Influenza

Note: This factsheet provides an overview of the various influenza viruses in animals and humans. For more detailed information on avian, swine, equine and canine influenza and influenza D, please see individual factsheets at http://www.cfsph.iastate.edu/DiseaseInfo/factsheets.php

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Importance

Influenza viruses are highly variable RNA viruses adapted to maintenance in various hosts, including humans. The four known viral species are designated influenza A, B, C and D. Influenza A viruses have multiple reservoirs in both birds and mammals. Wild aquatic birds are thought to be their natural hosts, but some viruses are maintained in poultry, and a limited number have adapted to circulate in people, pigs, horses or dogs. A separate, distinct group of influenza A viruses is maintained in bats. Influenza A viruses can, on occasion, affect other domesticated or wild mammals, including many that do not host their own influenza viruses. Cross-species transmission has also been reported with influenza B and C, which are viruses of humans, and influenza D, which seems to be maintained in cattle. Influenza viruses that infect a novel host do not usually not persist in that species; however, there are exceptions. In the last century, a few influenza A viruses adapted to circulate in pigs or dogs, avian influenza viruses caused or contributed to three pandemics in humans, and a virus from pigs caused a human pandemic in 2009.

The consequences of an influenza virus infection depend on the specific virus as well as other factors, notably the health of the host. Host-adapted mammalian influenza viruses usually cause respiratory illnesses with high morbidity but low mortality rates. While severe or fatal cases are possible in healthy individuals, they mainly occur in conjunction with other diseases and stressors, debilitation or immunosuppression, as well as during infancy or old age. The risk of serious illness may increase when a new virus is introduced into a population and immunity to that virus is limited or absent, e.g., during pandemics. Many influenza virus infections in novel mammalian hosts likewise seem to mostly cause mild to moderate illnesses, though some viruses appear to be more dangerous. Birds have two types of avian influenza viruses. Most resemble mammalian viruses, spreading readily but generally causing only mild illnesses in healthy birds. However, a subset of these viruses can mutate to become highly virulent for chickens and turkeys, and sometimes for other birds. Such viruses, which are called highly pathogenic avian influenza (HPAI) viruses, can cause devastating outbreaks with morbidity and mortality rates that frequently approach 90-100%. HPAI outbreaks can have major economic impacts due to trade restrictions as well as the effects of the virus.

Etiology

The family Orthomyxoviridae includes four genera of influenza viruses, Alphainfluenzavirus, Betainfluenzavirus, Gammafluenzavirus and Deltainfluenzavirus, which contain, respectively, influenza A, B, C and D viruses.

Nomenclature of influenza virus strains

Strains of influenza viruses are described by their type, host, place of first isolation, strain number (if any), year of isolation and subtype, if applicable. 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 generally omitted. Numerous variants may develop after an influenza virus lineage has circulated for a time. These variants are frequently classified into clades and subclades.

Influenza A viruses

Influenza A viruses (species influenza A virus, genus Alphainfluenzavirus) are the most common influenza viruses in birds and mammals. This large group of highly variable viruses is adapted to circulate in particular hosts, but can occasionally infect other species. Most influenza A viruses are maintained in birds (avian influenza viruses), but a few circulate in mammals. Mammalian reservoir hosts include people (human influenza A viruses), pigs (swine influenza viruses), horses (equine influenza viruses), dogs (canine influenza viruses) and bats (bat influenza viruses).

Influenza A viruses are classified into subtypes (e.g., H3N2, H5N1) based on two highly variable surface proteins, the hemagglutinin (HA) and neuraminidase (NA). These two proteins are critical for the virus to enter and exit a cell, and they are also major targets for the immune response. There are 18 recognized hemagglutinins (H1 to H18) and 11 neuraminidases (N1 to N11), with little or no immunological
cross-protection between different HA or NA types. Viruses with H1 through H16 and N1 through N9 can be found in birds, and a limited number of subtypes circulate in humans, horses, pigs and dogs. The H17N10 and H18N11 viruses, which only appear to infect bats, have distinctive hemagglutinins with a unique structure and binding properties, as well as unusual and distinctive neuraminidases.

### Variability and change in influenza A viruses

Influenza A viruses regularly undergo small to large changes in their genome. Mutations cause gradual changes in a virus’s HA and NA genes, a process called ‘antigenic drift.’ If these two proteins change enough, a host’s existing immune responses against that virus may no longer be protective. Genetic reassortment, which results from “re-shuffling” the 8 viral gene segments when two different viruses infect a single cell, can result in more rapid changes. Most influenza A viruses can reassort whether they are adapted to the same host species or originally came from different hosts (e.g., an avian influenza virus reassorting with a swine influenza virus). However, the bat H7N11 and H18N10 influenza viruses only seem to be able to reassort with each other. Reassortment can result in large or small changes in a virus, but an important aspect is that it can introduce a completely new HA, NA or both. Such abrupt changes, called ‘antigenic shifts,’ may be sufficient for the novel virus to completely evade the existing immunity in its usual host.

The high variability in influenza viruses also means that two viruses with the same subtype, for instance an H3N2 avian influenza virus and an H3N2 swine influenza virus, or two different H1N1 swine influenza viruses, may be only distantly related.

### Acquisition and loss of influenza viruses in a species

Each influenza A virus is adapted to circulate in a particular host, but viruses can occasionally infect other species. In most cases, the virus cannot be transmitted efficiently in the novel host and soon disappears. On rare occasions, however, a virus continues to circulate. Complex molecular adaptations, which are still not well understood, are likely to be required for a successful species jump. The viral surface proteins (HA and NA) and internal proteins both seem to be involved in host preferences. 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 instances, whole viruses have jumped successfully to new species. Two examples are an equine H3N8 virus that became a canine influenza virus, and an avian H1N1 influenza virus that adapted to circulate in pigs in Europe in the 1970s. At other times, a new virus reassorts with a virus already circulating in that host. Avian and human influenza viruses, for instance, regularly contribute gene segments to swine influenza viruses. Reassortment can occur either in the new host or in an intermediate host, which then transmits the virus further. For example, an avian influenza virus could reassort with a human influenza virus in a pig, then be transferred to humans. Host jumps are thought to be more likely when different species are regularly housed in close proximity.

Influenza A viruses can also disappear from host populations. Some viruses have vanished from humans, horses or pigs after circulating for years or even decades. For unknown reasons, the establishment of a new influenza virus in a species sometimes leads to the disappearance of an older viral lineage.

### Avian Influenza viruses

Avian influenza viruses are extremely diverse, with 16 hemagglutinins and 9 neuraminidases, each of which is also highly variable. These viruses form geographically distinct populations as the result of wild bird migration routes. The two major groups, the Eurasian and North American lineages, result from separate north-south flyways in the Eastern and Western Hemispheres. Overlap between these flyways in a few locations, such as in Alaska and Iceland, allows the occasional transfer of viruses between the two hemispheres, but this is uncommon and most lineages remain distinct.

