmitted to turkeys can be propagated within this species.[159] Not surprisingly, the 2009 pandemic H1N1 virus can cause outbreaks in pigs,[86,88,256-258,267,278,280,418-421] but evidence for limited transmission of this virus was also reported in experimentally infected dogs (although it was sporadic and inefficient) and cats (which seroconverted but did not become ill).[440,449] The length and size of a pandemic H1N1 outbreak at a cat colony, and the timing of infections, also suggested the possibility of cat-to-cat transmission, although the human caretaker was thought to be the original source of the virus.[438] Animal-to-animal transmission of this virus might have occurred between cats, cheetahs or ferrets in other cases, but concurrent exposure to an infected human was equally plausible.[61,64,65,437,439] Experiments have demonstrated that cats can transmit a human seasonal H3N2 virus, as well as some equine H3N8 viruses, to uninfected cats during close contact.[70a,608 cited in 609] There is no evidence for significant dog-to-dog transmission of H3N8 equine influenza viruses acquired from horses.[83,461]

Survival of influenza viruses in the environment

Avian influenza viruses

The survival of avian influenza viruses in the environment may be influenced by the initial amount of virus; temperature and exposure to sunlight; the presence of organic material; pH and salinity (viruses in water); the relative humidity (on solid surfaces or in feces); and in some studies, by the viral strain.[416,550,610-622] Avian influenza viruses survive best in the environment at low temperatures, and some studies suggest that they are more persistent in fresh or brackish water than salt water.[416,550,551,610,611,613,615,617,619,623-625] Some viruses from birds may survive for several weeks to several months or more in distilled water or sterilized environmental water, especially under cold conditions.[610,611,613-615] However, the presence of natural microbial flora may considerably reduce influenza virus survival in water, and at some temperatures, viruses remain viable for only a few days (or less, in some environments) to a few weeks.[416,614-616,626] Other physical, chemical or biological factors in natural aquatic environments may also influence persistence.[614,615,625,626] In cold climates, freeze-thaw cycles can inactivate influenza viruses, potentially reducing long-term survival.[618]

In feces, some anecdotal field observations stated that LPAI viruses can survive for at least 44 or 105 days, under unspecified conditions.[610] Under controlled laboratory conditions, LPAI or HPAI virus persistence in feces ranged from < 1 day to 7 days at temperatures of 15-35°C (59-95°F), depending on the moisture content of the feces, protection from sunlight and other factors.[416,551,617,620,623,624,627] At 4°C (39°F), some viruses survived for at least 30-40 days in two studies,[416,623] but they remained viable for times ranging from less than 4 days to 13 days in two recent reports.[617,624] On various solid surfaces and protected from sunlight, viruses were reported to persist for at least 20 days and up to 32 days at 15-30°C (59-86°F);[551] and for at least 2 weeks at 4°C if the relative humidity was low;[617] but also for less than 2 days on porous surfaces (fabric or egg trays) or less than 6 days on nonporous surfaces. at room temperature.[628] Virus survival was longer on feathers than other objects in two reports: at least 6 days at room temperature in one study,[628] and 15 days at 20°C (68°F) and 160 days at 4°C in another report.[624.] Some viruses survived for up to 13 days in soil (4°C),[,617] for more than 50 days (20°C) or 6 months (4°C) in poultry meat (pH 7),[612] and for 15 days in allantoic fluid held at 37°C (98.6°F).[622] Exposure to direct sunlight greatly reduced virus survival.[617] Environmental sampling in Cambodia suggested that virus survival in tropical environments might be brief: although RNA from Asian lineage H5N1 HPAI viruses was found in many samples including dust, mud, soil, straw and water, virus isolation was only successful from one water puddle.[629]

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Mammalian influenza viruses

Human influenza A viruses may also survive for months in cold (4°C) water under laboratory conditions, although infectivity was lost in approximately 2 weeks or less at 35°C (95°F).[630] Like avian influenza viruses, the survival of these viruses was influenced by salinity.[630] At room temperature, live human influenza viruses could not be recovered from a wide variety of surfaces after 24-48 hours, with recovery from porous surfaces often lasting less than 8-12 hours.[631-634] Survival on wooden surfaces differed between studies, with one study reporting prolonged survival between 48 hours and 60 hours.[634] However, one group reported that human influenza viruses remained viable for up to 3 days on Swiss banknotes, and for as long as 8-17 days if the viruses were contained in nasopharyngeal secretions.[635]

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).[636]

Disinfection

Influenza A viruses are susceptible to a wide variety of disinfectants including sodium hypochlorite, 60% to 95% ethanol, quaternary ammonium compounds, aldehydes (glutaraldehyde, formaldehyde), phenols, acids, povidone-iodine and other agents. [15,19,25,146,610,637] Common household agents, including 1% bleach, 10% malt vinegar or 0.01-0.1% dishwashing liquid (washing up liquid), as well as antimicrobial wipes, were found to destroy the viability of human influenza viruses, although hot water (55°C; 131°F) alone was ineffective in rapidly eliminating viruses.[638] Influenza A viruses can also be inactivated by heat of 56-60°C (133-140°F) for a minimum of 60 minutes (or higher temperatures for shorter periods), as well as by ionizing radiation or extremes of pH (pH 1-3 or pH 10-14).[19,146,551,610,637] The disinfectant and heat susceptibility of influenza B and C viruses has not been examined extensively, but is probably similar.16

Infections in Animals

[Note: for more detailed information on avian, swine, equine and canine influenza, please see individual factsheets on these diseases.]

Incubation Period

The incubation period for influenza is short in all species. In poultry, it can be a few hours to a few days in individual birds, and up to 2 weeks in the flock.[2,4,19] A 21-day incubation period, which takes into account the transmission dynamics of the virus, is used for bird populations in the context of disease control.[4] The incubation period for mammalian influenza viruses is often 1-3 days, although some cases may take a few days longer to appear.[5,17,19-25,29,30,70,75,76,281,448,449,467,571,572,593,639] In particular, incubation periods up to a week have been reported in some dogs and cats infected experimentally with the H3N2 canine influenza virus.[70,75,76,467]

Clinical Signs

Highly pathogenic avian influenza

HPAI viruses usually cause severe illness in chickens and turkeys, and few birds in infected flocks survive.[4,5,339], Decreased feed and water intake, with other nonspecific systemic, respiratory and/ or neurological signs (e.g., depression, edema and cyanosis of the unfeathered skin, diarrhea, ecchymoses on the shanks and feet, coughing) are common clinical signs, but no signs are pathognomonic, and sudden death can also be seen.[2-4,8,19,163,339,340,345,546,640-643] Because a virus can be defined as highly pathogenic based on its genetic composition alone, in rare cases an HPAI virus may be isolated from a chicken or turkey flock that has mild signs consistent with low pathogenic avian influenza.[3,169]

Infections with HPAI viruses may be asymptomatic, mild or severe in other domesticated or captive birds and wild avian species, including gallinaceous birds other than chickens and turkeys.[1,3-5,10,19,56,94,113,114,307,326,328,330,331,333-335,339-342,356,644-646] Clinical signs tend to be minimal or mild in domesticated ducks and geese infected with most viruses, but some recent Asian lineage H5N1 isolates can cause severe acute illness with neurological signs and high mortality rates.[4,102,112-114,333,347,348] These H5N1 viruses have also caused sudden deaths and severe systemic, respiratory and/or neurological signs in some free-living and captive wild birds, although mild signs or subclinical infections are possible.[56,102,113,114,307,330,331,333-336,348,359,647-649]

Low pathogenic avian influenza

LPAI viruses (including the Chinese H7N9 viruses) usually cause subclinical infections or mild illnesses in poultry and other birds.[1,4,228,358,374] In chickens and turkeys, there may be decreased egg production and egg quality, respiratory signs, lethargy, decreased feed and water consumption, or somewhat increased flock mortality rates.[2,4,151,546,650-658] Illnesses exacerbated by factors such as concurrent infections or young age can be more severe.[1-3,659] Wild birds have few or no obvious clinical signs,[10,660] although subtle effects (e.g., decreased weight gain, behavioral effects or transient increases in body temperature) have been described in some free-living birds.[175,661,662]

