

# Influenza

*Flu, Grippe, Avian Influenza, Grippe Aviaire, Fowl Plague, Swine Influenza, Hog Flu, Pig Flu, Equine Influenza, Canine 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. A new influenza C-related virus recently detected in livestock has been proposed as “influenza D.”<sup>1-6</sup>

Influenza A viruses are widespread and diverse in wild aquatic birds, which are thought to be their natural hosts. Poultry are readily infected, and a limited number of viruses have adapted to circulate in people, pigs, horses and dogs. In the mammals to which they are adapted, influenza A viruses usually cause respiratory illnesses with high morbidity but low mortality rates.<sup>7-29</sup> 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.<sup>7,9,11,12,14,20,30-47</sup> Two types of influenza viruses are maintained in birds. The majority of these viruses are known as low pathogenic avian influenza (LPAI) viruses. They usually infect birds asymptotically or cause relatively mild clinical signs, unless the disease is exacerbated by factors such as co-infections with other pathogens.<sup>7,46,48-56</sup> However, some LPAI viruses 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%.<sup>50-52</sup>

Although influenza A viruses are host-adapted, they may occasionally infect other species, and on rare occasions, a virus will change enough to circulate in 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.<sup>57-77</sup> Dogs have been sporadically affected by viruses from other species, but were not known to maintain any influenza viruses until the last 20 years, when two viruses, one from horses and another from birds, began to circulate in some canine populations.<sup>27,63,66,78-90</sup> New viruses have also emerged in pigs, especially in North America, where swine influenza viruses have become very diverse.<sup>40,91-95</sup> Some of the North American viruses have affected hundreds of people exposed to pigs at fairs.<sup>96-99</sup> Many influenza A virus infections in novel mammalian hosts have been mild, but some viruses can cause life-threatening illnesses.<sup>53,57-65,97-122</sup> 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,<sup>7,8,14,123-126</sup> while the 2009-2010 pandemic resulted from the acquisition of a virus from pigs.<sup>125,127,128</sup>

Influenza B and C viruses primarily affect humans, and seem to be less likely to cross species barriers.<sup>7,11,12,31,129-141</sup> However, infections have occasionally been reported in animals, and some species may be able to propagate these viruses short-term, and possibly even for longer periods.<sup>7,16,142-153;154 cited in 146; 155 cited in 156</sup> Little is known yet about influenza D, but these viruses are thought to circulate in cattle, and have also been isolated from pigs.<sup>1-6</sup> If influenza D viruses are capable of infecting humans, such infections seem to be rare.<sup>1,157</sup>

## Etiology

Influenza viruses belong to the genera *influenzavirus A*, *influenzavirus B* and *influenzavirus C* in the family Orthomyxoviridae.<sup>158</sup> All the members of each genus belong to the species *influenza A virus*, *influenza B virus* or *influenza C virus*, respectively.<sup>158</sup> 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, influenza D.<sup>2,3</sup>

## Influenza A viruses

Influenza A viruses are the most widely distributed influenza viruses in birds and mammals. These viruses contain two highly variable surface antigens, the hemagglutinin (HA) and neuraminidase (NA) proteins, which are used to classify

them into subtypes. Currently, 18 hemagglutinins (H1 to H18) and 11 neuraminidases (N1 to N11) are known.<sup>50,51,53,159-161</sup> A virus that contained H1 and N2 would have the subtype H1N2. As of 2016, H1 through H16 and N1 through N9 have been found in birds; H17N10 and H18 N11 viruses have only been detected in bats; and other mammals maintain a limited subset of the subtypes found in birds.<sup>15,55,160,161</sup> 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 types or between different NA types.<sup>9,162-170</sup> Considerable variation also exists within each HA or NA type, 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.<sup>7,15</sup> 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. Mutations cause gradual changes in the HA and NA proteins of the virus, a process called 'antigenic drift.'<sup>15</sup> Once these proteins have changed sufficiently, immune responses against the former HA and NA may no longer be protective.

Genetic reassortment can cause more rapid changes. The influenza A genome consists of 8 individual gene segments,<sup>169,170</sup> and when two different viruses infect the same cell, gene segments from both viruses may be packaged into a single, novel virion.<sup>8</sup> This 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 for a time and is maintained in another host species, then re-emerges in the original host.<sup>7,14</sup> 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 a similar virus circulating in the same species, or a different internal protein.

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

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

Each influenza A virus is adapted to circulate in a particular host; however, viruses can occasionally infect other species. In most cases, the virus cannot be transmitted efficiently in the novel host, and soon disappears.<sup>7,8,15,27,46,53,65,74,75,81,89,171-173</sup> 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.<sup>174</sup> 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 cases, whole viruses have jumped successfully to new species.<sup>27,79</sup> At other times, the newly acquired virus reassorted with a virus already adapted to its new host.<sup>8,14</sup> Reassortment can occur either in the new host or in an intermediate host, which then transmits the virus further.<sup>8,14,53</sup> 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.<sup>7,14,108</sup>

As well as appearing in new host populations, influenza A viruses can disappear from hosts where they previously circulated. Some viruses have vanished from human, equine and swine populations after circulating for years or even decades.<sup>7,13,93-95</sup> For unknown reasons, the establishment of a new influenza virus in a species sometimes leads to the disappearance of an older viral lineage.<sup>39</sup>

### Avian influenza viruses

Avian influenza viruses are extremely diverse, especially in wild birds, and can contain any of the HA and NA proteins other than H17, H18, N10 or N11. Whether all HA and NA combinations can occur in nature is uncertain, but more than 100 subtypes of avian influenza viruses have been detected.<sup>39</sup> 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.<sup>55</sup>

## [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).<sup>50,51</sup> 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.<sup>175-178</sup> 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 infected by the respiratory route.<sup>177</sup> Another H10 virus that fit the HPAI definition affected the kidneys and had a high mortality rate even in intranasally inoculated chickens.<sup>179</sup> In the laboratory, the insertion of genetic sequences from HPAI viruses into non-H7, non-H5 viruses has created some viruses that were pathogenic only after intravenous inoculation, and other viruses (containing H2, H4, H8 or H14) that were highly virulent after both intravenous and intranasal inoculation.<sup>180</sup> Recently, an H4N2 virus with a genetic signature characteristic of HPAI viruses was isolated from a flock of naturally infected quail.<sup>181</sup> This virus retained the characteristics of an LPAI virus, and was of low virulence in chickens.

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.<sup>182,183</sup> 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.<sup>55</sup> 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 detected in some areas or wild bird populations, but significant reassortment where there is overlap between migratory flyways, such as in Alaska and Iceland.<sup>55,184-196</sup>

Limited information from Central and South America suggests that many or most of the viruses in this region are closely related to the North American lineage, but cocirculate with some viruses unique to South America

(e.g., a highly divergent lineage first identified in Argentina).<sup>197-199</sup> The viruses in New Zealand and Australia might be geographically isolated to some extent, although there is also evidence of mixing with viruses from other areas.<sup>200-202</sup>

## [Important virus lineages circulating among poultry: Asian lineage H5 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 H5, H7N9 and H9N2 viruses are currently of particular concern.

### [Asian lineage H5 HPAI viruses](#)

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.<sup>53,203,204</sup> These H5N1 viruses have evolved into multiple genotypes, clades and subclades, and new variants are continuing to emerge as they circulate.<sup>53,204-209</sup> Some clades or subclades differ in their virulence for mammals and/or birds.<sup>110,121,208</sup> The primary reasons for concern, in addition to the severe outbreaks HPAI viruses cause in poultry, are the serious illnesses H5N1 viruses cause in humans, the wide variety of mammalian species they can infect, and the periodic (and unusual) detection of these viruses in wild birds, including migratory waterfowl.<sup>57,58,60-65,100-121,210,211</sup>

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 found in poultry in Asia.<sup>212-218</sup> Asian lineage HPAI H5N8 viruses became widespread, and reached Europe and North America in 2014, most likely in wild birds.<sup>219,220,220-222</sup> These viruses have reassorted with North American lineage viruses to produce several new variants, including H5N2 HPAI viruses, which caused extensive outbreaks among poultry in the Midwestern U.S.<sup>220-228</sup> Some H5 reassortants in Asia have caused illnesses in mammals. They include an H5N2 virus isolated from a sick dog, and H5N6 viruses in several human cases.<sup>66,229-234</sup> As of February 2016, no clinical cases have been linked to H5N8 viruses except in birds.