Avian influenza viruses are classified into two groups based on their virulence in chickens. The vast majority are ‘low pathogenic’ or ‘low pathogenicity’ (LPAI) viruses, which replicate at only a few sites such as the respiratory and intestinal tracts, and, on their own, usually cause only mild illnesses in both poultry and wild birds. LPAI viruses with the H5 or H7 hemagglutinin may sporadically mutate to become highly pathogenic (or high pathogenicity) avian influenza (HPAI) viruses, which cause a severe and often fatal systemic disease in chickens and turkeys, though they are not necessarily highly virulent in other birds. Whether LPAI viruses with hemagglutinins other than H5 or H7 can ever become true HPAI viruses is still an open question, but if this occurs, it is very rare.

LPAI virus lineages sometimes persist for a long time in poultry, generating numerous variants and reassorting with other avian influenza viruses. At present, there are two LPAI viruses of particular concern. One is an H9N2 lineage common in parts of the Eastern Hemisphere. The other is an H7N9 lineage that is currently limited to China. Both viruses are known to have caused a number of human infections, and the H7N9 infections are often serious in older people. The H7N9 LPAI viruses, which are mainly controlled by vaccination, have periodically generated H7N9 HPAI viruses.

HPAI viruses are overall uncommon, as government control programs usually eradicate these viruses before they can become widespread, and their high fatality rates also limit their persistence in isolated flocks. A notable exception is the A/goose/Guangdong/1996 lineage (‘Asian lineage’) of H5N1 HPAI viruses, which first emerged in poultry in China in the late 1990s and has become widespread and diverse. It remains endemic in some...
nations, where it is often controlled to some extent by vaccination; however, the virus continues to mutate, generating many variants. Asian lineage H5N1 HPAI viruses are a particular concern because they have caused life-threatening illnesses in people of all ages.

Asian lineage H5N1 viruses have reassorted with other avian influenza viruses, and several new subtypes belonging to this lineage (e.g., H5N2, H5N5, H5N6 and H5N8) have been identified among poultry and wild birds in Asia, Europe and Africa, though only some have persisted. During the last decade, some Asian lineage H5 viruses reached the Americas via wild bird migration and have generated new reassortants in this location.

**Human influenza A viruses**

H1N1, H1N2, H2N2 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. The existing viruses are under considerable selection pressure from naturally acquired and/or vaccine-induced immunity in a long-lived species, which results in a high rate of change. Human influenza A viruses tend to form a single global population, with the most successful variants spreading annually from region to region.

New viruses occasionally become established in people, typically resulting in a pandemic where mortality is elevated, followed by the establishment of the novel virus as a circulating seasonal influenza virus. Pandemics were most recently reported in 1918-1919, 1957-1958, 1968-1969 and 2009-2010. 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, while other studies indicate that it may have been a reassortant. This virus gradually changed as it circulated in the human population, then apparently disappeared in 1957 when an H2N2 virus emerged.

The 1957 and 1968 pandemics resulted from reassortment between avian and human influenza viruses. 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. These H2N2 viruses circulated in people between 1957 and 1968. 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. H1N1 viruses re-emerged into human populations in 1977, and then co-circulated with the H3N2 viruses. (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, and they did not enter a fully susceptible population.)

A novel swine-origin H1N1 virus emerged in human populations in 2009. This virus was a reassortant between North American H1N2 and Eurasian H1N1 swine influenza viruses, which contain some gene segments that originally came from avian and human influenza viruses. After the 2009-2010 pandemic, this virus became the predominant seasonal H1N1 virus in people. It is currently designated A(H1N1)pdm09 but had several other names over the course of the pandemic, such as swine influenza virus, swine-origin influenza virus and novel H1N1.

H1N2 viruses have not caused a pandemic to date, but viruses with this subtype been found at times in limited locations, and one H1N2 virus (which probably resulted from reassortment between H3N2 and H1N1 viruses) circulated globally between 2001 and 2003.

**Swine influenza viruses**

H1N1, H3N2 and H1N2 swine influenza viruses currently circulate in pigs. Other subtypes, such as H2N3 and H3N1, are also reported occasionally but are not widespread. Each of the three major subtypes includes multiple viruses with diverse origins.

One swine influenza virus, known as the classical H1N1 virus, seems to have circulated in pigs since the 1918 human flu pandemic. The timing of outbreaks in farmers and their herds suggests that pigs acquired this virus from people, though it has also been argued that the human virus originally came from pigs. The H1N1 viruses circulating in pigs and people subsequently diverged. A(H1N1)pdm09 has also been transmitted many times from people to pigs, and it has contributed gene segments, including those of the hemagglutinin and neuraminidase, to various swine influenza viruses. Another common H1N1 virus is an avian-like virus, originally from birds, that entered pigs in Europe in the 1970s.

H3N2 swine influenza viruses include multiple viruses that originated from various sources in Europe or Asia, as well as the North American triple reassortant H3N2 viruses, which contain HA and NA genes from human influenza viruses and internal protein genes from the classical H1N1 swine influenza virus, an avian influenza virus and a human influenza virus. The triple reassortant viruses, which are also called TRIG-containing viruses after their combination of internal genes, have become diverse, widespread and successful beyond North America, and sometimes carry other hemagglutinins and/or neuraminidases.

**Equine influenza viruses**

Equine influenza viruses seem to change more slowly than the viruses circulating in some other species; nevertheless, they do evolve. H7N7 and H3N8 viruses circulated widely in equids during the last century, but the H7N7 equine influenza viruses gradually became less common and are last known to have been isolated in 1979. The H3N8 viruses meanwhile became widespread, diverging into several lineages and sublineages, several of which disappeared or became uncommon. Most of the currently circulating H3N8 viruses belong to the Florida sublineage.
Influenza

**Canine influenza viruses**

No influenza viruses were known to circulate in dogs until the late 1990s or early 2000s, when a Florida sublineage H3N8 virus was acquired from horses in North America. This virus has adapted to dogs and diverged genetically from equine influenza viruses, to the point where it no longer readily infects horses. It was found regularly in North American dogs at one time, though lately it has become infrequent or apparently disappeared from many areas. Whether it will continue to circulate indefinitely is unclear.

An H3N2 canine influenza virus, with gene segments entirely of avian origin, became established in some Asian countries in the mid-2000s. It has since diversified, with some variants containing gene segments from human and avian influenza viruses. It can be found in pets as well as strays and dogs farmed for food.

**Bat influenza viruses**

H17N10 and H18N11 influenza viruses have been found in South American bats. These viruses appear to be unique among influenza A viruses; they do not grow in the cell lines and chicken embryos used to isolate and propagate other influenza A viruses, the structure and binding properties of the H17 and H18 proteins differ from those of other hemagglutinins, the viral internal genes are distinctive, and the function of their neuraminidases is still unclear.

An H9N2-like virus subsequently found in Egyptian fruit bats (Rousettus aegyptiacus) is more closely related to the influenza A viruses of other mammals and birds. It probably originated in birds, though it appears to be distinct from avian H9N2 influenza viruses.