The H9N2 viruses currently circulating among poultry in the Eastern Hemisphere can cause significant respiratory signs and malaise in chickens, including experimentally infected chickens that are not co-infected with other pathogens.[663,664] Clinical signs have been reported in quail, which are usually mildly affected by other viruses, and some experimentally infected quail became severely ill.[2,527,665] Some wild birds also developed clinical signs after experimental inoculation with H9N2 viruses.[663]

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Avian influenza viruses in mammals

Asian lineage H5N1 HPAI viruses have caused fatal disease, as well as milder illnesses or asymptomatic infections, in various mammalian species. A few clinical cases have been described, at most, in each species. One group of infected cats had no clinical signs, but a few other infected cats were found dead, and one cat developed fever, dyspnea and neurological signs before it died.[51,52,96,590] Conjunctivitis and fatal respiratory signs were described in experimentally infected cats.[105,107,109,593] Some captive tigers and leopards exhibited high fever, respiratory distress and neurological signs before death,[53-55,59] while a non-fatal outbreak among large felids was characterized by lethargy and inappetence without respiratory signs.[56] Fever, respiratory and/or neurological signs were also reported in a handful of cases in other species, including a dog, captive raccoon dogs, captive palm civets and a wild stone marten.[57-59,115] Infected donkeys had moderately severe respiratory signs, but responded well to antibiotics, suggesting that the illness may have been caused or exacerbated by bacterial pathogens.[115] Experimental infections in various species ranged from subclinical to severe, with systemic and/or respiratory signs reported in animals that became ill.[99,103,108-111,363,368] Experimental infections in dogs tended to be mild or asymptomatic unless the dogs were inoculated by a route (e.g., intratracheal) that bypasses natural respiratory defenses.[109,110,363] Experimental infections as well as reports of infected herds suggest that H5N1 HPAI virus-infected pigs usually remain asymptomatic or have only mild signs.[99,108,364,365,600]

There are only a few reports of naturally acquired or experimental infections with other avian viruses, except in animal models for human disease (ferrets and mice). Respiratory signs, but no deaths, were seen in an H5N2 HPAI-virus infected dog; dogs and one cat experimentally infected with this virus; and dogs inoculated with an H9N2 virus.[60,198,199,370] Few or no clinical signs were seen in cats inoculated with an H7N7 HPAI virus isolated from a fatal human case, cats inoculated with several LPAI viruses from waterfowl, or raccoons experimentally infected with an H4N8 virus.[383,384,390] Experimental inoculation of the Chinese (zoonotic) H7N9 LPAI virus resulted in fever alone in cynomolgus macaques and no clinical signs in miniature pigs.[375]

Swine influenza

Swine influenza is an acute upper respiratory disease with coughing and other respiratory signs, and nonspecific signs such as lethargy and weight loss.[5,18-21,45,523] Some outbreaks are more severe than others, and swine influenza viruses can circulate in pigs with few or no clinical signs.[5,9,18,85] Depending on the production system, illness may be seen in certain age groups, while others remain asymptomatic.[45,666] Concurrent infections with other pathogens can exacerbate the clinical signs.[18,20,21,666]

Swine influenza viruses in turkeys and ferrets

Turkeys infected with swine influenza viruses may develop respiratory disease, have decreased egg production, or produce abnormal eggs.[19,159]

During an outbreak caused by a triple reassortant H1N1 swine influenza virus, ferrets developed respiratory signs, including dyspnea, and some severely affected animals died.[161]

Equine influenza

Equine influenza is an acute respiratory disease, which usually begins with a high fever followed by a deep, dry, often paroxysmal cough, nasal discharge, and other respiratory and nonspecific signs.[5,17,19,22,24,25,457] Cases may be complicated by secondary bacterial infections, and rare complications such as neurological signs or myocarditis are possible.[17,22,24,25,288,457] Animals with partial immunity can have milder, atypical infections,[24] while young foals without maternal antibodies may develop severe viral pneumonia.[5,24,25] Healthy adult horses usually recover within 1-3 weeks, although the cough may persist longer, and sequelae such as chronic bronchitis are possible.[5,17,22,25] Convalescence can take up to 6 months in severely affected animals.[22]

Equine influenza viruses in dogs and cats

Both mild and severe respiratory signs have been reported in dogs infected with H3N8 equine influenza viruses after exposure to horses,[82,83,458,460] while experimental inoculation resulted in mild or no clinical signs.[460,461]

Cats that were inoculated (intranasally) with one recently circulating equine H3N8 virus developed respiratory signs.[70a] Naive cats in contact with these animals also became ill, although the signs were milder. Cats inoculated with a different (older) equine H3N8 virus developed antibodies to this virus, but remained asymptomatic and did not shed virus.[70a]

Canine influenza (H3N8)

The most common presentation seen with H3N8 viruses is relatively mild, with a low fever alone, or fever followed by malaise, a persistent cough and other respiratory signs, which may last for up to 3 weeks regardless of treatment.[26-31,72] Secondary bacterial infections seem to be common, resulting in mucopurulent nasal discharge and other signs.[29] Pneumonia or bronchopneumonia can develop in more severe cases, but this has generally been associated with concurrent bacterial or mycoplasmal infection.[26-28,30,32,72] Peracute deaths with evidence of hemorrhages in the respiratory tract occurred in racing greyhounds; however, this syndrome does not seem to be prominent in pets.[28,31]

Canine influenza (H3N2)

Like other influenza viruses, the H3N2 canine influenza virus causes respiratory signs; however, most reported cases in dogs and cats have been severe, and some

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were fatal.[70,74-77,79,80,466] Antibodies to this virus have also been reported in apparently healthy dogs and cats, suggesting that milder or asymptomatic infections may be possible.[79,81,211,465,468,667] Ferrets do not seem to be very susceptible to the canine H3N2 virus, but mild signs including sneezing were reported in some experimentally infected animals.[466,469]

Pandemic H1N1 and other human influenza virus infections in animals

Ferrets infected with seasonal human influenza viruses may develop a febrile respiratory disease with anorexia, depression, sneezing, nasal discharge and coughing.[14,406,407] Adult animals usually recover in five days to two weeks, but more severe or fatal cases can be seen in neonates.[14,406,408] The clinical signs in ferrets infected with pandemic H1N1 virus were similar, although they varied in severity, and dyspnea and deaths occurred in some animals.[427,428,430,437,439] Milder respiratory signs or systemic signs (e.g., lethargy and weight loss, with little sneezing) were reported in some ferrets inoculated with this virus,[442,443] but other studies suggested that it might be more pathogenic than seasonal H1N1 viruses.[445]

Mild as well as severe or fatal illnesses have been seen in housecats infected with pandemic H1N1 viruses.[61-65,431,434,438] The clinical signs included anorexia, lethargy, upper or lower respiratory signs ranging from sneezing and nasal discharge to dyspnea., and concurrent issues such as dehydration. Fever was not reported in some cases at presentation. Some cats remained ill for several weeks. One cat that died had evidence of myocarditis in addition to lung involvement at necropsy, but whether this was a pre-existing condition or a consequence of the viral infection is not known.[62] Experimentally infected cats became mildly to moderately ill with lethargy, loss of appetite and respiratory signs.[449] Two clinical cases reported in dogs were characterized by fever and radiological evidence of pneumonia, while a third dog had only a severe cough, with mild depression and anorexia.[435,440] Mild fever, occasional mild coughing, and nasal discharge were the only clinical signs in dogs inoculated with this virus.[440] Nasal discharge and conjunctivitis were reported in dogs inoculated with influenza C virus from humans.[5]

Pandemic H1N1 virus also caused respiratory signs in captive wild species including cheetahs, giant pandas, a black-footed ferret, an American badger and a binturong.[61,66,67] Some cases, including those in four cheetahs, the badger and binturong were severe, although the cheetahs recovered with supportive care including antibiotics.[61,66] The pandas (which were the only animals to receive antiviral drugs) and black-footed ferret also recovered.[66,67] Pandemic H1N1 virus was detected in wild striped skunks found dead with severe mixed bacterial bronchopneumonia, thought to be secondary to viral infection, and concurrent Aleutian disease virus infection.[436] These skunks came from a mink farm where many of the animals had nasal discharge; however, the clinical signs in the mink were not investigated. Another outbreak of respiratory disease in mink (see below) was, however, confirmed to be caused by pandemic H1N1.[668]

In pigs, infections with pandemic H1N1 virus are usually mild and resemble those caused by swine influenza viruses,[237,278,421,669-679] while the only significant effect reported in turkeys was decreased egg production and quality.[411,422-426]