### [Eurasian lineage H9N2 viruses](#)

A Eurasian lineage of H9N2 (LPAI) viruses is currently widespread among poultry in parts of Asia and the Middle East. These viruses have caused clinical cases (mostly mild) in people, and they can infect other mammals.<sup>94,95,235-252</sup> They have also become very diverse, and there is evidence of reassortment with Asian lineage H5 HPAI viruses and other lineages.<sup>236,245,253-257</sup> H9N2 variants may differ in their ability to replicate in mammals and/or cause disease.<sup>252,255,256</sup>

### [H7N9 LPAI viruses](#)

A lineage of H7N9 LPAI viruses in China causes little or no disease in poultry, but has been responsible for serious outbreaks in humans.<sup>258-264</sup> These viruses seem to



have arisen from reassortment between H7, N9 and H9N2 viruses.<sup>259,265</sup> Some evidence suggests that they may have circulated subclinically for a long time among poultry before emerging in people.<sup>266</sup> H7N9 viruses have diversified considerably since they were first recognized, and regionally distinct lineages now exist in China.<sup>267</sup> H7N7 viruses with similar internal H9N2 genes have been identified among poultry in China, and might also have the potential to infect mammals.<sup>265</sup>

## Human influenza A viruses

In people, influenza A viruses tend to form a single global population.<sup>248</sup> 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.<sup>7,30,31,268,269</sup>

Human influenza viruses are under considerable selection pressure from immunity (via infection or 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,<sup>8,123</sup> while other studies indicate that it may have been a reassortant,<sup>125,126,270</sup> and it is possible that it adapted to another host, such as a pig, before becoming established in people.<sup>125,271</sup> H1N1 viruses gradually changed as they circulated in the human population, then apparently disappeared in 1957 when an H2N2 virus emerged.<sup>8,14,124,272</sup> The next two pandemics seem to have been caused by reassortment between avian and human influenza viruses.<sup>8</sup> 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.<sup>8,14</sup> These H2N2 viruses circulated in people between 1957 and 1968.<sup>7,269</sup> 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.<sup>8,14</sup> H1N1 viruses re-emerged into human populations in 1977, and then co-circulated with the H3N2 viruses.<sup>7,124</sup> (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 have not caused 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.<sup>30,269,273,274</sup>

## 2009 pandemic H1N1 virus

A novel H1N1 virus emerged in human populations in 2009 and caused a pandemic.<sup>125,127,128,275</sup> This virus is thought to be a reassortant between North American H1N2 and Eurasian H1N1 swine influenza

viruses.<sup>125,127,128</sup> 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 originated from two or more swine influenza viruses including the North American triple reassortant H3N2 viruses (see swine influenza, next section) and a Eurasian virus. Some of the gene segments in these swine viruses originally came from avian and human influenza viruses.<sup>125,128</sup> How humans acquired pandemic H1N1 virus is not known, but genetic analyses suggest that it 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.<sup>125,128</sup> After the 2009-2010 pandemic, this virus became established as a seasonal influenza virus, and it continues to circulate throughout the world. It is currently the predominant circulating H1N1 virus in people.<sup>276</sup> This virus 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.<sup>8,14,40,46,91,93-95,248,277-282</sup> Different sets of viruses circulate on each continent, and sometimes in different countries or regions within a continent.<sup>8,14,40,46,93-95,248,282-284</sup>

## North America

The first influenza virus recognized in pigs was an H1N1 virus known as the 'classical' swine influenza virus.<sup>285-287</sup> Pigs are thought to have acquired this virus during the 1918 Spanish flu pandemic, possibly from infected people.<sup>7,8,14,46,270,286-289</sup> H1N1 viruses circulated in both species after this time, but diverged genetically in the two host populations.<sup>272,290</sup>

The classical H1N1 swine influenza virus was the major virus among swine populations in North America for approximately 70 years.<sup>40</sup> Low levels of H3 viruses from humans were also found during this period, and some of these viruses circulated locally for at least a short time; however, they did not become established as stable, widespread lineages.<sup>40,291</sup> 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.<sup>8,74,108,277,292-295</sup> 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.<sup>294</sup> 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.<sup>92</sup> 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.<sup>40,91,92,275,296,297</sup> Some North American herds have been infected with the 2009 pandemic H1N1 virus from humans, which has reassorted with other viruses circulating in pigs.<sup>75,298-303</sup> 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.<sup>40,91,92,296,297,303,304</sup> Other influenza variants and subtypes, such as H2N3 and H3N1 viruses, have been found occasionally in North American herds, but do not seem to have become established in swine populations.<sup>277-281</sup>

## Europe

The classical H1N1 swine influenza virus was found sporadically in Europe in the past (although records of its isolation and times of circulation are scarce), but a virus of wholly avian origins has been the major H1N1 swine influenza virus since the 1970s.<sup>8,14,39,46,93,94,282-284,305-308</sup> The 2009 pandemic H1N1 virus and its reassortants are also detected frequently, and currently seem to be maintained in swine populations in some areas.<sup>39,93,282-284,309</sup> Various human-origin H3N2 viruses have circulated at times in pigs, but a reassortant that contains human-origin H3 and N2 with internal gene segments from the avian-origin H1N1 virus has now become the dominant H3N2 virus in much of Europe.<sup>14,39,93,282-284,305</sup> Several H1N2 viruses (including pandemic H1N1 reassortants) also occur, either transiently or long-term.<sup>14,39,93,282-284,305,309,310</sup> Additional subtypes (e.g., H3N1 viruses) have been found occasionally.<sup>39,93,311</sup> One unique variant was an H1N7 virus, which was apparently a reassortant between swine and equine influenza viruses.<sup>39,93</sup>

## Asia

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.<sup>46,65,94,95,248,312-316</sup> Some of the circulating viruses contain the North American TRIG cassette. Some viruses have infected Asian pigs only transiently, and different swine influenza viruses may predominate in different regions.<sup>94,95</sup> The pandemic H1N1 virus and its reassortants have also been found, and novel subtypes (e.g., H3N1 viruses) have been isolated occasionally.<sup>94,95,317,318</sup>

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.<sup>94</sup> A long-term analysis conducted in Hong Kong abattoirs, where most 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.<sup>248</sup> This is also likely to be true of other regions and continents.

## Other locations

At present, there is little information about swine influenza viruses in some parts of the world. H3N2 and H1N1 viruses are known to circulate in Latin America, but limited information is available about their genetic composition.<sup>319</sup> A recent study found that viruses in northwestern Mexico included H3N2 viruses similar to those in the U.S., and H1N1 viruses that had 89% nucleotide identity with U.S. viruses.<sup>320</sup> One H3N2 virus isolated from sick pigs in Argentina was of wholly human origin, although it was highly transmissible in pigs.<sup>319</sup> 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, as well as a reassortant human-like H1N2 influenza virus, have been detected in Argentina and Brazil.<sup>321-324</sup> H1 viruses have been documented in Africa, and some recent studies report the presence of the 2009 pandemic H1N1 virus there in pigs.<sup>325-327</sup>

## Equine influenza viruses

Equine influenza viruses seem to change more slowly than human influenza A viruses or swine influenza viruses.<sup>13,15,328,329</sup> Two subtypes of influenza viruses circulated widely in equine populations during the last century, H7N7 (equine virus 1) and H3N8 (equine virus 2).<sup>7,13,15</sup> H7N7 equine influenza viruses were last isolated in 1979, and most authors believe they are likely to be extinct, although there have been a few anecdotal reports or serological studies suggesting that they might persist in some areas where surveillance is limited.<sup>7,13,19,328,330,331;332</sup> cited in 333

In the 1980s, equine H3N8 viruses diverged into distinct Eurasian and American evolutionary lineages.<sup>334-336</sup> The American lineage divided further into 3 sublineages: the classical American (or Kentucky) lineage, the Florida sublineage and the South American sublineage.<sup>329,335,336</sup> The Florida sublineage became widespread, and has diverged into 2 clades.<sup>329,334-336</sup> The Eurasian lineage is now uncommon (some reports indicate that it was last isolated in 2005), and the classical American lineage is found occasionally in some areas.<sup>329,334-336</sup>

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.<sup>13,19,65</sup> This virus appeared to be of avian origin. It did not persist long-term and is not known to have spread outside China.<sup>13</sup>