**Influenza B viruses**

Influenza B viruses (species influenza B virus, genus Betainfluenzavirus) are similar to influenza A viruses in structure, but less diverse. They are categorized into lineages (and strains) based on the viral hemagglutinin, but not into subtypes. The two important lineages in people, at present, are represented by B/Victoria/2/87 and B/Yamagata/16/88. Both lineages are widespread and co-circulate, although one lineage may predominate in an area in any given year. Reassortment can occur within, and occasionally between, the two lineages; and influenza B viruses can undergo infrequent antigenic shifts. Antigenic drift also occurs, though it generally happens more slowly than in influenza A viruses. Influenza B viruses can cause epidemics, but they are not known to have caused any pandemics.

**Influenza C viruses**

Influenza C viruses (species influenza C virus, genus Gamma1 influenza
d) have one surface glycoprotein, the hemagglutinin-esterase-fusion protein, rather than separate hemagglutinin and neuraminidase proteins. They are antigenically more stable than influenza A viruses and accumulate fewer changes over time. 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. Reassortment can occur between different strains or lineages. Influenza C viruses rarely cause epidemics and are not known to have caused any pandemics.

**Influenza D viruses**

Influenza D viruses (species influenza D virus, genus Delta1 influenza
d) are most closely related to influenza C viruses, sharing approximately 50% amino acid identity and a similar gene structure with a single hemagglutinin-
esterase-fusion protein. When they were first discovered, they were also called influenza C-related livestock viruses. There are several recognized lineages of influenza D viruses, which can circulate simultaneously and can reassort to generate new variants.

**Species Affected**

Birds, pigs, equids, dogs, cattle and humans act as reservoir hosts for certain influenza A, B, C or D viruses, but these viruses can occasionally infect other domestic animals and wildlife. Limited evidence, mainly based on the detection of nucleic acids (PCR) and/or antibodies to influenza viruses, also suggests the possibility of influenza or influenza-like viruses in reptiles (crocodiles, snakes), amphibians (toads), fish and even the primitive hagfish (Eptatretus burgeri).

**Avian influenza viruses**

LPAI viruses have been found in a wide variety of birds, and others are known to be susceptible based on experimental infections. The majority of LPAI viruses are thought to circulate in wild aquatic birds, their probable natural reservoir. Reports have generally suggested that these viruses are sporadic or uncommon among birds that reside on land (terrestrial birds, e.g., passerines, raptors); however, a few recent studies described significant virus circulation in some terrestrial species, such as migratory swallows in Africa.

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. HPAI viruses are usually uncommon in wild birds, though there are a few reports of isolated outbreaks, and they may also be found transiently near outbreaks in poultry. The Asian lineage H5N1 viruses and their reassortants (e.g., H5N8 viruses) are an exception to this pattern and occur regularly in wild birds.

Avian influenza virus infections have been seen sporadically in a wide variety of mammals, either with or without significant clinical signs. Affected mammals include species that do not act as maintenance hosts for any influenza A viruses (e.g., cats and zoo felids, cattle and other ruminants, mink, ferrets, guinea pigs, foxes, raccoons, marine mammals and many other wild species) as well as those that do (e.g., pigs, horses, dogs). Many of the published cases involve Asian lineage H5 viruses, possibly because they are more severe and/or there is particular interest in these viruses, but other HPAI and LPAI viruses can also be found. Infrequently, avian influenza viruses have adapted to circulate either short-term or indefinitely in other species.
**Human influenza viruses**

Human influenza A viruses mainly cause disease in people, but nonhuman primates and ferrets are also known to be susceptible, and infections or illnesses have been documented occasionally in other species. Particular interest has been paid to A(H1N1)pdm09, which has been found regularly in pigs and turkeys, and sporadically in other species. Sick animals have included dogs, cats, ferrets, farmed mink, and captive wildlife including cheetahs, an American badger (Taxidea taxus taxus); a Bornean binturong (Arctictis binturong penicillatus); giant pandas (Ailuropoda melanoleuca) and sloth bears (Melursus ursinus). Serological studies of healthy dogs and cats suggest that occasional A(H1N1)pdm09 infections may not be unusual in these species. There are also a few reports of A(H1N1)pdm09 in free-living wildlife such as wild boar, healthy northern elephant seals (Mirounga angustirostris) and sick striped skunks (Mephitis mephitis).

A few reports described virological and/or serological evidence for infections with H3N2 and older H1N1 viruses in cats, dogs, guinea pigs, cattle, yaks, water buffalo, small ruminants, Bactrian camels, horses, captive sloth bears and other mammals, though the strength of the evidence varies. There is one report of antibodies to H2N2 viruses in cats during the 1957 pandemic, though at the time it was dismissed as unlikely because cats were not thought to be hosts for influenza viruses. Some birds, including ducks, quail and certain seabirds, might also be susceptible to certain human influenza A viruses. Chickens do not seem to be readily infected by A(H1N1)pdm09.

**Swine influenza viruses**

Swine influenza viruses mainly affect pigs, but some viruses also cause disease in turkeys (chickens do not seem to be susceptible), and sporadic reports have described infections in other animals including farmed ferrets and mink, dogs, cattle, a duck and possibly a sheep. Calves, sheep and ducks have been infected experimentally. Once a virus enters turkey flocks, it can be maintained in this species.

**Equine influenza viruses**

Equine influenza viruses mainly affect horses and other equids. Sporadic infections have been seen in dogs, and one H3N8 virus became established as a canine influenza virus. An H3N8 equine influenza virus was found during surveillance of healthy Bactrian camels, an H1N7 reassortant between swine and equine influenza viruses was detected in pigs in Europe, and an H3N8 virus was isolated from sick pigs in China, though another equine H3N8 virus did not replicate well in experimentally infected swine. Experimental infections with equine influenza viruses have been reported in dogs, cats, ferrets, mink and a yak (Bos grunniens). Cattle were also susceptible in an older study, but a more recent report found they were not infected by an aerosolized H3N8 virus.

**Canine influenza viruses**

The H3N8 canine influenza virus only seems to affect dogs. While this virus can still infect horses under some experimental conditions, this does not seem to occur readily. Laboratory studies found that chickens, turkeys, ducks and pigs did not seem to be susceptible.

The H3N2 canine influenza virus is maintained in dogs, but it also causes clinical cases in cats, and it is able to infect ferrets and guinea pigs. One serological study suggested the possibility of infections in some horses exposed to dogs in Asia, but this remains to be confirmed.

**Bat influenza viruses**

No species other than bats is known to be susceptible to the H17N10 and H18N11 viruses. An H18N11 virus replicated poorly in experimentally infected ferrets, which are susceptible to many influenza A viruses, and mice. The H9N2-like virus from Egyptian fruit bats replicated in the lungs of experimentally infected mice, but did not infect chickens.