Horses experimentally infected with one human influenza virus (H3N2 'Hong Kong') developed a mild febrile illness.[5] Raccoons that were experimentally infected with human H3N2 viruses remained asymptomatic.[390]

Influenza viruses in mink

Outbreaks in mink caused by an H10N4 avian influenza virus, H3N2 and H1N2 swine influenza viruses and pandemic H1N1 virus were characterized by respiratory signs of varying severity.[5,59,68,69,450,668] Little mortality was seen in some of these outbreaks, but pneumonia and an increased mortality rate were reported in others, particularly during the avian influenza outbreak, and in kits and on farms where the mink were co-infected with other pathogens. In the H1N2 swine influenza virus outbreak, the mink were co-infected with hemolytic *E. coli*, and developed severe respiratory disease with hemorrhagic bronchointerstitial pneumonia.[450] The hemorrhagic pneumonia and high mortality rate were attributed to the secondary bacterial component.[450] Mink that were experimentally infected with H1N1 or H3N2 human influenza viruses, H1N1 swine influenza virus, H3N8 equine influenza virus, and H3N8 and H4N6 avian influenza viruses remained asymptomatic despite shedding virus.[59]

Influenza in marine mammals

Influenza A (avian origin) viruses have been associated with outbreaks of pneumonia in seals.[5,160,473,639] Experimental infections with these viruses were milder or asymptomatic, suggesting that co-infections may have increased the severity of the illness.[59] An influenza virus was also isolated from a diseased pilot whale, which had nonspecific signs including extreme emaciation, difficulty maneuvering and sloughing skin.[639] Whether this virus was the cause of the disease or an incidental finding is uncertain.[444] Other influenza viruses were isolated from whales that had been hunted, and were not linked with illness.[680] Influenza B infections have been reported in some stranded seals.[59]

Novel livestock-associated influenza C virus

The novel livestock-associated influenza C virus (C/Oklahoma/1334/2011) was found in a herd of pigs exhibiting respiratory signs that resembled influenza.[143] It was also detected in clinical samples that had been submitted from cattle with respiratory signs.[144] Neither pigs nor ferrets developed clinical signs or gross lesions after experimental infection.[143]

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Post Mortem Lesions Click to view images

Highly pathogenic avian influenza in birds

The lesions in chickens and turkeys are highly variable and resemble those found in other systemic avian diseases.[6,681] Classically, they include edema and cyanosis of the head, wattle and comb; excess fluid (which may be blood-stained) in the nares and oral cavity; edema and diffuse subcutaneous hemorrhages on the feet and shanks; and petechiae on the viscera and sometimes in the muscles.[2,4,681] There may also be other abnormalities, including hemorrhages and/or congestion in various internal organs, as well as severe airsacculitis and peritonitis (caused by yolk from ruptured ova).[4] However, the gross lesions in some outbreaks may not fit the classical pattern,[681] and birds that die peracutely may have few or no lesions.[2,4,681] Lesions reported from fatal cases in other species of birds vary.[331,333,334,359,682]

Low pathogenic avian influenza and pandemic H1N1 viruses in birds

Poultry infected with LPAI viruses may exhibit rhinitis, sinusitis, congestion and inflammation in the trachea, but lower respiratory tract lesions such as pneumonia usually occur only in birds with secondary bacterial infections.[2,4] Lesions (e.g., hemorrhagic ovary, involuted and degenerated ova) may also be observed in the reproductive tract of laying hens, and the presence of yolk in the abdominal cavity can cause air sacculitis and peritonitis.[4] A small number of birds may have signs of acute renal failure and visceral urate deposition.[2] Reproductive lesions, with peritonitis in some cases, were the only lesions reported in turkeys infected with pandemic H1N1 virus.[422]

Influenza lesions in mammals

The major lesions caused by the influenza viruses of mammals are usually lung consolidation and/or pneumonia, or upper respiratory tract involvement alone in milder cases.[20,23-25,28,30-32,45,59,160,470,571,572,639,683] Concurrent bacterial infections, common in naturally infected animals, can result in more extensive lesions.[18,45] Lower respiratory tract lesions were reported in some animals infected with 2009 pandemic H1N1 virus.[62,64,448]

Severe illnesses caused by some viruses resulted in hemorrhagic lesions in the lungs. Hemorrhagic pneumonia occurred in fatal cases caused by the H3N8 canine influenza virus in greyhounds, although this syndrome seems to be uncommon in other dogs infected with this virus.[30-32,72,683] Severe hemorrhagic bronchointerstitial pneumonia was reported in most fatal cases of canine H3N2 influenza in dogs (although few necropsies were done),[684] and dogs inoculated with this virus had pneumonia with consolidation, edema and hemorrhages.[74,75,77,684] Hemorrhagic lesions were also found in the respiratory tract and intestinal serosa of two cats that died during a pandemic H1N1 outbreak in a cat colony,[438] although more typical influenza lesions were reported from other cases in cats.[62,64] The lungs were hemorrhagic in a whale infected with influenza virus,[639] although the lesions could not be definitively attributed to this virus.[444]

Avian H5N1 influenza viruses in mammals

Asian lineage H5N1 HPAI viruses can cause systemic lesions as well as pulmonary lesions in some animals. Gross lesions reported in some cats and other felids included pulmonary congestion and/or edema, pneumonia, hemorrhagic lesions in various internal organs, and in some cases, other lesions such as multifocal hepatic necrosis, or cerebral, renal and splenic congestion.[51,52,54,96,105,107,593] Bloody nasal discharge, severe pulmonary congestion and edema, and congestion of the spleen, kidney and liver were reported in a naturally infected dog.[57] Pulmonary lesions including interstitial pneumonia have been noted in some experimentally infected pigs,[99] while others had mild to minimal gross lesions.[108]

Diagnostic Tests

Infections with influenza viruses can be diagnosed by virus isolation, the identification of viral nucleic acids or antigens, and serology. Avian influenza viruses, their antigens and nucleic acids can be detected in respiratory and/or intestinal samples (e.g., cloacal swabs) of birds. with differing recovery rates from each site depending on the virus, species of bird, and other factors.[3] Samples from various internal organs are also tested in dead birds suspected of having HPAI.[3,4] Various respiratory samples (e.g., nasal or nasopharyngeal swabs from living animals, or lung tissue samples at necropsy, are usually collected from mammals.[19-21,30,457,685]

Virus isolation is useful for the characterization of influenza viruses, and can be used in diagnosis, although faster and simpler techniques such as RT-PCR tend to be used in most clinical cases. Avian influenza viruses are isolated in embryonated eggs,[3] while mammalian influenza viruses can be isolated in embryonated chicken eggs or cultured cell lines (e.g., MDCK cells).[18,21,457,685] Both eggs and cell cultures can be used to maximize the recovery of some mammalian viruses.[30,457] A virus detected in culture can be identified as an influenza A virus with agar gel immunodiffusion (AGID), antigen-detection ELISAs or other immunoassays, or by a molecular test such as RT-PCR.[2,3] Virus shedding is usually brief in mammals, and respiratory samples should be collected very soon after the onset of clinical signs.[21,28,457,571,572] Isolation of the H3N8 canine influenza virus from live dogs can be difficult.[28,571,572] In contrast, some birds may shed avian influenza viruses for prolonged periods, from a week to a month or more.[18,550,551] Influenza viruses can be subtyped with specific antisera in hemagglutination and neuraminidase inhibition tests, by RT-PCR, or by sequence analysis of the viral HA and NA genes.[3,18,685] Genetic tests to identify characteristic patterns in the HA (at its cleavage

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site) and/or virulence tests in young chickens are used to distinguish LPAI viruses from HPAI viruses.[3,4]

RT-PCR assays can also detect influenza viruses in clinical samples.[3,4,17,18,21,22,457,685,686] Real-time RT-PCR is the method of choice for the diagnosis of avian influenza in many laboratories,[3,4] and it is also one of the two most reliable techniques for diagnosing H3N8 canine influenza (the other is serology).[30,687,688] Viral antigens can be identified in clinical samples with various tests (e.g., ELISAs in various species; immunohistochemistry or immunofluorescent techniques; and other individual tests validated for a species).[3,17,18,21,22,30,457,685,686] The sensitivity and uses of these tests can differ between species.[3,30,688]