## Canine influenza viruses

The first canine influenza virus to be recognized was an H3N8 (Florida sublineage) virus acquired from horses in North America in the late 1990s or early 2000s.<sup>27,79,80</sup> This virus has diverged genetically from equine influenza viruses, and adapted to circulate in dogs.<sup>27,79,337-339</sup> It may now be evolving into two lineages.<sup>340</sup>

An H3N2 canine influenza virus, with gene segments entirely of avian origin, became established in some Asian countries in the mid-2000s.<sup>76,81-88,341</sup> These viruses have diversified and may be evolving separately in different countries.<sup>342</sup> They have also reassorted with other viruses. An H3N1 virus, which appears to be a reassortant between a canine H3N2 virus and the human pandemic H1N1 virus, was isolated from one dog with respiratory signs in Korea.<sup>343</sup> There is also evidence of occasional reassortment with avian influenza viruses from poultry (e.g., H9N2, H5N1).<sup>341,342,344</sup>

## Bat influenza viruses

Two new subtypes of influenza viruses were identified recently in South American bats, using genetic techniques.<sup>160,161</sup> These viruses have distinct hemagglutinins, which have provisionally been designated H17 and H18, unique neuraminidases, and distinctive internal genes.<sup>160,161</sup> They cannot be isolated in the cell lines and chicken embryos used to grow other influenza A viruses. The inability to recover infectious virus has made it difficult to study bat influenza viruses; however, various analyses suggest that they are unusual and differ from other influenza A viruses in multiple ways.<sup>160,345-348</sup>

## Influenza B viruses

Influenza B viruses are categorized into lineages (and strains) based on the HA, but not into subtypes. Currently, the two important lineages in people are represented by B/Victoria/2/87 and B/Yamagata/16/88.<sup>349</sup> Both lineages are currently widespread and co-circulate, although one lineage may predominate in an area in any given year.<sup>349-351</sup> Recombination can occur within, and occasionally between, the two lineages; and influenza B viruses can undergo infrequent antigenic shifts.<sup>350,352,353</sup> Antigenic drift also occurs, although it generally happens more slowly than in influenza A viruses.<sup>7,268,353</sup>

## Influenza C viruses

Influenza C viruses have one surface glycoprotein, the hemagglutinin-esterase-fusion protein, rather than HA and NA proteins. They are antigenically more stable than influenza A viruses, and accumulate fewer changes over time.<sup>130,354</sup> At least six lineages (Taylor/1233/47-, Sao Paulo/378/82-, Kanagawa/1/76-, Aichi/1/81-, Yamagata/26/81- and Mississippi/80-related lineages) have been identified.<sup>354</sup> Reassortment can occur between different strains or lineages.<sup>130,131,157,354</sup>

## Influenza D (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.<sup>1,2</sup> Initially, this virus was thought to be a new subtype of influenza C, but subsequent studies suggest that it might represent a new genus of influenza viruses.<sup>2-4</sup> The name “influenza D” has been proposed,<sup>2,3</sup> although it is not yet formally accepted by the ICTV.<sup>158</sup> At least two lineages of influenza D viruses have been found in North

American cattle, and these lineages can reassort.<sup>355</sup> Influenza D viruses found in China, Italy and France were closely related to viruses from North America.<sup>4-6</sup>

## Species Affected

### Avian influenza viruses

#### Wild birds

Birds are thought to be the natural reservoir hosts from which all influenza A viruses originated.<sup>7,46,49,51,54,55,108</sup> The vast majority of LPAI viruses are maintained in asymptomatic wild birds, particularly species found in wetlands and other aquatic habitats.<sup>7,46,49,51,54-56,159,356</sup> Infections are especially common in some members of the order Anseriformes (waterfowl, such as ducks, geese and swans) and two families within the order Charadriiformes, the Laridae (e.g., gulls) and Scolopacidae (shorebirds).<sup>7,14,46,49,51,55,56,159,188,193,196,201,356,357,357-361</sup> Aquatic species belonging to other orders occasionally have high infection rates, and might also be involved in the epidemiology of this disease.<sup>56,362,363; 364 cited in 363</sup> While LPAI viruses can infect birds that live on land (terrestrial birds), most studies have reported low infection rates, suggesting that these birds are not important reservoir hosts in most environments.<sup>56,356,365-374</sup> 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.<sup>367,373</sup> Recently, influenza virus RNA was found in an unusually high percentage of passerine birds in Central and West Africa.<sup>375</sup>

The most common influenza subtypes in wild birds may differ between species and regions, and can change over time.<sup>55,359,360,363,376-378</sup> 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.<sup>55</sup> A few avian influenza subtypes seem to have a limited host range, and may rarely (or never) be transferred to poultry.<sup>55,184,188,360,379-385</sup>

HPAI viruses are not usually found in wild birds, although they may be isolated transiently near outbreaks in poultry.<sup>369</sup> Exceptions include the Asian lineage H5N1 viruses and some of their reassortants (e.g., H5N8 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.<sup>62,101,108,109,119-121,219,221,222,224-226,228,386,387,387-404</sup>

#### Domesticated birds

Poultry and game birds, including gallinaceous birds and domesticated waterfowl, are readily infected by LPAI and HPAI viruses.<sup>51,109,119-121,165,395,405-419</sup> 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



H5N1 viruses.<sup>53,54,175</sup> Infections also occur in other domesticated birds, although they do not appear to be very common in either cage birds or pigeons.<sup>48,101,109,119,370,390,396,402-424</sup> Once a virus has adapted to poultry, it rarely re-establishes itself in wild birds.<sup>175</sup>

## Host range of the Asian lineage H5N1 HPAI avian influenza viruses and reassortants including H5N8

Asian lineage H5N1 HPAI viruses have an unusually wide host range. These viruses can infect domesticated and wild birds belonging to many different orders.<sup>62,101,108,109,119-121,391-400</sup> They can be highly virulent in some birds, but some infections are subclinical.<sup>101,396,399,403,425</sup> Likewise, Asian lineage H5N8 viruses and/or their reassortants have been detected in various domesticated and wild birds including sick, dead and apparently healthy waterfowl, and sick or dead birds in other orders including raptors.<sup>219,221,224,226,386,387,401,402,404</sup> Wild migratory birds have introduced some Asian lineage H5 viruses (e.g., H5N1 and H5N8 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.<sup>219,219,220,222,225,228,386,387,391,394,399,426-428</sup>

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*).<sup>53,57-65,100-104,106,107,122,211,246,429,430</sup> Antibodies to these viruses were detected in horses and raccoons.<sup>65,104,106,107,122,246,430-433</sup> Experimental infections have been established in housecats, dogs, foxes, pigs, ferrets, laboratory rodents, cynomolgus macaques (*Macaca fascicularis*) and rabbits.<sup>65,101,105,106,108-118,429,434</sup> Viruses isolated from cats could infect cattle in the laboratory,<sup>118</sup> but serological studies in Egypt suggest that cattle, buffalo, sheep and goats are not normally infected with H5N1 viruses.<sup>431</sup>

Some Asian lineage H5 reassortants, such as an H5N2 virus, recovered from a sick dog in China, may cause illnesses in mammals.<sup>66,229,230</sup> This H5N2 virus could be transmitted from experimentally infected dogs to dogs, chickens and cats.<sup>66,229,230</sup> There have been no reports of illnesses caused by Asian lineage H5N8 viruses, as of February 2016, although seropositive dogs were detected on some infected farms in Asia.<sup>435</sup> An H5N8 virus replicated inefficiently in experimentally infected dogs, but cats were more likely to become infected in this study.<sup>435</sup> Initial laboratory experiments in ferrets and mice suggested that these H5N8 viruses may be less pathogenic for mammals than some H5N1 isolates.<sup>435-437</sup> Asian lineage H5N6 viruses have been isolated from apparently healthy pigs.<sup>438</sup>

## Host range of Eurasian H9N2 (LPAI) avian influenza viruses

H9N2 viruses have been detected in poultry and some wild birds including terrestrial species.<sup>245,439,440</sup> They have also been found in pigs, dogs and farmed mink,<sup>94,95,236,246,247,249,250,252,441,442</sup> and serological evidence of infection has been reported in cats, captive nonhuman primates (performing macaques) and wild plateau pikas.<sup>251,443,444</sup> Experimental infections have been established in mink and pika.<sup>441,444</sup> Dogs and cats could also be infected experimentally with some isolates, although virus replication was limited in some studies.<sup>445-447</sup>