**Influenza B viruses**

Influenza B viruses are maintained in people. Natural and/or experimental evidence of susceptibility has been reported occasionally in seals, pigs, dogs, cats, guinea pigs, horses, captive nonhuman primates, and some birds (e.g., pheasants, mallard ducks), with clinical signs reported in ferrets, seals and experimentally infected pheasants. The evidence for a species’ susceptibility may sometimes be equivocal. For instance, one group recovered an influenza B virus from dogs during an outbreak in Japan, and older studies described experimental infection of this species, but a recent study found no evidence of productive infections in the dogs they inoculated.

Most species are probably infected only transiently with influenza B viruses, though some evidence suggests that either seals or an unknown marine host might maintain a subset of viruses distinct from those in humans. Pigs can transmit these viruses to other pigs, but surveillance found no evidence for prolonged virus maintenance in infected herds. Limited animal-to-animal transmission was also demonstrated in experimentally infected guinea pigs, pheasants and mallards, but not chickens.

**Influenza C viruses**

Influenza C viruses are maintained in people, but these viruses have been also been isolated from pigs and cattle, and serological evidence of infections has been found in pigs, dogs, horses and camels. Experimental infections have been established in hamsters, rats, nonhuman primates, dogs, pigs and ferrets, though only the dogs and pigs became ill.
Influenza D viruses

Cattle appear to be the reservoir hosts for influenza D viruses, but they also infect pigs, and antibodies have been detected in wild boar, sheep, goats, horses, water buffalo, dromedary camels and some cervids. Experimental infections have been established in horses, ferrets and guinea pigs.

Zoonotic potential of influenza viruses

Swine and avian influenza viruses of various subtypes have caused occasional clinical cases in people, and serological studies suggest the possibility of additional mild or subclinical infections. A few infections were acquired from animals other than the reservoir host, for example seals infected with avian influenza viruses or turkeys infected with swine influenza viruses. Experimental infections in volunteers also demonstrated susceptibility to equine influenza viruses and one possible case was reported in the literature, though there is no definitive evidence for any naturally acquired cases.

There are currently no known clinical cases from canine influenza viruses or influenza D viruses, though serosurveys and PCR testing of nasal swabs suggest that exposure to influenza D viruses may be common among people who work with livestock. The zoonotic potential of H17N10 and H18N11 bat influenza viruses is likewise unknown, but some sources consider human infections to be unlikely.

Geographic Distribution

Human influenza A, B and C viruses are cosmopolitan, and similar sets of viruses tend to circulate in most populations. With a few exceptions (e.g., island nations maintained free of equine influenza), swine influenza viruses, equine influenza viruses and LPAI viruses also occur wherever their maintenance hosts exist. However, the specific composition of these viruses often differs between regions. Influenza D viruses likewise seem to be widely distributed, and have been found on all major continents.

Canine influenza viruses are more limited in their distribution. The H3N8 canine influenza virus has mainly been found in North America, with a few reports of its possible presence outside this area, while the H3N2 canine virus circulates in parts of Asia and has been reported periodically in North America, often in outbreaks associated with imported dogs. The distribution of bat influenza viruses is still poorly understood. The H17N10 and H18N11 influenza viruses were found in South America, while the H9N2-like bat virus was detected in Egypt and might exist in other parts of the Eastern Hemisphere, based on serology.

Transmission

Influenza viruses spread most readily during close contact and in closed environments. The possibility of wind-borne aerosol transmission has also been suggested in rare instances, if there are large concentrations of infected animals and suitable climatic conditions, but remains controversial.

Avian influenza viruses can be shed in both the feces and respiratory secretions of birds, but the relative amount of virus found at each site depends on the specific virus and host species. Most viruses in waterfowl are mainly spread by fecal-oral transmission; however, respiratory spread is also important in terrestrial birds, such as gallinaceous poultry, and can be the predominant route in some species. HPAI viruses are sometimes found in the internal contents of eggs, though this either does not happen or is very rare with LPAI viruses.

Mammalian influenza viruses are usually transmitted by the respiratory route, with the eye acting as an additional entry point. These viruses and/or their nucleic acids have been found occasionally in the feces, and fecal-oral spread is thought to be the predominant route for H17N10 and H18N11 influenza viruses in bats. Whether there is any significance fecal shedding of other influenza viruses in mammals is unclear, and it may simply reflect swallowed viruses from the respiratory tract. Some avian and human influenza A viruses are capable of replicating in the mammary gland of ruminants. Experiments on human influenza viruses employed direct instillation of the virus into the udder and demonstrated virus proliferation in both lactating and non-lactating cattle. Whether the Asian lineage H5N1 viruses, which have been found in the milk of some naturally infected cattle, reach this site by direct contact or after respiratory infection is still uncertain.

Occasionally, influenza viruses may be transmitted by other routes. Carnivorous birds or mammals can acquire these viruses by eating raw tissues, eggs, or milk from infected hosts. Some of these viruses may contaminate the respiratory tract during the process of eating, but direct gastrointestinal exposure has been demonstrated to result in infections in some cases. Transplacental transmission of influenza viruses is thought unlikely in most instances; however, viral antigens and nucleic acids were found in the fetus of a woman who died of an Asian lineage H5N1 infection, and a ferret model confirms that some viruses might cross the placenta in systemic infections with high viremia. Turkeys can be infected by A(H1N1)pdm09 via artificial insemination as well as other routes.

Influenza viruses may or may not spread efficiently in species other than their usual hosts. In many cases, such infections remain limited to a single individual or a few close contacts. However, there are also reports of larger outbreaks, including some that affected hundreds or thousands of individuals. A few viruses seem well adapted to propagate in certain incidental hosts, such as some swine influenza viruses in turkeys.

Survival of influenza viruses in the environment

Environmental persistence of viable influenza viruses is influenced by the type of surface and ambient conditions. Low temperatures and protection from sunlight enhance
Influenza

Incubation Period

Influenza viruses can also survive longer suspended in liquids, which protect them from desiccation. Both mammalian and avian influenza viruses are reported to remain viable for several weeks to several months or more when suspended in distilled water or sterilized environmental water in the laboratory; however, this may be reduced to a few days (or less) to a few weeks in some natural water sources. The prolonged persistence of influenza viruses in water is thought to facilitate transmission among aquatic birds.

Disinfection

Influenza A viruses are susceptible to a wide variety of common disinfectants, such as sodium hypochlorite, 60-95% ethanol, acids, povidone-iodine and other agents. Common household agents including 1% bleach, 10% malt vinegar or a 0.01-0.1% solution of dishwashing soap in water (“washing up liquid”) were found to be effective for human influenza viruses, although hot water (55°C; 131°F) alone did not rapidly eliminate them. 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).

The disinfectant and heat susceptibility of influenza B, C and D viruses to disinfectants has not been examined extensively, but it is probably similar. However, an apparently higher resistance of influenza D to acid pH suggests that some disinfection methods (e.g., 10% malt vinegar) should be tested rather than assuming efficacy.