Serological tests may be used for diagnosis and/or other purposes. Cross-reactivity between influenza viruses can be an issue, particularly when investigating cross-species transmission. Serology can be valuable in birds for surveillance, but it is not very useful in diagnosing HPAI infections in highly susceptible birds, as they usually die before developing antibodies. Serological tests used in poultry include AGID, hemagglutination inhibition (HI) and ELISAs.[3] AGID tests and ELISAs to detect conserved influenza virus proteins can recognize all avian influenza subtypes, but HI tests are subtype specific and may miss some infections. Tests that can distinguish infected from vaccinated birds (DIVA tests) should be used in surveillance when vaccination is part of a control program.[153,689,690] Serological tests employed in mammals include HI, and in some species, other tests such as single-radial hemolysis, ELISAs and virus neutralization.[17,18,20,21,28,30,457,685,687] Swine influenza and equine influenza can be diagnosed retrospectively by a rising antibody titer in paired serum samples.[20,22,457] Acute and convalescent titers are also ideal in dogs;[28,687,691] however, a single sample (collected more than 7 days after the onset of clinical signs) can be useful in H3N8 canine influenza.[30,691] An ELISA able to differentiate infected from vaccinated horses (when using a canarypox-vectored vaccine) was used to help eradicate an equine influenza virus from Australia in 2007-2008.[281,288,559]

Diagnostic testing for the livestock-associated, influenza C-related virus has not been established; however, this virus can be isolated readily in mammalian cell lines (unlike human influenza C viruses).[143] RT-PCR and serology were also employed in the initial studies.[143,144].

Treatment

Mammals with influenza are usually treated with supportive care and rest.[2,17,20,22] Antibiotics may be used to control secondary bacterial infections.[2,17,20,22,27] Antiviral drugs used in humans are not generally given to animals, although ferrets infected with human influenza viruses have been treated with amantadine.[406] (The usefulness of this drug will vary with the antiviral resistance patterns of the circulating strains, see Human Treatment section, below.) Antiviral drugs (oseltamivir) were used in captive giant pandas infected with pandemic H1N1,[67] and some authors have speculated that they might be of use in valuable horses.[6,692] One issue with the use of antiviral drugs is that the brief period when viruses are most susceptible has often passed by the time the animal is seen.[30] The potential for influenza viruses to develop resistance to these drugs is an additional concern.

Poultry flocks infected with HPAI viruses are depopulated (this is generally mandatory in HPAI-free countries) and not treated.

Control

Disease reporting

Some influenza viruses are reportable. This is particularly the case for HPAI viruses, but other viruses (e.g., LPAI viruses, equine influenza viruses) are reportable in some countries. A quick response is vital for containing outbreaks in regions that are free of a virus, and in some cases, for minimizing the risk of zoonotic transmission. Veterinarians who encounter or suspect a reportable disease should follow their national and/or local guidelines for informing the proper authorities (state or federal veterinary authorities in the U.S. for diseases in animals). Unusual mortality among wildlife should also be reported (to state, tribal or federal natural resource agencies in the U.S.[693])

Prevention

Vaccines

Vaccines are available for avian, swine and equine influenza viruses, and in some countries, for H3N2 or H3N8 canine influenza viruses.[2,4,5,17,19-22,30,288,457,694,695] Influenza vaccines do not always prevent infections or virus shedding, but the disease is usually milder if it occurs, and virus shedding may be decreased.[2] A poor match between the vaccine and virus can compromise protection.[255] In pigs, some combinations of swine influenza vaccines and poorly matched challenge viruses were reported to exacerbate disease, at least in a laboratory setting.[84,696-698]

In birds, vaccine use may be complicated by need to keep commercial flocks free of LPAI viruses, and to quickly recognize the introduction of HPAI viruses into a country. Although routine vaccination can suppress clinical signs, it may also mask infections if good surveillance programs are not used simultaneously.[4,699-701] In addition, it can place selection pressures on influenza viruses, which may encourage the evolution of vaccine-resistant isolates.[702-705] While avian influenza vaccines are used routinely in some regions, other countries (including the U.S.) restrict their use.[2,3] Avian influenza vaccines may also be used as an adjunct control measure during an outbreak (in conjunction with surveillance and movement controls), or to protect valuable species such as zoo birds.[3,470,699]

Influenza vaccines are changed periodically to reflect the current subtypes and strains in the area, although antigenic drift tends to be lower than in human influenza

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viruses.[17-19,288]. A multi-country surveillance program for equine influenza viruses recommends changes in vaccine strains.[281,695] Although such programs do not currently exist for swine influenza viruses, surveillance has increased since the 2009-2010 human pandemic. Swine influenza viruses in North America have recently become very diverse,[44,255] making vaccination in this area a challenge.

Other preventive measures

Biosecurity measures help prevent influenza viruses from being introduced into a flock, herd or exhibit. In addition to routine hygiene and sanitation, some sources of infection to consider are contact with susceptible wild species (e.g., wild birds for avian influenza, and wild or feral pigs for swine influenza), fomites, drinking water, raw feed (e.g., pork or poultry fed to mink), and humans who may be infected with viruses transmissible to animals.[6,8,19,20,43,51,53-55,57,61-63,68,96,105,258,427-437,450,470,610,706-708] Management measures such as all-in/all-out production can help prevent the introduction of viruses in new animals.[6,8,9,18-20,246] Isolation of newly acquired animals (or animals returning to a facility) and testing before release also decreases the risk of transmission to the rest of the herd or flock.[22,258] Isolating infected animals may help reduce transmission within a facility during an outbreak,[17,707] and quarantines (voluntary self-quarantine or government-imposed) reduce transmission between premises.[17,19] Management measures, such as resting horses, can help decrease the severity of disease.[5,9,17,18,246]

Preventive measures for pets include awareness of potential susceptibilities (e.g., human seasonal influenza viruses in ferrets, pandemic H1N1 in cats, Asian lineage H5N1 in multiple species) and, to the extent practical, avoidance of close contact with the source of the infection. If contact is unavoidable, good hygiene and measures to prevent accidental transmission from coughs and sneezes may be helpful. Although the effectiveness of masks in interrupting influenza transmission is still under investigation,[36,554,555,557,709-714] they may help by intercepting droplets.

Eradication

HPAI viruses are normally eradicated by depopulation of infected flocks, combined with other measures such as movement controls, quarantines and perhaps vaccination. Infected swine herds can be cleared of influenza viruses by depopulation[9,246] or management measures.[258] Elimination of a mammalian influenza virus from an entire country is unusual; however, Australia successfully eradicated an introduced equine influenza virus with quarantines, movement controls, vaccination, and both serological and virological testing (including the use of an ELISA that could distinguish vaccinated and infected horses).[559,715]

Morbidity and Mortality

Birds

Exposure to influenza viruses and shedding patterns among wild birds are complex and likely to reflect their exposure to different habitats, as well as gregariousness and other social factors, and pre-existing immunity.[11,303] The reported prevalence of LPAI viruses among wild birds ranges from <1% to more than 40%, with much higher rates in birds from aquatic environments than terrestrial species.[175,180,298,300-302,305,308,309,314,315,318,716,717] Currently, surveillance suggests that carriage of H5N1 viruses in wild bird populations without unusual mortality events is rare.[362,718] The prevalence of influenza viruses in poultry differs between nations, but commercial poultry in developed countries are generally free of LPAI and HPAI viruses.[2]

LPAI viruses usually cause mild illnesses or asymptomatic infections in poultry, including chickens and ducks, but the outbreak can be more severe when there are concurrent infections or other exacerbating factors.[1,3,4] Chicken and turkey flocks infected with HPAI viruses have high cumulative morbidity and mortality rates, which may approach 90-100%.[4,7] HPAI viruses can cause mild or severe disease in other species, and domesticated or wild waterfowl are often mildly affected.[312,339-346] However, some Asian lineage H5N1 HPAI viruses cause severe illness even in waterfowl, and the introduction of these viruses may be heralded by unusual deaths among wild birds (e.g., swans in Europe and recently crows in Pakistan).[5,6,18,56,113,114,330,331,336,718,719] Some H5N1 HPAI outbreaks, such as one at Qinghai Lake, China in 2005, have killed thousands of wild birds.[720].