## Host range of the zoonotic H7N9 avian influenza viruses

The zoonotic H7N9 LPAI viruses in China have mainly been found in poultry, although live viruses and/or viral nucleic acids were also detected in a few wild birds (e.g., two pigeons, an asymptomatic tree sparrow, and wild waterfowl).<sup>264,448,449</sup> 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.<sup>424,450,451</sup> H7N9 viruses are not reported to have caused any illnesses in mammals other than humans,<sup>264</sup> as of February 2016. Stray dogs living near live poultry markets did not appear to have been infected,<sup>246</sup> and a serological survey found little or no evidence of exposure in pigs.<sup>452</sup> In experimental studies, isolates from humans could infect miniature pigs, ferrets, laboratory mice and cynomolgus macaques.<sup>451,453-455</sup> Experimentally infected black rats (*Rattus rattus*) did not shed measurable amounts of virus, although they seroconverted.<sup>451</sup>

## Other avian influenza viruses in mammals

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.<sup>94,95,171,236,452,456-460</sup> An H10N4 virus was responsible for an epidemic among farmed mink in Europe,<sup>65</sup> and experimental infections with H3N8, H4N6, H5N3, H7N7, H8N4 and H11N4 avian influenza viruses have been established in this species.<sup>7,65</sup> 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.<sup>461-463</sup> Some dogs in China have antibodies to H10N8 viruses,<sup>464</sup> and surveillance found an H6N1 LPAI virus in one dog coinfecting with canine distemper virus in Taiwan.<sup>465</sup> Dogs were also susceptible to experimental infection with an H6N1 virus.<sup>466</sup> Some domesticated guinea pigs in South America had antibodies to H5 influenza viruses.<sup>152</sup>

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 raccoons in Japan.<sup>467-469</sup> Raccoons could be infected experimentally with an avian H4N8 LPAI virus, striped skunks (*Mephitis mephitis*) with H4N6 and H3N8 LPAI viruses, and cottontail rabbits with an H4N6 LPAI virus.<sup>468,470,471,472</sup> Avian influenza viruses have been associated with disease outbreaks in seals (see Marine Mammals, below).

Laboratory mice (*Mus musculus*) and ferrets serve as models for mammalian infections with influenza viruses, including avian influenza viruses.<sup>473-481</sup> Most laboratory mice have a defective gene (Mx1), which increases their susceptibility to influenza viruses compared to their wild-type progenitors.<sup>482-484</sup> However, one recent study suggested that wild *Mus musculus* mice may also be susceptible to experimental inoculation with certain LPAI viruses.<sup>482</sup>

## Human influenza viruses

Human influenza A viruses mainly cause disease in people, but nonhuman primates are also susceptible to these viruses, and pet ferrets can become ill.<sup>10,153,251,485-488</sup> Most primate studies have been done in captive animals, but there was also evidence of infections in pet, performing and wild macaques in Asia.<sup>251</sup> Human influenza virus infections are reported occasionally in pigs, and human or part-human viruses can become established in these animals.<sup>8,14,39,40,93-95,248,277,282,291,294,313,314,319,489</sup> Serological and/or virological evidence of infection has been reported sporadically in other animals such as dogs, cats, cattle and even birds (including poultry),<sup>7,15,142,151,153,251,277,313,331,490-493</sup> and experimental infections have been established in cats, dogs, mink, raccoons and ducks.<sup>7,19,468,488,491,493-497</sup> Some domesticated guinea pigs in South America have antibodies to H1 and H3 viruses that might be of human origin.<sup>152</sup> Human influenza A viruses can replicate, to a limited extent, in the nasal epithelium of experimentally infected horses,<sup>19</sup> and there was some evidence for inapparent infections in horses at the time of the human 'Asian flu' epidemic.<sup>498</sup>

The 2009 pandemic H1N1 virus (now a seasonal human influenza virus) is often found in domesticated pigs,<sup>93,95,298-300,309,322,326,499-502</sup> and has been detected in wild boar.<sup>503</sup> It has caused outbreaks in turkeys,<sup>283,284,490,504-509</sup> 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.<sup>67-73,510-527</sup> This virus was found 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.<sup>528</sup> Experimental infections have been established in cats, dogs, ferrets, mice, cynomolgus macaques, turkeys and quail.<sup>523-526,529-532</sup> Chickens do not seem to be susceptible to this virus.<sup>530,531,533</sup>

## Swine influenza viruses

Swine influenza viruses mainly affect pigs, but some viruses can also cause disease in turkeys, ferrets and mink.<sup>7,15,65,74,75,171,173,278,290,503,534-538</sup> Some swine influenza viruses found in turkeys can be transmitted back to pigs, but others no longer readily infect this species.<sup>171</sup> 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.<sup>171</sup> One H1N1 swine influenza virus, which was avirulent for both poultry and pigs, was isolated from a duck in Hong Kong,<sup>539</sup> and ducks can be infected experimentally.<sup>497</sup> Two H3N2 viruses isolated from pet dogs in China had high homology to human-like H3N2 swine influenza viruses found among pigs in the area.<sup>540</sup> Experimental infections have been reported in calves.<sup>539,541</sup> 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.<sup>542</sup>

## Equine influenza viruses

Equine influenza viruses mainly affect horses and other Equidae (e.g., donkeys, mules and zebras).<sup>7,13,18,543</sup> In several instances, dogs have been infected by H3N8 viruses from nearby horses, without the virus becoming established in canine populations.<sup>24,89,90,544,545</sup> One H3N8 virus was found during surveillance of healthy Bactrian camels (*Camelus bactrianus*),<sup>546</sup> another H3N8 virus was isolated from sick pigs in China,<sup>547</sup> and a reassortant between swine and equine influenza viruses (H1N7) was detected in pigs in Europe.<sup>39,93</sup> Experimental infections have been established in dogs, cats, ferrets and mink;<sup>65,77,478,548,549</sup> however, one group found that an equine H3N8 virus did not replicate well in experimentally infected swine.<sup>550</sup> Cattle were susceptible to an equine influenza virus in an older experiment,<sup>7,19</sup> but in a recent study, there was no evidence of infection when they were exposed to an aerosolized H3N8 virus.<sup>542</sup>

## Canine influenza viruses

The H3N8 canine influenza virus has only been reported in dogs.<sup>22,23,25,27,28,79</sup> One group reported finding viral nucleic acids in two cats, but concluded that the cats were not infected as they never developed measurable antibody (HI) titers to the virus.<sup>551</sup> Although the H3N8 canine influenza virus can still infect horses under some experimental conditions, its ability to replicate in equids appears to be significantly reduced.<sup>338,339</sup> One study reported that horses were not infected when kept in close contact with experimentally infected dogs.<sup>552</sup> In laboratory studies, this virus was not transmitted readily to chickens, turkeys or ducks,<sup>553</sup> and it did not replicate well in pigs.<sup>550</sup>

The H3N2 canine influenza virus has caused clinical cases in dogs and cats.<sup>76,81,86,87,554</sup> Antibodies to this virus have been found in both species in Asia, dogs and cats are susceptible to experimental infection by contact with



infected dogs, and cats can transmit the virus to other cats.<sup>76,81-88,246,555-558</sup> Ferrets have also been infected experimentally, but seem to be less susceptible, and animal-to-animal transmission only occurred to a limited extent.<sup>556,559,560</sup> Guinea pigs can also be infected experimentally; however, attempts to transmit the H3N2 canine influenza virus to chickens, ducks, mice and pigs were unsuccessful.<sup>83,560</sup>

## **Influenza viruses in marine mammals**

A number of influenza viruses (H3N3, H3N8, H7N7, H4N5, H4N6 and H10N7), which were closely related to avian viruses, have been isolated from seals, and human pandemic H1N1 virus was found in northern elephant seals in 2010.<sup>7,65,528,561-564</sup> An avian-origin H3N8 virus, isolated during North American outbreak in 2011, appeared to have adaptations that would increase its transmissibility in mammals.<sup>562</sup> This virus also replicated well in experimentally infected pigs.<sup>550</sup> Avian-origin H10N7 viruses, isolated from outbreaks among European seals in 2014-2015, likewise appeared to be adapting to replication in seals.<sup>564</sup> 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*).<sup>65,147,148,561,565</sup>