Infections in Animals

Incubation Period

Clinical signs of influenza typically appear within a few days in all species, though there are occasional reports of longer incubation periods, for instance in some dogs and cats experimentally infected with H3N2 canine influenza viruses, or turkeys and ostriches infected with some avian influenza viruses.

Clinical Signs

Common clinical signs in mammals are acute onset cough, sneezing and serous to mucopurulent nasal discharge, which may be accompanied by nonspecific signs of illness such as lethargy, reduced appetite and fever. Subclinical and very mild infections are also possible. Healthy animals usually recover from uncomplicated influenza within a few days to a week or two, but prolonged signs such as persistent coughing are possible. More severe illnesses are seen occasionally, especially in very young, old or debilitated animals, and can include primary viral pneumonia (e.g., in young foals without maternal antibodies), secondary bacterial infections that exacerbate the clinical signs, and other respiratory and systemic complications. Some of these cases can be fatal. To date, clinical signs have not been reported in bats infected with bat influenza viruses.

LPAI and HPAI viruses cause very different syndromes in poultry. LPAI viruses often infect birds subclinically or cause mild illnesses, though the clinical signs can be exacerbated by concurrent infections or stressors such as poor husbandry. Respiratory and/or nonspecific signs, as well as disorders of egg laying (decreased egg production, misshapen eggs, decreased fertility or hatchability), are common during outbreaks in chickens and turkeys, and may be accompanied by somewhat increased flock mortality. Similar signs may be seen in other species infected with HPAI viruses.

In chickens and turkeys, HPAI viruses usually cause a systemic illness that can kill most of the flock. Diarrhea, neurological and/or respiratory signs, ecchymoses on the shanks and feet, edema and cyanosis of the unfeathered skin, and severe effects on egg production are common. Sudden death is also seen. The effects of HPAI viruses on other species can vary. In particular, many HPAI virus infections in waterfowl are mild, though there may sometimes be respiratory signs (e.g., sinusitis), diarrhea, corneal opacity and occasional cases with neurological signs, and flock mortality may be somewhat increased. Some recent Asian lineage H5 HPAI viruses appear to be more virulent across species, and have caused various combinations of nonspecific signs, respiratory signs, greenish diarrhea, neurological disease and/or sudden death in many domesticated and wild birds, including waterfowl.

Influenza A viruses in incidental hosts

Some infections in incidental hosts resemble influenza caused by host-adapted influenza viruses, with most animals developing mild to moderate respiratory illnesses, and more severe cases or outbreaks often attributed to co-infections or host factors such as age. In birds, such as turkeys infected with swine influenza viruses, the signs can include effects on egg laying. There are also reports of viruses that cause severe or fatal influenza in apparently healthy animals, with dyspnea and/or systemic disease that may include neurological signs. Hemorrhagic pneumonia was common in H3N8 virus-infected racing greyhounds when these viruses first adapted to dogs. Asian lineage H5 HPAI viruses have caused a number of fatal cases in various mammalian hosts, though not all illnesses caused by these viruses are severe. The latter include the recent H5N1 outbreaks among cattle in North America, where the illnesses are usually mild and self-limited, and mastitis is often a prominent sign.
Human influenza A viruses in animals

Human influenza A viruses can cause occasional illnesses in animals. Ferrets, which are regularly affected by these viruses, typically develop respiratory and nonspecific signs of varying severity, e.g., fever, anorexia, depression, sneezing, nasal discharge and a cough. Conjunctivitis, otitis and diarrhea have also been reported. While most ferrets recover without complications, the illness can be severe in neonates and occasionally in older animals, particularly those that are elderly, stressed, have other health issues or develop secondary bacterial infections.

Sporadic reports have also described nonspecific and/or upper or lower respiratory signs, ranging from sneezing and nasal discharge to dyspnea, in cats and dogs. Most cases were described during and after the 2009 pandemic, but there are a few published reports of H3N2 virus-infected dogs with respiratory signs in the 1970s. A few A(H1N1)pdm09 infections were fatal, sometimes progressing rapidly to the terminal stage, and some cats that recovered were sick 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 caused by the virus is not known. Clinical signs in cats and dogs experimentally infected with A(H1N1)pdm09 or H3N2 viruses were often mild or absent, and serological studies in healthy dogs and cats also suggest that many naturally-acquired infections may be subclinical or mild.

A(H1N1)pdm09 has caused numerous swine influenza-like outbreaks, which were generally mild, in pigs. Decreased egg production and quality often seem to be the only significant signs in turkey herds infected with this virus, though co-infections may result in additional signs. A few reports described respiratory illnesses in various A(H1N1)pdm09-infected captive wildlife. Some of these cases were severe, though most animals recovered with supportive care. This virus was also found in dead wild striped skunks with severe secondary bacterial bronchopneumonia and concurrent Aleutian disease virus infections. It is possible that these skunks acquired the virus from farmed mink.

Acute respiratory disease outbreaks among Bactrian camels in Mongolia between 1978 and 1988 were attributed to a reassortant H1N1 human influenza virus that might have been an improperly inactivated vaccine strain. Although the case fatality rate was 9%, experimentally infected camels had milder signs and there were no deaths, suggesting that secondary bacterial infections or other factors may have contributed to the outbreaks’ severity. There are also some older studies in cattle reporting an association between various human influenza A viruses and/or rising serologic titers to these viruses with a drop in milk yield and/or nonspecific or respiratory signs. Antibodies that reacted with human H3N2 viruses were found in a yak/zebu cross, and an experimentally infected yak had a mild cough and malaise. Horses experimentally infected with a human H3N2 virus developed a mild febrile illness, while sheep and calves inoculated with these viruses had influenza-like respiratory signs in some experiments but were subclinically infected in others. One study reported that there were no signs after inoculation of calves with three H3N2 viruses isolated from people, but an H3N2 virus recovered from a naturally infected, sick calf caused mild, transient rhinitis and nasal discharge.

Influenza B

Ferrets are known to be susceptible to influenza B as well as influenza A viruses, and can develop similar clinical signs. One old field report suggested that an influenza-like outbreak in pigs might have been caused by influenza B viruses acquired from people, based on serology and the timing of the illness, which occurred concurrently with a human outbreak. Subsequent studies found mild respiratory signs and/or lesions in some experimentally infected pigs. Ponies inoculated with influenza B viruses sometimes had a transient fever, and one animal became ill, with the signs described as sweating, listlessness and unusually heavy breathing. Influenza B infections have also been reported in some stranded seals, though their role in the stranding, if any, may be difficult to ascertain.

Influenza C

Influenza C viruses have been found in pigs and cattle, though their contributions to the reported clinical signs, if any, are still unclear. Experimentally infected pigs had nasal discharge and slight dyspnea without fever, while experimentally infected dogs developed conjunctivitis and nasal discharge. Experimentally infected rats, hamsters, ferrets and nonhuman primates did not become ill.