Mammals

Mammalian influenza viruses differ in prevalence in their host species. Some viruses are very common: a number of studies report that approximately 20-60% of domesticated pigs have antibodies to swine influenza viruses, with lower rates in feral swine and wild boar.[5,9,18,86,135,258,685] In contrast, the North American H3N8 canine influenza virus does not seem to spread extensively between dogs in the community and it is currently uncommon in pets, possibly because virus shedding is low.[30,721,722] .However, this virus is more prevalent where dogs are in close contact, such as kennels and animal shelters.[722-724] During outbreaks, influenza viruses can spread rapidly in fully susceptible, exposed populations. The morbidity rate can be 60-90% or higher for equine influenza viruses in naïve populations during epidemics.[5,17,24,25] Similarly, the infection rate for canine H3N8 outbreaks in kennels may approach 100%, and clinical signs can occur in a high percentage of the dogs infected.[29,30]

In healthy mammals, uncomplicated infections with host-adapted equine and swine viruses are usually associated with low mortality rates and rapid recovery

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from the acute stage of the illness, although signs such as a cough may linger.[5,17-25] However, the severity of the illness can vary with the dose and strain of virus, and host factors such as species, young age, pre-existing immunity (or maternal antibodies), stressors such as transport and concurrent illnesses, and secondary bacterial infections.[18,20-22,24,43-46,457] More severe clinical signs have also been reported in pregnant mares close to parturition.[46] The H3N8 canine influenza virus follows this pattern of generally high morbidity and low mortality, except in racing greyhounds, where the initial outbreaks were severe and fatal cases were common.[26-31] Clinical cases caused by the H3N2 canine influenza virus have been severe, to date, with a case fatality rate of 50% in two small case series in pets, and 25% in dogs and 40% in cats during one explosive outbreak at an animal shelter.[70,74,79] The possibility of milder or asymptomatic infections is suggested by reports of antibodies to this virus in significant numbers of pet dogs and cats in some Asian countries.[78,79,81,211,465,468,667,725-727]

Viruses acquired from other species

Few generalizations can be made about influenza viruses acquired from other species; however, pigs seem to be infected fairly often by viruses from birds and humans, often with only minor consequences even when the virus belongs to the Asian lineage of H5N1 HPAI viruses.[5,9,18-20,31,87,88,97,99,102,108,122,135,137,364,365,441,448,476,600,728] The consequences of infection with these H5N1 viruses have varied widely in other mammals. Infections in felids ranged from asymptomatic to fatal, while sporadic deaths were reported in other species such as a dog, raccoon dogs and palm civets.[51-59,96,103,105,107-110,590] Studies have reported antibodies to H5 viruses in some cats, dogs, horses, donkeys and pigs tested in Asia or Egypt, and while some of these reactions may have been due to cross-reactivity with other viruses, a recent study from China found H5N1 viral nucleic acids in apparently healthy feral dogs that had been exposed to poultry.[59,97,99,100,211,364,365,600] Together with experimental infections in animals, which ranged from subclinical or mild to severe and fatal,[103,108-110,363,368] the evidence at present suggests that, while H5N1 viruses can cause very serious illnesses in animals, milder cases are also possible.

Mink seem to be susceptible to a variety of influenza viruses, and while morbidity rates can approach 100%, mortality rates differed between outbreaks, and were probably influenced by co-infections and other factors.[5,59,68,69,450,668] During one extensive and severe outbreak caused by a avian H10N4 virus, the morbidity rate was nearly 100% and the mortality rate was 3%.[5,59] In contrast, one H3N2 swine influenza virus caused respiratory signs but few deaths.[69] In seals, the case fatality rate was estimated to be 20% in one outbreak caused by an H7N7 virus, and 2-4% in an outbreak caused by an H4N5 virus.[5,471] Explosive epidemics in seals are thought to be exacerbated by high population densities and unseasonably warm temperatures, as well as co-infections.[59,639]

Reports of illnesses caused by the 2009 pandemic H1N1 viruses in pet cats, dogs, ferrets and zoo animals have been uncommon, but a number of these cases were severe or fatal.[61-67,427-431,434,435,437,439,440] In one outbreak at a cat colony, half of the cats had clinical signs, and 25 of the 90 cats died.[438] However, it is possible that milder cases have not been recognized. Two surveys found increasing levels of antibodies to pandemic H1N1 virus among cats, with recently reported rates as high as 22% and 31% among pet cats in the U.S. and China, respectively, and 11% among cats in animal shelters in China.[609,727] Infections with this virus have also encouraged research into the possibility that dogs and cats may be infected with other human influenza viruses. A number of surveys found that only a few animals (less than 5%) had antibodies to various human seasonal influenza viruses including pandemic H1N1 virus, and a few reported no reactivity, but others reported seroreactivity of up to 44% for some viruses (and rarely, even higher), depending on the animal population, virus and test used.[285,609,725,727,729-739;608 cited in 609]

Only a few instances of cross-species transmission have been reported in horses, but an avian H3N8 virus resulted in a 20-35% mortality rate when it was introduced into horses in China, although little or no mortality occurred in subsequent years.[17,23]

Infections in Humans

[Note: for more detailed information on zoonotic influenza caused by avian and swine influenza viruses, please see individual factsheets on these animal diseases]

Incubation Period

The incubation period for seasonal human influenza, including infections caused by pandemic H1N1 virus, is short, with most cases appearing in one to 4 days.[5,15,35,41,50,740,741] Most zoonotic infections caused by North American H3N2 swine influenza viruses and Asian lineage H5N1 HPAI viruses also seem to become apparent within approximately 5 days, although the incubation period for some H5N1 cases might be as long as 8-17 days.[184,188,585] Estimates of the mean incubation period for the zoonotic H7N9 viruses have ranged from 3 days (in one analysis of a large number of cases) to 5-6 days.[502,604,605,742]

Clinical Signs

Seasonal human influenza

Uncomplicated infections with human influenza A or B viruses are usually characterized by nonspecific symptoms and upper respiratory signs, which may include fever, chills, anorexia, headache, myalgia, weakness, photophobia, sneezing, rhinitis, sore throat and a cough.[5,13-16,35] Intestinal signs (vomiting, nausea, diarrhea, abdominal

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pain), otitis media and febrile seizures may be seen, especially in children, and dehydration is a particular concern in very young patients.[13,14,34,35,743] Most people recover from the acute, uncomplicated illness within a week, but coughing and tiredness may persist longer and secondary bacterial or viral infections can exacerbate or prolong the symptoms.[5,13,34,35]

More severe syndromes, including pneumonia, can be seen in some individuals.[13,15,16,34,35] Influenza may also result in the decompensation or exacerbation of serious underlying diseases such as chronic lung conditions, cardiac conditions, poorly controlled diabetes, chronic renal failure or end-stage liver disease.[36,39,41,42,49,744-746] Other possible complications include various neurological syndromes including encephalitis, myositis (e.g., benign acute childhood myositis), rhabdomyolysis and myocarditis.[15,34,132-134,743] Influenza-related deaths are usually the result of pneumonia, the exacerbation of a cardiopulmonary condition or other chronic disease, or complications associated with age or pregnancy.[35]

Influenza C virus infections, which typically occur in children and young adults, are mainly characterized by mild upper respiratory disease, with some studies also reporting gastrointestinal signs or otitis; however, more severe cases with lower respiratory signs including pneumonia have been reported.[5,122-131] Fever was a common symptom in some studies;[125,127-129] but a study of young adults in Finland found that most had mild upper respiratory signs without fever.[131] Neurological signs have been reported in a few cases, and included seizures/ unconsciousness in an infant, and drowsiness and hemiparesis in a child.[129,747] Mixed infections can occur with other viruses, including influenza A viruses.[131]

Pandemic H1N1

In most people, 2009 pandemic H1N1 virus causes a relatively mild illness similar to other human influenza A infections, although the average duration of the illness may have been slightly longer during the initial outbreak, and some reports suggested that vomiting and diarrhea might have been more prominent.[39,41,42,48-50,521,741,744] In most cases the illness is self-limiting, with recovery within a week.[39,42] Complications reported with older seasonal influenza viruses, as well as secondary bacterial infections and decompensation of existing medical conditions, are also seen.[50,743,748] Severe primary viral pneumonia and/or acute respiratory distress syndrome, as well as multiple organ failure and other serious syndromes, occur in a small percentage of cases (including children and young adults), and may be fatal.[36,42,48,50,741,745,749,750] Symptoms of serious illness may include shortness of breath, which is uncommon with uncomplicated influenza, hemoptysis, frothy pink sputum and purulent sputum with diffuse lung crackles.[36] Deterioration can occur rapidly in these cases.[39,750]