Influenza A infections have been reported sporadically in cetaceans, and H1N3, H13N2 and H13N9 viruses have been isolated from whales.<sup>7,65</sup> Sequence analysis of the limited isolates available suggests that whales do not maintain influenza viruses, but are infected from other species, most likely birds.<sup>566</sup> Antibodies to influenza A viruses have been reported in porpoises.<sup>65</sup>

## **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, such as yak, sheep, goats, reindeer and deer.<sup>65,542</sup> Definitive identification of the virus source can be difficult in serological studies, but some of these viruses might have come from humans.<sup>65</sup> 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.<sup>65</sup> Some of these viruses might have been avian, human and equine influenza viruses.<sup>65</sup>

## **Bat influenza viruses**

The two known bat influenza viruses (H17N10 and H18N11) may be genetically isolated from other influenza A viruses, and there is currently no evidence that they have been transmitted to any other species.<sup>348</sup>

## **Influenza B viruses**

Virological and/or serological evidence of, influenza B infections has been reported in seals, pigs, dogs, horses, captive nonhuman primates, guinea pigs and some avian

species, and these viruses have been associated with illnesses in ferrets, seals and experimentally infected pheasants.<sup>7,14,16,65,142,145-153,567;154</sup> cited in 146; 568-570 cited in 150; 155 cited in 156 One recent study suggested that influenza B viruses might be more common in pigs when the animals are co-infected with PRRS virus.<sup>149</sup> Experimental infections have been established in pigs,<sup>149,156</sup> horses,<sup>571</sup> guinea pigs,<sup>572</sup> pheasants,<sup>150</sup> mallard ducks (*Anas platyrhynchos*)<sup>150</sup> and chickens.<sup>150</sup> Older studies also described experimental infections in cats, dogs and nonhuman primates,<sup>494,496,573-575</sup> cited in 150 and one group recovered an influenza B virus from dogs during an outbreak in Japan.<sup>151</sup> However, one recent study found no evidence of productive infection in experimentally infected dogs.<sup>493</sup>

Influenza B viruses are proven to circulate only in human populations, although some evidence suggests that either seals or an unknown marine host might maintain a distinct subset of viruses.<sup>145-148;154</sup> cited in 146] Serological studies suggest that infections in pigs are acquired sporadically from humans and influenza B viruses are not maintained long-term in swine populations.<sup>142,149</sup> Limited animal-to-animal transmission has been demonstrated in experimentally infected guinea pigs, pigs, pheasants and mallard ducks, but experimentally infected chickens did not transmit the virus to uninfected chickens.<sup>149,150,156</sup>

## **Influenza C viruses**

Influenza C viruses are maintained in people, but these viruses have been also been isolated from pigs.<sup>7,9,12,14-16,129,576-578</sup> Experimental infections have been established in hamsters, rats, nonhuman primates, dogs, pigs and ferrets, although only the dogs and pigs became ill.<sup>577,579-581</sup> Serological evidence of infection has been found in pigs, dogs and horses.<sup>7,142-144,582,583</sup>

## **Influenza D (influenza C-related livestock virus)**

Influenza D viruses have been isolated from cattle, which are thought to be the primary hosts, and from pigs.<sup>1,2,4-6,355</sup> These viruses might be able to cause illness in both species, but this is still uncertain. Experimental infections have been established in pigs and ferrets.<sup>1</sup>

## **Zoonotic potential of influenza viruses**

To date, zoonotic infections have mainly been caused by swine and avian influenza viruses.

Clinical cases caused by H1N1, H3N2 or H1N2 swine influenza viruses are reported sporadically in humans,<sup>7,14,97-99,159,286,287,293,584-598</sup> and serological evidence suggests that mild or asymptomatic infections might occur occasionally in people exposed to pigs.<sup>7,14,159,309,337,599-610</sup> Certain genotypes of swine influenza viruses might 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.<sup>96,98,99</sup>

The two avian influenza viruses reported most often in clinical cases are the Asian lineage H5N1 HPAI viruses

and recently, H7N9 LPAI viruses in China.<sup>14,54,108,258-264,611</sup> 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 to people.<sup>453,612</sup> 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.<sup>203,237,258-264,613</sup> As of February 2016, Asian lineage H5N8 viruses are not known to have caused any clinical cases in people, although four cases caused by H5N6 viruses have been reported in China since 2014.<sup>231-234</sup> Illnesses caused by other subtypes, including H6N1, Eurasian lineage H9N2 and multiple H7 and H10 avian influenza viruses, have been reported sporadically in people.<sup>14,53,54,108,159,235,237,238,241-244,598,611,614-618</sup> Serological surveys in some highly exposed populations suggests the possibility of low level exposure to various HA types found in birds, including H4, H5, H6, H7, H9, H10, H11 and H12.<sup>236,237,239,240,600,605,609,619-629</sup> 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.<sup>237</sup>

Very few human infections have been linked to species other than birds and swine. One person was infected by an H7N7 (avian origin) virus from a seal,<sup>561</sup> and a laboratory technician acquired an H1N1 swine influenza virus via an infected turkey herd.<sup>287,630</sup> Serological evidence and one experiment in volunteers suggest that humans might be susceptible to equine viruses,<sup>7</sup> but there is no evidence of recent natural infections.<sup>13</sup> A survey from Mongolia found that very few people had antibodies to H3N8 equine influenza viruses, despite high levels of exposure to horses.<sup>631</sup> No infections with either canine influenza virus have been reported, and initial studies from the U.S. and Scotland suggest that humans have little or no seroreactivity to influenza D viruses.<sup>1,157</sup>

## Geographic Distribution

Human seasonal influenza viruses, including 2009 pandemic H1N1 virus, are cosmopolitan.<sup>7,52,632,633</sup> Because people travel extensively, similar sets of viruses tend to circulate in all populations. However, this is not necessarily the case in animals.

Avian influenza (LPAI) viruses occur worldwide in wild birds, but the circulating viruses can differ between regions, and especially between the Eastern and Western Hemispheres.<sup>7,55,197,200</sup> Many countries maintain a HPAI-free status for all poultry. LPAI viruses were once common in poultry, but control programs in developed nations now usually exclude these viruses from commercial, confinement-raised flocks.<sup>49</sup> However, LPAI viruses may still be present in backyard flocks, live poultry markets and similar sources,<sup>49</sup> Eurasian lineage H9N2 LPAI viruses and Asian lineage HPAI H5N1

viruses are currently endemic only in parts of Eurasia, and have not been detected in the Americas, Australia or New Zealand.<sup>53,101,184-190,634-639</sup> However, Asian lineage HPAI H5N8 viruses have reached North America and reassorted with local strains to produce new variants, including some that contain North American lineage neuraminidases (e.g., H5N2, H5N1).<sup>220-222</sup> These viruses occur in wild birds,<sup>221,222</sup> but whether they will persist in the Americas is still uncertain. The zoonotic H7N9 LPAI viruses in China have not been reported from other regions, with the exception of a few imported cases in travelers.<sup>262,263,640,641</sup>

The influenza viruses of pigs and horses tend to occur wherever their maintenance hosts are found, unless there are good control programs to exclude them.<sup>40,46,93-95,642</sup> As described in the Etiology section, different sets of swine influenza viruses can be maintained on each continent. Only a few countries, such as New Zealand, Iceland and Australia, are known to be free from all equine influenza viruses.<sup>18,19,42,643</sup> At one time, Florida lineage clade 1 equine influenza viruses circulated in North America and clade 2 viruses in the Eastern Hemisphere; however, some clade 1 viruses have now also become endemic in Europe.<sup>336,644,645</sup>

The H3N8 canine influenza virus has been found, at least sporadically, in most states in the U.S., but its distribution appears to be patchy.<sup>22,25,26,80,646-649</sup> There is no evidence that this virus is currently circulating outside the U.S. As of 2016, the H3N2 canine influenza virus has been reported from South Korea, China, Thailand and North America (the U.S.).<sup>76,81,83,85-88,650</sup> One study reported antibodies to H3N8 and H3N2 viruses in a few dogs in Italy,<sup>651</sup> but the significance of this finding remains to be evaluated, as the serological tests were based on reactivity with equine H3N8 or swine H3N2 viruses, respectively.