Influenza D

Whether influenza D viruses are significant pathogens is still unclear, but some authors have suggested that they may contribute to multifactorial illnesses in cattle and pigs, in particular the bovine respiratory disease complex (shipping fever). These viruses are also found in asymptomatic pigs and cattle. Experimentally infected horses remained asymptomatic.

Post Mortem Lesions

Gross lesions caused by LPAI viruses are usually limited to tracheitis, rhinitis, sinusitis and ovarian lesions (e.g., inviolated and degenerated ova), though lower respiratory tract lesions may be seen in birds with secondary bacterial infections. HPAI viruses cause severe lesions, similar to those of other systemic avian diseases, in chickens and turkeys. Common lesions include superficial edema and cyanosis of unfeathered tissues, internal and external hemorrhages (e.g., ecchymoses, petechiae), edema and congestion in internal organs, and severe airsacculitis and peritonitis. The lesions may be minimal in birds that die in the early stages of the illness. HPAI lesions in other species of birds vary, but wild or domestic birds severely affected by Asian lineage H5 HPAI viruses often have necrotic lesions in the pancreas.
Upper respiratory tract involvement alone is common in mild influenza in mammals, while more severe cases may have diffuse congestion and edema in the lungs, bronchopneumonia with consolidation, or lesions of bacterial pneumonia. Hemorrhagic pneumonia is generally rare, but it was seen in a number of fatal H3N8 canine influenza cases in greyhounds during the early stages of that outbreak, as well as some of the early fatal cases of canine H3N2 influenza reported in dogs in Asia. Later infections caused by these viruses resembled typical mammalian influenza. Hemorrhagic lesions were found in the respiratory tract and intestinal serosa of two cats that died during an early A(H1N1)pdm09 outbreak in a cat colony, though the other cats have more typical influenza lesions, including those of secondary bacterial pneumonia.

Systemic and/or respiratory lesions, such as hemorrhages and/or congestion in various internal organs and multifocal hepatic necrosis have been described in some mammals with severe illnesses causes by Asian lineage H5 HPAI viruses. However, some animals have only limited mild lesions, and mastitis was the most prominent lesion in many infected cattle.

**Diagnostic Tests**

Influenza A viruses, their antigens and/or nucleic acids can be detected in respiratory samples from mammals and respiratory and/or intestinal samples (e.g., cloacal swabs) from birds. They can also be found in affected internal organs, such as the lungs, at necropsy. Virus shedding is usually brief in mammals, and samples from live animals should be collected as soon as possible after the onset of clinical signs. Routine diagnosis is usually with RT-PCR and/or antigen detection assays (e.g., ELISAs, immunostaining). Some of these tests can detect viruses of certain subtypes, while others only recognize the agent as an influenza A virus.

Virus isolation is done infrequently, and is particularly useful for the characterization of the virus. Avian influenza viruses and the H9N2-like virus found in bats can be isolated in embryonated eggs, and either eggs or cultured cell lines can be used for most mammalian influenza viruses; however, H17and H18 bat viruses can only be grown in a few cell lines not normally employed in influenza virus isolation (e.g., MDCK II, RIE 1495 and Calu-3 cells). The subtype of a recovered virus can be identified with specific antisera (hemagglutination and neuraminidase inhibition tests), or various genetic tests e.g., RT-PCR, sequencing). Genetic tests to identify characteristic patterns in the HA’s cleavage site and/or virulence tests in young chickens distinguish LPAI viruses from HPAI viruses. A virus’s susceptibility to antiviral drugs can also be determined after isolation.

Serology may occasionally be employed in diagnosis, though it is more likely to be used in surveillance and vaccine testing. It generally requires paired serum samples and a rising antibody titer, though a single antibody test may be suggestive if a region is virus-free or the virus is unusual in that host. Cross-reactivity between influenza viruses can be an issue, and anti-HA titers may be low or absent in some animals infected with viruses adapted to other species. Chickens and turkeys infected with HPAI viruses usually die before any antibodies develop.

Similar tests, especially RT-PCR, can be used to identify influenza D virus infections or aberrant influenza B or C infections in animals. Isolation of live virus, as opposed to PCR alone, strengthens the case that an unusual virus is responsible for the clinical signs. A rising antibody titer can also be helpful.

**Treatment**

Mammals with influenza are usually treated symptomatically with rest and supportive care, including antibiotics as needed to control secondary bacterial infections. With rare exceptions, administering the antiviral drugs used in humans is considered inadvisable. One issue is that the brief period when viruses are most susceptible to these drugs (48 hours) has often passed by the time the animal is seen. Another is that indiscriminate use of antivirals can contribute to drug resistance in the circulating viruses. There may, however, be instances where these agents are useful. For instance, oseltamivir was given to giant pandas infected with A(H1N1)pdm09. One antiviral drug, amantadine, was suggested for some sick ferrets infected with human influenza viruses in the past; however, its efficacy is now doubtful, as a high proportion of the currently circulating viruses are amantadine-resistant.

**Control**

**Disease reporting**

Veterinarians who encounter or suspect a reportable form of influenza should follow their national and/or local guidelines. HPAI viruses are usually reportable, but the requirements for other viruses vary.

**Prevention**

Biosecurity measures help reduce the risk that influenza viruses will be 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 or domestic animals, fomites, and contaminated drinking water or feed, including pork or poultry meat fed to mink, as well as contact with people who may be infected with viruses transmissible to animals. Measures such as all-in/all-out production or isolation and testing of newly acquired animals are also helpful.

Management measures, such as resting horses, can help decrease the severity of the illness if an outbreak occurs. Isolating sick animals may decrease transmission within a facility, and quarantines reduce transmission between premises. HPAI outbreaks are controlled by depopulating infected flocks, combined with other measures to ensure elimination of the virus, such as movement controls, quarantines and perhaps vaccination. Testing and movement controls, together with a vaccine that could distinguish infected from vaccinated animals, were used
during an equine influenza virus outbreak in Australia, which is normally free of these viruses. Infected swine herds have sometimes been cleared of influenza viruses by depopulation or management measures, but virus-free status may be difficult to maintain.

Preventive measures for pets include awareness of potential susceptibilities (e.g., human seasonal influenza viruses in ferrets) and, to the extent practical, avoidance of close contact with the source of the infection.

Vaccines

Vaccines are available for avian, swine, equine and canine influenza viruses. Vaccines must be well-matched with the virus and may reduce transmission but do not reliably prevent infection and virus shedding. They can also place selection pressures on influenza viruses, which can promote the evolution of vaccine-resistant isolates. Swine influenza viruses have become very diverse in some areas, making vaccination of this species a particular challenge. Vaccination of poultry flocks is either restricted or limited to flocks participating in surveillance programs in some countries, as the birds can become infected while displaying few or no clinical signs.

Morbidity and Mortality

Influenza viruses other than HPAI viruses tend to be widespread and common in their reservoir hosts. However, canine influenza viruses appear to be patchy in their distribution, and the H3N8 canine influenza virus is uncommon in pets, probably due to the relatively low frequency of contact between dogs from different households in North America. Whether it will persist indefinitely is uncertain.