Avian influenza infections in humans

Asian lineage H5N1 HPAI viruses

Most infections with Asian lineage H5N1 HPAI viruses have been severe.[7,101,202] The initial signs are often a high fever and upper respiratory signs resembling human seasonal influenza, but some patients may also have mucosal bleeding, or gastrointestinal signs such as diarrhea, vomiting and abdominal pain.[184,188,751] Lower respiratory signs tend to develop soon after the onset of the illness.[184,188] Most patients deteriorate rapidly, and serious complications including multiorgan dysfunction are common in the later stages.[184,188,751] Milder cases have been reported occasionally, particularly among children.[202,752] Rapid treatment with antiviral drugs may have been a factor in some mild cases;[753-755] however, at least one child with upper respiratory signs made an uncomplicated recovery after antibiotic treatment alone.[752]

H9N2 LPAI viruses

Most illnesses caused by H9N2 viruses have been reported in children and infants.[101,200,202,203,206-209] These cases were usually mild and very similar to human influenza, with upper respiratory signs, fever, and in some cases, gastrointestinal signs (mainly vomiting and abdominal pain) and mild dehydration.[101,200,202,203,206-209] All of these patients, including a 3-month-old infant with acute lymphoblastic lymphoma,[206] made an uneventful recovery. Acute, influenza-like upper respiratory signs were also reported in two adults.[208] However, severe lower respiratory disease, which developed into respiratory failure, was seen in an immunocompromised woman who had serious underlying conditions.[206]

H7N9 LPAI viruses in China

Most clinical cases caused by H7N9 viruses in China have been serious, to date.[222,226,227,566,756,757] The most common symptoms were fever and coughing, but a significant number of patients also had dyspnea and/or hemoptysis on initial examination, and most cases progressed rapidly to severe pneumonia, frequently complicated by acute respiratory distress syndrome and multiorgan dysfunction.[567,742,758] Diarrhea and vomiting were sometimes reported, but conjunctivitis was uncommon, and most patients did not have nasal congestion or rhinorrhea as the initial signs..[742,759]

A few uncomplicated cases were characterized by mild upper respiratory signs or fever alone, especially in children.[222,604,742,757,759,760] Some of these cases may have been mild due to prompt treatment with oseltamivir, but others were admitted to the hospital for observation alone or identified only after the person had recovered.[222,742,757,760] At least one asymptomatic infection has been reported in an adult.[566,742]

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Other avian influenza viruses

Mild illnesses, characterized by conjunctivitis and/or upper respiratory signs, have been reported in a number of people infected with various H7 LPAI or HPAI viruses and an H10N7 virus.[160,470,504,505,601,603,761-765] One H7N7 HPAI virus, which caused only mild illnesses in most people, resulted in fatal acute respiratory distress syndrome and other complications in one otherwise healthy person.[601] His initial symptoms included a persistent high fever and headache but no signs of respiratory disease. Severe pneumonia was reported in a person infected with an LPAI H7N2 virus who had serious underlying medical conditions.[606] He was hospitalized but recovered. A 20-year-old woman infected with an H6N1 virus in China had a persistent high fever and cough, progressing to shortness of breath, with radiological evidence of lower respiratory tract disease.[506] She made an uneventful recovery after treatment with oseltamivir and antibiotics. Three people with H10N8 infections in China developed severe lower respiratory tract disease, progressing in some cases to multiple organ failure and septic shock.[507,607] Two cases in elderly patients were fatal. The third patient, who was 55 years of age, was hospitalized but eventually recovered.

Swine influenza virus infections in humans

Most laboratory-confirmed, symptomatic swine influenza virus infections have been characterized by upper respiratory signs that resemble human influenza, including gastrointestinal signs in some patients, although acute parotitis was reported in a 6-year-old with H3N2 influenza, and one young patient had only fever and vomiting.[5,18,91,92,245,251,417,478,480,485,487,489,580,584,585,766,767] In a recent series of infections caused by North American triple reassortant H3N2 viruses, eye irritation appeared to be more common than with seasonal influenza viruses.[585] Most healthy people infected with these H3N2 viruses had a mild illness, although young children were sometimes hospitalized for dehydration.[91,92,245,251,478,480,485,487,489,580,585,766] Serological evidence suggests that mild or asymptomatic cases might occur sporadically among people who are occupationally exposed.[5,18,147,289,491-496]

Influenza viruses of various subtypes have occasionally caused pneumonia, serious illnesses and deaths, usually in people who had underlying health conditions or were immunocompromised by disease or pregnancy.[92,245,479,482-484,489,490,580,585,768], A few of these cases occurred in healthy people.

Equine and canine influenza virus infections in humans

There are no reports of clinical cases caused by natural exposure to equine influenza viruses or canine influenza viruses, although human volunteers inoculated with an equine influenza virus became ill.[5]

Diagnostic Tests

Infections caused by influenza A and B viruses

A number of assays can be used to diagnose influenza A and B infections in humans, but test availability differs between laboratories.[35,769] Upper respiratory samples are generally collected for routine seasonal influenza diagnosis, but samples from the lower respiratory tract are appropriate in some cases.[7,188] RT-PCR techniques are now the method of choice for detecting and subtyping influenza viruses in many laboratories, due to their speed and sensitivity.[769,770] These tests can also be used for zoonotic influenza virus infections.[188,604,771,772] Virus isolation is also a possibility, although traditional techniques take 3-14 days, and are too slow for the initial diagnosis and management of the case.[49,769] Some newer assays (e.g., shell vial-based culture techniques) are faster, if available.[769] Antigen-detection assays used in humans include immunofluorescence and immunoassays such as ELISAs.[13,35,49,770] Commercial rapid diagnostic test kits can provide a diagnosis within 15 minutes, but are less sensitive than some other methods (e.g., RT-PCR), differ in complexity and in the viruses they can distinguish, have limitations in detecting pandemic H1N1 virus, and may not detect novel infections including zoonotic viruses.[7,35,49,769,770,773,774] Improved rapid tests are in development.[770] Testing that identifies the presence of influenza A, but does not detect the subtypes found in common human influenza viruses, might indicate a novel, possibly zoonotic, influenza virus.[7] Testing for novel influenza viruses is generally performed by state, regional or national public health laboratories, and in some cases by reference laboratories capable of handing dangerous human pathogens such as H5N1 HPAI viruses.[7,188]

Resistance to antiviral drugs can be detected either with phenotypic tests or by gene-based testing to detect molecular markers of resistance.[769] The need to perform susceptibility testing depends on the composition of circulating viruses and the individual case.[769] These tests are available in a limited number of laboratories and takes several days to perform.[769]

Because people have antibodies to the subtypes found in circulating influenza viruses, serology is not generally useful for the routine diagnosis of seasonal influenza.[35] However, zoonotic influenza virus infections are occasionally diagnosed retrospectively by serology.[581] Tests used to detect influenza virus antibodies in humans include hemagglutination inhibition, virus neutralization, enzyme immunoassays and complement fixation.[769,775] The microneutralization assay is considered to be the most reliable test for detecting antibodies to avian influenza viruses.[188,202] Although a rising titer must be seen for a definitive diagnosis, single titers may be helpful in some circumstances. No seroconversion occurred with some avian influenza viruses, even in virologically confirmed cases.[504,603]

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Infections caused by influenza C viruses

RT-PCR or culture can be used to diagnose influenza C.[776,777.] It can be difficult to isolate these viruses in cell lines, and isolation in embryonated eggs is not widely available in diagnostic laboratories.[777]

Treatment

Supportive care for uncomplicated influenza in humans includes fluids and rest. Adjunct and supportive treatments for severe, hospitalized cases vary, and can include various drugs, including antibiotics to treat or prevent secondary bacterial pneumonia, and mechanical ventilation.[36]