There is relatively little information about some influenza viruses. Bat-adapted influenza viruses appear to be common in South America.<sup>161</sup> Influenza D viruses have been detected in North America, Asia (China) and Europe (Italy, France), and might be cosmopolitan in their distribution.<sup>1,4-6,355</sup>

## Transmission

### *Transmission of avian influenza viruses among birds*

Avian influenza viruses can occur in both the feces and respiratory secretions, although the relative amount of virus may differ, depending on the specific virus, host species and other factors.<sup>7,15,50,51,371,652,653</sup> While there are some exceptions (including recent Asian lineage H5N1 HPAI viruses<sup>121,413,654,655</sup>), influenza viruses are predominantly spread by fecal-oral transmission in aquatic birds such as waterfowl.<sup>55,121,656</sup> On farms, these viruses can spread by both fecal-oral and respiratory routes in poultry, due to the close proximity of the birds. Fomites can be important, and flies may act as mechanical vectors.<sup>51,54,657,658</sup> One study suggested the possibility of

wind-borne transmission of HPAI viruses between farms,<sup>659</sup> but this remains to be confirmed. HPAI viruses have also been found in the yolk and albumen of eggs from some infected chickens, turkeys and quail.<sup>660-666</sup> While these eggs are unlikely to hatch, broken eggs could transmit the virus to other chicks in the incubator. It might be possible for birds to shed LPAI viruses in eggs, but the current evidence suggests this is very rare, if it occurs at all.<sup>660,667</sup>

How long birds remain contagious differs between species, and varies with the severity of the infection. For example, chickens and turkeys infected with HPAI viruses die very quickly, and so do not shed these viruses very long. Most chickens usually excrete LPAI viruses for a week, and a minority of the flock for two weeks, but individual birds of some species, including waterfowl, can shed some LPAI or HPAI viruses for a few weeks in the laboratory.<sup>14,370,408,668-670</sup>

## **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.<sup>7,11,12,15,17,31,46,300,671</sup> Close contact and closed environments favor transmission.<sup>31,672,673</sup> 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.<sup>454,479,481,674,675</sup> While aerosol transmission is usually thought to occur only during close contact, swine influenza viruses have been isolated from air samples inside densely populated pig barns and immediately outside exhaust fans.<sup>676,677</sup> One study also detected small amounts of viral RNA up to 2 km downwind of infected barns,<sup>676</sup> but another group did not find any viral RNA outside barns, at a distance of 25 m either upwind or downwind.<sup>677</sup> The possibility of local airborne spread was suggested during a recent equine influenza epidemic among naive horses in Australia.<sup>678</sup>

Mammals often begin shedding influenza viruses before the onset of clinical signs, but the period of virus excretion is relatively brief in most cases, and typically no longer than 7 to 10 days after infection.<sup>11,13,15,17,21,26,30,31,41,287,329,679,680</sup> Children and adults can occasionally shed human influenza viruses for 10 days or more, and viruses may be detected for weeks in patients who are severely ill or immunocompromised.<sup>11,12,30,47,681-688</sup> Viral loads are reported to vary widely between people infected with human influenza viruses, and environmental contamination might differ depending on the viral load.<sup>688</sup>

Fecal shedding of influenza viruses has been reported in mammals, although its significance (if any) is still uncertain. Viral RNA was found 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),<sup>689-693</sup> and in severely ill patients infected with pandemic H1N1 virus, zoonotic H7N9 LPAI viruses in China, and Asian lineage H5N1 HPAI viruses.<sup>694-698</sup> 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.<sup>691,693</sup> However, Asian lineage HPAI H5N1 viruses, which can cause systemic infections, seem to be able to replicate in human intestinal tissues.<sup>699</sup> H5N1 viruses were also found in the feces of experimentally infected cats and foxes (but not some other species, such as pigs),<sup>103,114-117,434</sup> while minimal intestinal shedding of an H3N2 human influenza virus was reported in experimentally infected raccoons.<sup>468</sup>

A ferret model suggests that some influenza viruses might be transmitted to the fetus when there is high viremia<sup>10</sup> and viral antigens and nucleic acids were found in the fetus of a woman who died of an Asian lineage H5N1 infection.<sup>700</sup> However, most influenza viruses replicate only in the respiratory tract, and transplacental transmission seems much less likely in these cases. A recent experiment in pigs found no evidence for transplacental transmission of swine influenza viruses.<sup>701</sup>

## **Acquisition of influenza viruses from other species**

Viruses are usually transmitted to other species during close contact with the host or its tissues, although indirect contact (e.g., via fomites) is also thought to be possible.<sup>7,14,53,57,59-61,63,64,90,97-99,103,112,263,293,337,548,584,586,595,596,599-602,605,607,608,612,702-714</sup> Most of these viruses probably enter the body by the respiratory tract. However, a few H5N1 HPAI virus infections in animals, and rare cases in humans, have been linked to eating raw tissues from infected birds.<sup>57,59-61,63,64,103,112,705,712-714</sup> Feeding experiments provide evidence that H5N1 viruses can enter the body orally 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.<sup>59,63,112,114,115,713,715,716</sup> Similarly, uncooked meat from pigs or turkeys might have transmitted swine influenza viruses to mink during two outbreaks,<sup>74,534</sup> although it is uncertain whether these animals became infected by ingestion or by contamination of the respiratory mucous membranes.

Other routes of virus acquisition have been suggested in a few cases. Some experiments suggest that turkeys might be more susceptible to intrauterine than respiratory inoculation of pandemic H1N1 virus,<sup>717-719</sup> and accidental transmission during artificial insemination may have been responsible for some outbreaks.<sup>490,504</sup> (Turkeys can also be infected experimentally by intranasal inoculation.<sup>531,720</sup>)

## **Host-to-host transmission of novel influenza viruses**

Animals or people 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 sometimes occurs.<sup>7,65,94,95,236,458,528,561,562</sup> These events may be difficult to distinguish from exposure to a common source of the virus, or transmission on fomites.



Limited host-to-host transmission of Asian lineage H5N1 HPAI viruses has been reported rarely in humans during close, prolonged contact,<sup>708-711</sup> among tigers in one outbreak at a zoo,<sup>61</sup> and experimentally between cats.<sup>112</sup> There was no transmission of this virus between small numbers of experimentally infected dogs and cats.<sup>116</sup> or between experimentally infected pigs.<sup>106</sup> Nevertheless, a recent analysis of H5N1 outbreaks in Indonesia found evidence for limited pig-to-pig transmission within (but not between) herds.<sup>721</sup> Experimentally infected dogs were able to transmit one Asian lineage H5N2 virus to dogs, chickens and cats.<sup>66,229,230</sup> Another study found that there was no dog-to-dog transmission of an Asian lineage H5N8 virus in the laboratory, and little or no transmission of this virus was observed in cats despite virus shedding.<sup>435</sup>

In rare cases, limited person-to-person transmission has been suspected for some H7 LPAI or HPAI avian influenza viruses, including LPAI H7N9 viruses in China.<sup>259,263,612,722-727</sup> Transmission typically occurred to family members in close contact,<sup>259,263,612,722-727</sup> but one H7N9 case was thought to have been acquired nosocomially in the hospital.<sup>728</sup> There was no evidence that close contacts became infected in a number of other avian influenza cases,<sup>616,722,729,730</sup> although seroconversion to some avian viruses may be unreliable in people.<sup>614,724</sup> H9N2 viruses did not seem to spread readily between pigs in one experiment, although these animals did shed virus.<sup>252</sup>

People have occasionally transmitted swine influenza viruses to family members or other close contacts, and a limited outbreak occurred on a military base in the 1970s; however, most cases of swine influenza seem to be acquired by direct contact with pigs.<sup>714,97-99,286,293,584,586,592,595,702,706,707</sup> In contrast, swine influenza viruses transmitted to turkeys can propagate within this species.<sup>171</sup>

Not surprisingly, the 2009 pandemic H1N1 virus can cause outbreaks in pigs.<sup>93,95,298-300,309,322,326,499-502</sup> One study found no evidence for dog-to-dog transmission of this virus in the laboratory, although some animals did shed the virus.<sup>493</sup> Other studies did observe limited transmission of pandemic H1N1 virus between dogs (although it was sporadic and inefficient) or between cats (contact cats seroconverted but did not become ill).<sup>523,530</sup> The length and size of one pandemic H1N1 outbreak at a cat colony, and the timing of infections, suggested the possibility of cat-to-cat transmission, although the human caretaker was thought to be the original source of the virus.<sup>521</sup> Animal-to-animal transmission of pandemic H1N1 virus also appeared possible in a few clustered cases in cats, cheetahs and ferrets, but concurrent exposure to an infected human was equally plausible.<sup>67,70,71,520,522</sup> Animal-to-animal transmission of H3N2 human influenza viruses was demonstrated experimentally in both dogs and cats during close contact.<sup>493;731 cited in 732</sup>