Influenza viruses often spread rapidly and may affect most or all of the animals in a closed group, such as a kennel or stable. The pattern of infections and disease also reflects the level of immunity, including waning protection from maternal antibodies, and periods of increased contact with other hosts. In wild birds, LPAI virus infection rates are particularly high at sites where young birds are first exposed to these viruses, e.g., gathering areas for migration. Similarly, endemic swine influenza viruses in some production systems mainly affect young animals as their maternal antibodies wane and they are mixed with other pigs.

Illnesses caused by LPAI viruses and mammalian influenza viruses are usually characterized by high morbidity and low mortality, with severe disease more likely to occur in animals that are elderly or very young, have underlying illnesses, or are stressed by conditions such as transport or poor management. Serious cases in healthy animals may, however, increase when a new virus is introduced to the population. HPAI virus infections are usually severe in chickens and turkeys, regardless of their health, with cumulative morbidity and mortality rates that approach 90-100%. Nevertheless, there have been reports of milder and more limited outbreaks in poultry, including some caused by recent Asian lineage H5 viruses in Europe.

The effects of HPAI viruses on other birds vary, but some recent Asian lineage H5 HPAI viruses seem to be highly virulent for many hosts, including some that are relatively resistant to other HPAI viruses.

It is difficult to generalize about influenza virus infections in incidental hosts, as the reported infections range from mild to severe. In addition, severe cases or outbreaks are more likely to be investigated, while a mild illness assumed to be a common respiratory disease will probably be treated empirically, without testing. Asian lineage H5 HPAI viruses, which have caused many of the sporadic severe cases and deaths in healthy animals in recent decades, appear to be particularly virulent in a number of species, though some hosts, such as pigs or cattle, mostly seem to experience milder cases.

Human influenza viruses in animals often seem to be relatively mild. While some A(H1N1)pdm09 cases documented in pets and zoo animals during the 2009 pandemic were serious or fatal, subsequent studies reported seroprevalence from < 0.5% to approximately 45% in cats and dogs, suggesting that many mild or subclinical infections might be missed. These studies also found that some dogs and cats were seropositive for human H3N2 viruses or H1N1 viruses that circulated before 2009, and sometimes documented increasing seroprevalence to A(H1N1)pdm09 and decreasing seroprevalence to the latter viruses.

Infections in Humans

Incubation Period

The incubation period for seasonal human influenza is usually a few days or less. It appears to be similar in most zoonotic cases, though illnesses caused by avian influenza viruses have occasionally appeared up to 2 weeks after exposure.

Clinical Signs

Seasonal human influenza

Uncomplicated infections with human influenza A or B viruses are usually characterized by acute upper respiratory and nonspecific signs that may include headache, myalgia, weakness, anorexia, photophobia, sneezing, rhinitis, sore throat and a cough. Fever is common in children, but may be absent in a significant number of adults. Conjunctivitis is possible but uncommon. Intestinal signs (vomiting, nausea, diarrhea, abdominal pain), otitis media and febrile seizures can also be seen, especially in children. Dehydration is a particular concern in very young patients. Most people recover from uncomplicated influenza within a week, but coughing and tiredness may persist longer, and secondary bacterial infections can exacerbate or prolong the symptoms.

Severe illnesses occur most often in the elderly or those with underlying diseases, though they can be seen rarely even in young, healthy people. Patients with viral or secondary bacterial pneumonia can deteriorate rapidly and may develop acute respiratory distress syndrome, multiple organ failure.
and other serious syndromes. Influenza can also result in the decompensation or exacerbation of underlying diseases such as chronic lung or cardiac conditions, poorly controlled diabetes, chronic renal failure or end-stage liver disease. Infrequent complications include various neurological syndromes (e.g., encephalitis), benign acute childhood myositis, rhabdomyolysis and myocarditis. Influenza-related deaths are usually the result of pneumonia, the exacerbation of a cardiopulmonary condition or other chronic disease, or complications associated with conditions such as old age.

Influenza C virus infections are mainly characterized by mild upper respiratory disease, with or without fever, with some studies also reporting gastrointestinal signs or otitis. Cases with lower respiratory signs have been reported, but seem to be unusual. There are rare reports of patients with neurological signs, including seizures/ unconsciousness in an infant, and drowsiness and hemiparesis in a child.

Influenza viruses from animals

Most reported swine influenza virus infections have been relatively mild and resembled human influenza, though ocular inflammation/conjunctivitis seems to be more common than with human-adapted viruses. Occasional severe disease has been seen mainly in people with underlying health conditions, the elderly or the very young, though there are a few reports of serious illnesses and deaths in healthy younger adults. Naturally-occurring equine influenza cases have not been described, but healthy volunteers inoculated with equine influenza viruses either remained asymptomatic or developed flu-like upper respiratory signs.

Avian influenza viruses sometimes cause isolated conjunctivitis, conjunctivitis accompanied by upper respiratory signs, or relatively mild respiratory signs without eye involvement. There are also reports of more severe or fatal illnesses, sometimes in those who are elderly and/or in poor health, but also sporadically in younger, healthy people. Serious illnesses caused by H7N9 and Asian lineage H5 viruses can progress quickly from fever and upper respiratory signs to lung involvement with rapid deterioration. Gastrointestinal signs such as diarrhea, vomiting and abdominal pain have been seen in some of these patients, and the H5 viruses have occasionally caused mucosal bleeding. Concurrent bacterial and/or fungal infections, including respirator-associated infections, seem to be relatively common in severe H7N9 cases, and may contribute to the clinical picture. The H7N9 viruses can also cause uncomplicated illnesses with mild upper respiratory signs, especially in younger, healthy individuals. Until recently this seemed to be rare with the H5 viruses and was mostly documented in children. However, sporadic reports of milder illnesses such as conjunctivitis or mild upper respiratory signs have now been reported occasionally in people infected with Asian lineage H5 viruses in Europe or North America. Whether the treatment of these individuals with antiviral drugs contributed to the mildness of these cases is unclear.

Diagnostic Tests

A number of assays, similar to those used in animals, can diagnose influenza A and B infections in humans. 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. Influenza C cases can be diagnosed with either RT-PCR or culture; however, the latter technique is limited by the need for embryonated eggs, which are not widely available in diagnostic laboratories. 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.

Serological tests are not useful for the routine diagnosis of seasonal human influenza, due to widespread exposure. Zoonotic influenza virus infections are occasionally diagnosed retrospectively by serology, most definitively by a rising titer. People infected with some avian influenza viruses do not reliably seroconvert, even in virologically confirmed cases.

Treatment

Influenza is treated supportively (e.g., fluids and rest) in uncomplicated cases, with antibiotics as needed for secondary bacterial pneumonia, and hospital care in more severe illnesses. Antiviral drugs can also be given. They are most effective when started within 48 hours of the onset of symptoms. Their use outside high risk patients or severe disease is controversial, as the indiscriminate use of some agents resulted in widespread resistance among some influenza viruses in the past, thus rendering them ineffective in those patients who most need them.