Two groups of antiviral drugs – adamantanes (amantadine, rimantadine), and neuraminidase inhibitors (zanamivir, oseltamivir, peramivir and laninamivir) – are used to treat some cases of influenza.[13,15,34,35,49,778,779] Oseltamivir is the most commonly used neuraminidase inhibitor; zanamivir is more difficult to administer, and peramivir and laninamivir are not licensed in all countries. Adamantanes are active against human influenza A viruses, while neuraminidase inhibitors can be used in both influenza A and influenza B infections.[13,15,16,27,35,49,778,779] Antiviral drugs are most effective if they are started within the first 48 hours after the clinical signs begin, although they may also be used in severe or high risk cases first seen after this time.[15,16,27,35,49,778,779] Specific recommendations for antiviral use can vary, but these drugs are usually recommended for severe cases of influenza, or infections that have an elevated risk of complications, and they may also be recommended for some milder cases of seasonal influenza.[35,49,184,188,271,751,780] Side effects including gastrointestinal and CNS effects are possible, particularly with some drugs.[35,49] There has been some debate about the reported benefits of oseltamivir for uncomplicated seasonal influenza in healthy patients.[13,34,35,49,778,781-785]

The development of antiviral resistance is a concern, especially if drugs are used indiscriminately. Resistance can develop rapidly in influenza viruses, and may even emerge during treatment.[5,13,34,35] In the U.S., adamantanes were used most often to treat seasonal influenza in the past, but many H1N1, H3N2, and influenza B viruses had become resistant to these drugs by the 2006-2008 flu seasons.[5,13,34,35,769,778,779] Seasonal H1N1 influenza viruses then rapidly became resistant to oseltamivir (although many had lost their resistance to adamantanes), and these H1N1 viruses co-circulated with adamantane-resistant, oseltamivir-sensitive H3N2 and influenza B viruses.[769] Increasing numbers of seasonal influenza A viruses resistant to both drug classes have been reported recently, and oseltamivir-resistant influenza B viruses have also been found.[769,786] The 2009 pandemic H1N1 virus is usually sensitive to oseltamivir and resistant to adamantanes, at present, although this could change.[35,774,787] Asian lineage H5N1 HPAI viruses and Chinese H7N9 LPAI viruses have a similar resistance pattern.[7,188,223,530,758,788,789] One recent study documented pre-existing resistance to neuraminidase inhibitors, at low levels, among avian influenza viruses in wild birds, and in 9% of viruses isolated from swine that contain the N2 neuraminidase (H1N2, H3N2 and H9N2).[790]

Guidance on the influenza viruses circulating during the current season, with treatment recommendations, is often available from national or local health authorities (e.g., the CDC in the U.S.). Antiviral susceptibility testing can be done, but it is too slow to guide the initial treatment, which should be started during the period of maximum virus susceptibility.[769]

Prevention

Annual vaccines, usually given in the fall before the flu season, are available for influenza A and B.[5,13,231] They contain the viral strains that are most likely to produce epidemics during the following winter, including pandemic H1N1 virus, and are updated annually. Details on vaccine efficacy, vaccine types, and current recommendations are available from government sites (e.g., the CDC in the U.S.) and professional advisory groups.[35,231,791,792] Immunization recommendations may differ between countries, although vaccination of some groups (e.g., the elderly) is consistently recommended.[35,793]

Antiviral drugs may be used for prophylaxis in some high-risk populations such as the elderly or immunocompromised, or people may be monitored and treated at the first sign of disease.[34,35,49,778] The use of antiviral prophylaxis should be balanced against the risk of encouraging the emergence of drug-resistant strains.[49] Other preventive measures include avoiding close contact with people who have influenza symptoms, and common sense hygiene measures such as frequent hand washing and avoidance of unnecessary hand contact with the eyes, nose or mouth.[7,35,90,794] To protect others, the mouth and nose should be covered when coughing or sneezing.[35,90,794] Recommendations on the use of face masks, respirators and other barrier precautions (e.g., gloves, gowns) vary, and current setting-specific guidelines (e.g., for hospitals vs. the community) should be consulted.[35,36,555] The effectiveness of face masks and respirators in decreasing influenza virus transmission is still under investigation, although some studies suggest that they may reduce the amount of virus transmitted by the wearer, and/or provide some protection to the wearer.[554,555,557,709-713]

Additional measures that have been recommended during pandemics or outbreaks with novel viruses include avoidance of crowds and gatherings, cancellation of social events, and voluntary self-isolation of individuals who develop influenza-like signs (other than necessities such as seeking medical care).[794-800]

Zoonotic influenza viruses

Protective measures for zoonotic influenza viruses include controlling the source of the virus (e.g., eradicating viruses from domesticated birds, closing infected poultry markets); using sanitation and hygiene measures such as

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hand washing; avoiding contact with sick animals or animals known to be infected; and using personal protective equipment where appropriate (for instance, when working with infected birds or swine).[7,90,184,582] While zoonotic infections are usually acquired during close contact with animals,[7,90] some recent research suggests that aerosolized viruses may be present in confined areas such as production barns with large numbers of swine.[558] Because HPAI viruses have been found in meat and/or eggs from several avian species,[152,352,542-548,652,801-805] careful food handling practices are important when working with poultry or wild game bird products in endemic areas, and all poultry products should be completely cooked before eating.[7,693,806] Swine influenza viruses can also be inactivated by cooking,[90,807,808] although these viruses are respiratory pathogens and are not likely to be present in retail meat.[523]

More detailed recommendations for specific groups at risk of exposure (including the general public) have been published by some national agencies, including the CDC, the Department of the Interior and U.S. Geological Survey National Wildlife Health Center in the U.S.,[7,90,693,809] and international agencies such as the World Health Organization. In some cases, recommendations may include antiviral prophylaxis (e.g., for people who cull birds infected with Asian lineage H5N1 HPAI viruses) and/or vaccination for human influenza to reduce the risk of reassortment between human and animal influenza viruses.[7] Recommendations are also available for people who plan fairs in North America (http://www.cdc.gov/flu/swineflu/h3n2v-fairs-planning.htm), where zoonotic infections with some H3N2 swine influenza viruses have been acquired.[90] Currently, the CDC recommends that people who are at elevated risk of complications with human influenza viruses avoid pigs and pig barns in North America, and that other people take precautions to reduce the risk of infection.[90] When visiting a physician for an illness that began soon after contact with animals, the potential for zoonotic exposure should be mentioned.

Morbidity and Mortality

Human influenza A and B viruses

Human influenza can occur as a localized outbreak, an epidemic, a pandemic or as sporadic cases.[12] Epidemics are seasonal in temperate regions, typically beginning after school starts in the fall, and spreading from children to adults, although some virus transmission occurs outside this time.[5,13,810] In tropical and subtropical areas, influenza patterns are very diverse, with transmission occurring year-round in some countries, and seasonal epidemics, sometimes coinciding with the rainy season or occurring in two peaks, in others.[811,812]

Uncomplicated infections with seasonal influenza viruses are rarely fatal in most healthy people, although the morbidity rate can be high.[5,12-16] Approximately a third of influenza virus infections are thought to be asymptomatic.[50] Groups at higher risk for severe illness include the elderly; young children under the age of 2 years (due to risks from complications such as severe dehydration); people with chronic respiratory or cardiovascular disease and various other medical conditions; members of some ethnic groups at high risk (see pandemic H1N1, below); and those who are immunosuppressed including pregnant women.[13,15,16,34-42,47] Obesity was first recognized as a risk factor during the 2009-2010 pandemic.[35,47]

Since 1968, H3N2 influenza A viruses have caused the most serious epidemics with the highest mortality rates.[34,35] Except after the introduction of a new virus, over 90% of influenza-related deaths occur in the elderly.[34,231] Although deaths can occur in children, they are rare when only established seasonal human influenza viruses are circulating.[34,35] Morbidity and mortality rates usually increase during influenza A pandemics, sometimes dramatically.[5,7,9,13,18,35] Historical evidence suggests that pandemics occur every 10 to 40 years.[5,15,18] The pandemic of 1918 is notorious for its severity, with some estimates suggesting a morbidity rate of 25-40% and case fatality rate of 2-5%.[12] 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 (or its variants[813]) usually becomes established in the population and circulates for years.[5,12,18,117] Influenza B viruses can cause epidemics, but they have not, to date, been responsible for pandemics.[5]

2009 pandemic H1N1 virus

Serological studies have estimated that approximately 30-50% of all school-aged children, and a smaller percentage of the entire population (10-40% worldwide) were infected during the initial stages of the 2009-2010 pandemic.[41,814,815] Overall, infections with this virus have been relatively mild, and the estimated case fatality rate is less than 0.5%, with a number of estimates suggesting that it is less than 0.05%.[41,50] Nevertheless, viral pneumonia has been a significant concern in a minority of patients, and case fatality rates in younger age groups have been higher than with seasonal influenza viruses.[39,41,48,49,750,816]