Although one H3N8 equine influenza virus adapted to circulate in dogs, other H3N8 equine influenza viruses do not seem to spread readily between dogs.<sup>90,549</sup> Experimentally infected cats transmitted some equine H3N8 viruses to uninfected cats in one study.<sup>77</sup>

## 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.<sup>497,668,733-746</sup> 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.<sup>497,668,669,733,734,736,738,740,742,746-749</sup> 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.<sup>733,734,736-738</sup> However, the presence of natural microbial flora can considerably reduce this period, resulting in persistence in water for only a few days (or less, in some environments) to a few weeks.<sup>497,737-739,750</sup> Other physical, chemical or biological factors in natural aquatic environments may also influence viability.<sup>737,738,749,750</sup> In cold climates, freeze-thaw cycles can inactivate influenza viruses, potentially reducing long-term survival.<sup>741</sup>

In feces, some anecdotal field observations stated that LPAI viruses can survive for at least 44 or 105 days, under unspecified conditions.<sup>733</sup> 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.<sup>497,669,740,743,747,748,751</sup> At 4°C (39°F), some viruses survived for at least 30-40 days in two studies,<sup>497,747</sup> but they remained viable for times ranging from less than 4 days to 13 days in two recent reports.<sup>740,748</sup> 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);<sup>669</sup> and for at least 2 weeks at 4°C if the relative humidity was low,<sup>740</sup> 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.<sup>752</sup> Virus survival was longer on feathers than other objects in two reports: at least 6 days at room temperature in one study,<sup>752</sup> and 15 days at 20°C (68°F) and 160 days at 4°C in another report.<sup>748</sup> Some viruses survived for up to 13 days in soil (4°C),<sup>740</sup> for more than 50 days (20°C) or 6 months (4°C) in poultry meat (pH 7),<sup>735</sup> and for 15 days in allantoic fluid held at 37°C (98.6°F).<sup>745</sup> Exposure to direct sunlight greatly reduced virus survival.<sup>740</sup> Environmental sampling in Cambodia suggests 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, live virus could only be isolated from one water puddle.<sup>753</sup>

## 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).<sup>754</sup> Like avian influenza viruses, their survival was influenced by salinity.<sup>754</sup> 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.<sup>755-758</sup> Survival on wooden surfaces differed between studies, with one study reporting prolonged survival between 48 hours and 60 hours.<sup>758</sup> 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 in nasopharyngeal secretions.<sup>759</sup>

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).<sup>760</sup>

## 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.<sup>11,15,21,158,733,761</sup> 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 for rapidly eliminating viruses.<sup>762</sup> Influenza A viruses can 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).<sup>15,158,669,733,761</sup> The disinfectant and heat susceptibility of influenza B and C viruses has not been examined extensively, but it is probably similar.<sup>12</sup>

## Infections in Animals

[Note: for more detailed information on avian, swine, equine and canine influenza, please see individual factsheets on these diseases at <http://www.cfsph.iastate.edu/DiseaseInfo/factsheets.php>.]

## 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.<sup>15,49,51</sup> 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.<sup>51</sup> The

incubation period for mammalian influenza viruses is often 1-3 days, although some cases may take a few days longer to appear.<sup>7,13,15-21,25,26,76,82,83,330,530,533,557,679,680,715,763</sup>

In particular, incubation periods up to a week have been reported in some dogs and cats infected experimentally with H3N2 canine influenza viruses.<sup>76,82,83,557</sup>

## Clinical Signs

### Highly pathogenic avian influenza

HPAI viruses usually cause severe illness in chickens and turkeys, and few birds in infected flocks survive.<sup>7,51,405</sup> Decreased feed and water intake, with other nonspecific systemic, respiratory and/or neurological signs (e.g., depression, edema and cyanosis of 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.<sup>15,49-51,54,175,405,406,411,664,764-767</sup> Because a virus can be defined as highly pathogenic based on its genetic composition alone, HPAI viruses may rarely be isolated from chicken or turkey flocks that have mild signs consistent with low pathogenic avian influenza.<sup>50,182</sup>

Infections with HPAI viruses may be asymptomatic, mild or severe in other domesticated and wild (or captive wild) avian species, including gallinaceous birds other than chickens and turkeys.<sup>7,15,48,50,51,55,62,101,120,121,365,388,390,392,393,395-397,405-408,422,768-770</sup> Domesticated waterfowl tend to have minimal or mild signs, but respiratory signs (e.g., sinusitis), diarrhea, corneal opacity, occasional neurological signs, and somewhat increased mortality may be seen, and some Asian lineage H5N1 HPAI viruses can cause severe acute disease with neurological signs and a high mortality rate.<sup>15,51,52,109,119-121,395,413,414,771,772</sup> These H5N1 viruses have 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 also possible.<sup>62,109,120,121,365,392,393,395-398,414,425,451,773-775</sup> H5N8 HPAI viruses and their reassortants may likewise be associated with a wide range of outcomes in wild birds: these viruses have been found in sick, dead and apparently healthy waterfowl, and sick or dead birds in several other orders including raptors.<sup>219,221,224,226,386,387,401,402,404</sup>

### Low pathogenic avian influenza

LPAI viruses (including the Chinese H7N9 viruses) usually cause subclinical infections or mild illnesses in poultry and other birds.<sup>48,51,264,424,450,451</sup> 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.<sup>49,51,163,664,776-784</sup> Illnesses exacerbated by factors such as concurrent infections or young age can be more severe.<sup>48-50,785</sup> Wild birds have few or no obvious clinical signs,<sup>55,786</sup> although subtle effects (e.g., decreased weight gain, behavioral effects or transient increases in body temperature) have been described in some free-living birds.<sup>188,787,788</sup>

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.<sup>789,790</sup> Clinical signs have been reported in quail, which are usually mildly affected by other viruses, and some experimentally infected quail became severely ill.<sup>49,637,791</sup> Some wild birds also developed clinical signs after experimental inoculation with H9N2 viruses.<sup>789</sup>

## **Avian influenza viruses in mammals**

Asian lineage H5N1 HPAI viruses have caused fatal disease, as well as milder illnesses or asymptomatic infections, in mammals. 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.<sup>57,58,103,712</sup> Conjunctivitis and severe or fatal respiratory signs were described in experimentally infected cats.<sup>112,114,116,715,792</sup> Some captive tigers and leopards exhibited high fever, respiratory distress and neurological signs before death,<sup>59-61,65,211</sup> while a non-fatal outbreak among large felids was characterized by lethargy and inappetence without respiratory signs.<sup>62</sup> 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.<sup>63-65,122</sup> Experimental infections in various mammals ranged from subclinical to severe, with systemic and/or respiratory signs reported in animals that became ill.<sup>106,110,115-118,429,434</sup> 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.<sup>116,117,429,792</sup> A recent comparative study also suggested that experimentally infected dogs were much less likely to develop clinical signs than cats.<sup>792</sup> Experimental infections, as well as reports of infected herds, suggest that H5N1 HPAI virus-infected pigs usually remain asymptomatic or have only mild signs.<sup>106,115,430,431,721</sup> One H5N1 virus was isolated from donkeys during a respiratory disease outbreak in Egypt, although a causative role is uncertain, and antibodies to these viruses were detected in healthy donkeys and horses.<sup>122,431</sup>

Relatively little is known, at present, about other Asian lineage H5 viruses. One dog naturally infected with an H5N2 HPAI virus developed nonfatal respiratory signs, and similar signs occurred in dogs and one cat inoculated with this virus.<sup>66,229,230,445</sup> No clinical signs were seen in dogs experimentally infected with an Asian lineage H5N8 HPAI virus, while cats had mild and transient signs, including fever and marginal weight loss.<sup>435</sup>

There are few reports of animals infected with other avian viruses, except as animal models for human disease (ferrets and mice). However, H9N2 LPAI viruses have

been found occasionally in sick pigs in China, and pigs inoculated with some H9N2 viruses (but not others) had lesions of pulmonary congestion.<sup>252</sup> Dogs and cats inoculated with H9N2 viruses remained asymptomatic in two studies,<sup>446,447</sup> but dogs in another study had nonfatal respiratory signs.<sup>445</sup> 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.<sup>461,462,468</sup> The Chinese (zoonotic) H7N9 LPAI virus caused fever alone in experimentally infected cynomolgus macaques and no clinical signs in miniature pigs.<sup>453</sup> Avian influenza viruses have occasionally caused outbreaks in marine mammals and mink (see separate sections on these species, below).