The two major classes of antiviral drugs used for influenza viruses are the adamantanes (amantadine, rimantadine) and neuraminidase inhibitors (e.g., oseltamivir, zanamivir, peramivir, laninamivir). A novel antiviral, baloxavir, is also used in human seasonal influenza. Adamantanes are active against some human influenza A viruses, while neuraminidase inhibitors can be used for both influenza A and B. Antiviral drugs can also be effective against some influenza A viruses of animals, and neuraminidase inhibitors are commonly employed in zoonotic infections. The tests to evaluate a virus’s susceptibility to antiviral agents take several days to perform; thus, the initial choice of drug is often empirical, based on the susceptibility of a particular virus group in the past.

Prevention

Annual vaccines, usually given in the fall before the flu season, or as appropriate for local patterns of virus circulation, are available for human influenza A and B. They contain the viral strains considered most likely to produce epidemics during the following winter, and are updated annually. Immunization recommendations differ between countries, though vaccination of some higher risk groups, such as the elderly, is consistently recommended.
Antiviral drugs may sometimes be useful for prophylaxis in the elderly or immunocompromised (e.g., transplant patients), or these individuals may be monitored and treated at the first sign of disease. The use of antiviral prophylaxis should be balanced against the risk of encouraging the emergence of drug-resistant strains. 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. To reduce transmission to others, the mouth and nose should be covered (e.g., with the elbow or a tissue) when coughing or sneezing.

Precautions against zoonotic influenza viruses, likewise, rely on good hygiene and, especially for those at higher risk, avoidance of potentially infected animals, particularly those that are ill and/or held in enclosed, poorly ventilated spaces. Personal protective equipment (PPE), including a well-fitted and correctly handled N95 or equivalent respirator, is appropriate in some circumstances, such as for personnel handling flocks infected with HPAI viruses. Because HPAI viruses have been found in meat and/or eggs from several avian species, careful food handling practices are important when working with raw poultry or wild game bird products in endemic areas, and all poultry products should be completely cooked before eating. Viruses in milk are inactivated by pasteurization. More detailed recommendations for specific groups at risk of exposure, including the general public, have been published by some national and international agencies.

**Morbidity and Mortality**

**Human influenza A and B viruses**

Human influenza epidemics are seasonal in temperate regions, typically beginning after school starts in the fall, and spreading from children to adults, although some transmission also occurs at other times of the year. The patterns are more diverse in tropical and subtropical areas, with transmission occurring year-round in some countries, and seasonal epidemics sometimes coinciding with the rainy season or occurring in two peaks, in others.

Uncomplicated infections with seasonal influenza viruses are rarely fatal in healthy people, though the morbidity rate can be high. Approximately a third of influenza virus infections are thought to be asymptomatic. Groups at higher risk for severe illness include the elderly; young children (mainly due to risks from complications such as severe dehydration); people with chronic respiratory or cardiovascular disease and other significant medical conditions; and those who are immunosuppressed. Pregnant women are also thought to be at somewhat higher risk, and obesity was first recognized as a risk factor during the 2009-2010 pandemic. Except after the introduction of a new virus, over 90% of influenza-related deaths occur in the elderly.

Morbidity and mortality rates usually increase during a pandemic, sometimes dramatically. The 1918 pandemic is notorious for its severity, with some estimates suggesting a morbidity rate of 25-40% and case fatality rate of 2-5%. However, it should be noted that neither antiviral drugs nor antibiotics to treat secondary bacterial infections (a common cause of influenza deaths) were available at the time, hospital care was limited to skilled nursing and other general supportive measures, and the onset of the pandemic occurred at the end of WWI, a period when many had experienced prolonged challenges to physical and mental health.

The 1957-58 and 1968-69 pandemics were similar in pattern, though with lower estimated mortality rates. However, the 2009-2010 H1N1 pandemic was unusual in sparing the elderly: most hospitalized or severely affected patients were children and young adults, with relatively few patients older than 50 years and even smaller numbers older than 60. This phenomenon was probably the result of older people having been exposed previously to similar H1N1 viruses, and is thought to have contributed significantly to the low overall mortality rate (estimated case fatality rate of < 0.05% to < 0.5%). Many seriously ill younger patients recovered with hospitalization and intensive care. Nevertheless, an increased number of influenza patients developed viral pneumonia during the pandemic, and case fatality rates in younger age groups were higher than with established viruses.

**Influenza C**

Influenza C viruses mainly cause sporadic clinical cases and minor localized outbreaks, though a nationwide epidemic was reported in Japan in 2004. Many people seem to be exposed to these viruses in childhood, typically resulting in a mild illness, but infections can continue to occur occasionally in adults, and one study suggested that there may be second peak of mild illness in adults over the age of 45 years. Very young children may occasionally be hospitalized; however, it appears that many or most hospitalized children and infants have comorbidities such as prematurity, asthma, IgG deficiency, congenital heart disease or cancer. Very few influenza C infections in adults, including older adults, appear to be severe enough to result in medical visits.

**Zoonotic influenza**

How often humans are infected by swine or avian influenza viruses is still uncertain, but clinical cases are reported sporadically, surveillance programs that test people with influenza-like illnesses have revealed additional cases, and serology suggests that a number of mild or subclinical cases may be missed. The H7N9 avian influenza viruses currently circulating among poultry in China seem to be particularly common in people, with approximately 1500 laboratory-confirmed clinical cases reported between 2013 and 2017. These cases mainly occurred as annual winter outbreaks coinciding with high virus circulation in poultry. The H7N9 viruses are still found in poultry, but vaccination has reduced their prevalence, and
human cases are now sporadic and infrequent. Other avian influenza viruses appear to be transmitted less often to people, but the cumulative number of cases may sometimes reach high levels when the virus is maintained in poultry for a long time. Asian lineage H5N1 HPAI viruses, for instance, seem to infect humans rarely but have caused more than 850 confirmed human cases since the late 1990s when they first emerged.

Zoonotic influenza virus infections vary in severity. Asian lineage H5N1 HPAI viruses in Eurasia appear to kill around half the people they infect. The lethality of the variants circulating in the Americas for humans remains to be established, but both mild and severe illnesses have been reported. H7N9 LPAI and HPAI viruses are also fatal in a significant percentage of elderly patients, and diverse other avian influenza viruses have caused sporadic serious or fatal cases. However, some avian influenza virus infections are much milder, with transient and self-limited symptoms, and many cases of swine influenza seem to resemble human influenza.

### Internet Resources

- U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS)
- USGS Wildlife Health Bulletin #05-03 (with recommendations for field biologists, hunters and others regarding contact with wild birds)
- World Health Organization. Influenza. Avian and Other Zoonotic
- World Organization for Animal Health (WOAH)
- WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
- WOAH Terrestrial Animal Health Code

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Avian Influenza


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Influenza C


Influenza


Influenza


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