Most hospitalized or severely affected patients during the 2009-2010 pandemic were children and young adults, with relatively few patients older than 50 years and even smaller numbers older than 60.[40,41] The relative sparing of older populations appears to result from immunity to similar, previously circulating viruses (pandemic H1N1 was antigenically very similar to the 1918 virus), and possibly other factors.[37,40,50,817-820] The concentration of severe illnesses mainly in younger, healthier age groups is thought to have contributed significantly to the low overall mortality rate, with many seriously ill patients recovering with hospitalization and intensive care.[36,41] Older patients who do become infected with this virus have an elevated risk of severe illness and death.[50]

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The prevalence of pre-existing conditions among seriously ill children differs between studies, but predisposing conditions (e.g., asthma, immunosuppression, neurological diseases) were relatively common in some series.[36,821,822] However, a significant number of serious or fatal cases were reported in healthy children or young adults.[36,39,41,42,48-50,750,823,824] Obesity and pregnancy were recognized as risk factors for more serious illness during this pandemic.[35,47] The impact of pandemic H1N1 virus was also greater in indigenous groups.[37,41,50] The reason is still uncertain, but might involve access to healthcare, concurrent illnesses, increased crowding or other factors.[41,50]

Influenza C

Serological studies suggest that many people are exposed to influenza C viruses in childhood, although infections can continue to occur in adults.[129-131,825-828] Until recently, these viruses were thought to cause only sporadic cases of influenza and minor localized outbreaks.[5,13,122] However, in 2004, a nationwide influenza C epidemic was reported in Japan.[776] Infections seem to be most serious in very young children. In one study, 30% of children hospitalized with severe influenza C infections were less than two years old, and an additional 12% were between the ages of 2 and 5 years.[125]

Zoonotic swine influenza

The overall prevalence of swine influenza virus infections in humans is uncertain. Although the interpretation of serological studies is complicated by cross-reactivity with human influenza viruses, antibodies to these viruses have been reported in some people who work with pigs.[5,18,147,267,289,491-496,498,499] If most infections resemble human influenza, they may not be investigated and recognized as zoonoses. Virologically confirmed clinical cases caused by H1N1, H1N2 and H3N2 viruses have been reported sporadically since the 1970s (with one localized outbreak in 1976), and more regularly in recent years.[5,18,90-92,147,245,246,251,478-490,580,584,585,766-768] While zoonotic cases have also been seen in Europe and Asia, most recent cases were documented in the U.S., where this disease has been reportable since 2005.[90] In the U.S., the number of reported cases increased from approximately one every 1-2 years to 21 between 2005 and June 2011, 13 between August 2011 and April 2012, and 306 confirmed cases (mainly associated with fairs) in summer 2012.[90-92] This increase may be related to changes in swine influenza viruses (particularly the establishment of triple reassortment H3N2 viruses in swine populations, and their reassortment with 2009 pandemic H1N1 virus), but other factors, such as increased surveillance and the new reporting requirements may also play a role.[89-92]

Many cases of swine influenza (including most of the recently reported cases in the U.S.) have been seen in children, but adults are also affected.[91,92,245,251,478-480,482-485,487,489,490,580,585,766,768] While most cases have been mild and resembled human influenza, a few severe or fatal illnesses have also been reported, often but not always in people who had underlying health conditions or predisposing factors.[91,92,245,251,478-480,482-485,487,489,490,580,585,766,768]

Asian lineage H5N1 avian influenza viruses

Between 1997 and May 2014, Asian lineage H5N1 viruses were responsible for approximately 665 human infections, generally as the result of close contact with poultry.[191] Most patients were young and had no predisposing conditions.[188] The case fatality rate for all laboratory confirmed cases reported to WHO has consistently been about 59-60% in the last few years.[501] However, it differs between countries, and is particularly low in Egypt, where 28% of confirmed, suspect and probable cases between 2006 and 2010 were fatal.[751,753,755,829-831] A high proportion of the reported cases in Egypt occurred in young children, and their young age, early diagnosis and, treatment-related factors, as well as the virulence of the circulating viruses, might be factors in the relatively high survival rate.[753-755] Antibodies to H5 viruses have been reported (generally at low rates of seroconversion) in some poultry-exposed populations that have no history of severe H5N1 disease, fueling speculation on the likelihood of asymptomatic or mild infections.[365,509,510,512,518,832-834] Rare, laboratory confirmed, asymptomatic or mild cases have also been recognized.[202,752,835] Recent prospective studies documented seroconversion in rare instances, but detected no clinical cases.[508,510,511]

H7N9 avian influenza viruses in China

More than 400 clinical cases have been caused by LPAI H7N9 viruses in China, as of April 2014.[226,227] They mainly occurred in two waves, the first consisting of approximately 130 cases between February and May 2013, and the second from October 2013 to May 2014, with sporadic cases reported between the two outbreaks.[222,223,225-227,836] This virus seems to circulate subclinically in poultry, and human cases have mainly been associated with live bird poultry markets, although the source of the virus in some cases is uncertain, and exposure to backyard poultry or poultry farms was an additional risk factor in rural patients.[227,228,502,581,582,837] Most reported cases in both waves were serious, except in children, who often (though not always) presented with mild cases.[222,227,228,566,742,756,757] Elderly people were overrepresented among the clinical cases, due to increased exposure and/or increased susceptibility.[502,756,838] The reported case fatality rate in hospitalized, laboratory confirmed cases was approximately 36%, and the risk of death increased significantly with age.[222,227,228] Concurrent diseases or predisposing causes have been reported in a significant number of patients, although serious cases and fatalities also occurred in previously healthy individuals.[222,228,502,531,566,604,742,756,839]

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The likelihood of additional, undiagnosed mild or asymptomatic infections is still being assessed, although few cases were found during national virological sampling of people with influenza-like illnesses.[222,228,757] Some serological studies found no H7N9 reactivity among poultry market workers, healthcare staff, patient contacts and other populations.[223,605,840-843] However, recent surveys detected antibodies to these viruses in up to 14% of poultry workers, and less than 1% of the general population.[844,845]

H9N2 avian influenza viruses

Clinical cases caused by H9N2 viruses have mainly been reported in children,.[7,101,200-203,207-209] Most cases, including an infection in an immunocompromised infant, have been mild, and were followed by uneventful recovery. Severe illness was reported in an adult with serious underlying medical conditions.[206] Serological studies suggest that exposure to H9N2 viruses may occur in some people who are exposed repeatedly to poultry in endemic areas,[201,204,205,497,509,510,512,513,846] and a prospective study of adults with poultry exposure in rural Thailand reported rare instances of seroconversion, although no clinical cases were detected.[508]

Other avian influenza viruses

Most reported infections with H7 viruses other than the H7N9 virus in China have been mild in healthy people, whether they were caused by an LPAI or HPAI virus; however, one H7N7 HPAI virus caused a fatal illness in a healthy person, while affecting others only mildly.[160,470,505,601,603,761-765] Mild signs were reported in poultry workers infected with an H10N7 virus;[504] , but H10N8 viruses caused fatal infections in two elderly patients in China and a serious illness in a 55-year-old,[507,607] and a young woman infected with an H6N1 virus in China developed lower respiratory tract complications.[506] The possibility of other, unrecognized infections may be suggested by the occurrence of antibodies, generally at a low prevalence, to H4, H6, H7, H10, H11 and H12 viruses (as well as H5 and H9 viruses) in people who are exposed to poultry or waterfowl.[201,202,204,205,492,508,510,514-518,520,847,848]

Internet Resources

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

CDC. Seasonal Influenza . (with links to avian, swine and other influenza viruses)
http://www.cdc.gov/flu/

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

Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices
http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html

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

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

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

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

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

USDA APHIS. Biosecurity for the Birds
http://www.aphis.usda.gov/animal_health/birdbiosecurity/

United States Geological Survey [USGS]. National Wildlife Health Center. List of Species Affected by H5N1 (Avian Influenza)
http://www.nwhc.usgs.gov/disease_information/avian_influenza/affected_species_chart.jsp.

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

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

World Health Organization. Zoonotic Influenza
http://www.who.int/influenza/human_animal_interface/en/

World Organization for Animal Health (OIE)
http://www.oie.int/

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/en/international-standard-setting/terrestrial-manual/access-online/

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

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