## **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.<sup>7,14-17,41,642</sup> Some outbreaks are more severe than others, and swine influenza viruses can circulate in pigs with few or no clinical signs.<sup>7,14,46,92</sup> Depending on the production system, illness may be seen in certain age groups, while others remain asymptomatic.<sup>41,793</sup> Concurrent infections with other pathogens can exacerbate the clinical signs.<sup>14,16,41,793</sup>

## **Swine influenza viruses in turkeys and ferrets**

Turkeys infected with swine influenza viruses may develop respiratory disease, have decreased egg production, or lay abnormal eggs.<sup>15,171</sup>

During an outbreak caused by a triple reassortant H1N1 swine influenza virus, ferrets developed respiratory signs, including dyspnea, and some severely affected animals died.<sup>173</sup>

## **Equine influenza**

Equine influenza is an acute respiratory disease, which usually begins with a high fever, followed by a deep, dry, often paroxysmal cough, serous to mucopurulent nasal discharge, and other respiratory and nonspecific signs.<sup>7,13,15,18,20,21,329,543</sup> Animals with partial immunity can have milder, atypical infections,<sup>20</sup> while young foals without maternal antibodies may develop severe viral pneumonia.<sup>7,20,21</sup> Some cases may be complicated by secondary bacterial infections, sequelae such as chronic bronchitis, or rare complications such as neurological signs, myocarditis, myositis or limb edema.<sup>13,18,20,21,329,336</sup> Healthy adult horses usually recover within 1-3 weeks, although the cough may persist longer.<sup>7,13,18,21,329</sup> Convalescence can take months in severely affected animals.<sup>18</sup>

## **Equine influenza viruses in other animals**

Mild to severe respiratory signs have been reported in dogs naturally infected with H3N8 equine influenza viruses.<sup>89,90,544,548</sup> while experimental inoculation resulted in mild or no signs.<sup>548,549</sup> One recent H3N8 isolate caused



respiratory disease in experimentally infected cats, but an older isolate did not make cats ill.<sup>77</sup>

Depression and respiratory signs, including coughing, were reported in pigs infected with an H3N8 equine influenza virus in China.<sup>547</sup> *Streptococcus suis* was also recovered from these herds, and hemorrhagic pleuritis was noted in some animals at necropsy. Another equine H3N8 virus did not replicate well in experimentally infected pigs.<sup>550</sup> One H3N8 virus was recovered from a healthy camel.<sup>546</sup>

## Canine influenza (H3N8)

H3N8 viruses tend to cause a relatively mild illness, with a low fever alone, or fever followed by malaise, a persistent cough and other respiratory signs.<sup>22-27,79</sup> The clinical signs may last for up to 3 weeks regardless of treatment. Secondary bacterial infections seem to be common, resulting in mucopurulent nasal discharge and other signs.<sup>25</sup> Pneumonia or bronchopneumonia can develop in more severe cases, but this has generally been associated with concurrent bacterial or mycoplasmal infection.<sup>22-24,26,28,79</sup> Peracute deaths with evidence of hemorrhages in the respiratory tract occurred during the initial outbreaks among racing greyhounds; however, this syndrome does not seem to be prominent in pets.<sup>24,27</sup>

## Canine influenza (H3N2)

Like other influenza viruses, H3N2 canine influenza viruses cause respiratory signs.<sup>76,81-84,86,87,554,556</sup> Most reports from Asia have described severe or relatively severe outbreaks and case series in dogs, or dogs and cats.<sup>76,81-84,86,87,554,556</sup> Deaths were common in several of these reports, but coinfections with other pathogens may have sometimes played a role. Experimentally infected cats developed elevated temperatures, lethargy and respiratory signs,<sup>556</sup> while experimentally infected dogs had fever, respiratory signs and severe pathology.<sup>81,82,84,794</sup> Serological surveys of healthy dogs and cats in Asia have suggested that some animals might have mild or asymptomatic infections and recover without treatment.<sup>86,88,246,443,555,558,795-799</sup> There are currently no published articles describing the outbreaks in the U.S., but informal reports suggest that most cases have been characterized by relatively mild upper respiratory signs, with few deaths.<sup>800</sup>

Ferrets do not seem to be very susceptible to the canine H3N2 virus, although some experimentally infected animals developed mild signs including sneezing.<sup>556,559</sup> Experimentally infected guinea pigs remained asymptomatic, but had lung lesions.<sup>560</sup>

## Pandemic H1N1 and other human influenza A virus infections in animals

Ferrets that are naturally infected with seasonal human influenza viruses may develop a febrile respiratory disease with anorexia, depression, sneezing, nasal discharge and coughing.<sup>10,485,486</sup> Adult ferrets infected with viruses circulating before 2009 usually recovered

within 2 weeks, although neonates sometimes became severely ill or died.<sup>10,485,487</sup> Similar signs were reported in ferrets infected with pandemic H1N1 virus; however, some cases in adults were severe or fatal.<sup>510,511,513,520,522,527</sup> Experimental infections differed in severity, with some ferrets developing milder respiratory signs or systemic signs (e.g., lethargy and weight loss, with little sneezing),<sup>525,526</sup> but other studies suggesting that pandemic H1N1 virus might be more virulent in ferrets than other human H1N1 viruses.<sup>529</sup>

Mild as well as severe or fatal illnesses have been seen in cats infected with pandemic H1N1 virus.<sup>67-71,514,517,521</sup> 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.<sup>68</sup> Experimentally infected cats became mildly to moderately ill with lethargy, loss of appetite and respiratory signs.<sup>530</sup> 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.<sup>518,523</sup> Mild fever, occasional mild coughing, and nasal discharge were the only signs in experimentally infected dogs.<sup>523</sup>

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.<sup>67,72,73</sup> Some cases, including those in four cheetahs, the badger and binturong were severe, although the cheetahs recovered with supportive care including antibiotics.<sup>67,72</sup> The pandas (which were the only animals to receive antiviral drugs) and black-footed ferret also recovered.<sup>72,73</sup> 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.<sup>519</sup> 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.<sup>801</sup>

In pigs, infections with pandemic H1N1 virus are usually mild and resemble swine influenza.<sup>275,322,502,802-812</sup> Decreased egg production and quality were the only significant signs in most turkeys,<sup>490,504-509</sup> although one flock coinfecting with *Pasteurella multocida* (fowl cholera) developed mild clinical signs and had slightly increased mortality.<sup>509</sup>

Horses experimentally infected with one human influenza virus (H3N2 'Hong Kong') developed a mild febrile illness.<sup>7</sup> Raccoons inoculated with human H3N2 viruses remained asymptomatic.<sup>468</sup>

## **Influenza viruses in mink**

Outbreaks in mink caused by H10N4 and H9N2 avian influenza viruses, H3N2 and H1N2 swine influenza viruses and pandemic H1N1 virus were characterized by respiratory signs of varying severity.<sup>7,65,74,75,441,534,801</sup> There were few or no deaths during some of these outbreaks, but pneumonia and an increased mortality rate were reported in others, particularly during the H10N4 avian influenza outbreak, and in kits and on farms where the mink were co-infected with other pathogens. Mink infected with an H1N2 swine influenza virus were co-infected with hemolytic *E. coli*, and developed severe respiratory disease with hemorrhagic bronchointerstitial pneumonia.<sup>534</sup> The hemorrhagic pneumonia and high mortality were attributed to the secondary bacterial component.<sup>534</sup> 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.<sup>65</sup> Mink inoculated with an H9N2 avian influenza virus developed mild signs.<sup>441</sup>

## **Influenza in marine mammals**

Influenza A (avian origin) viruses have been associated with outbreaks of pneumonia or mass mortality in seals.<sup>7,172,563,564,566,763</sup> The clinical signs in some outbreaks (including outbreaks in well-fed captive animals) included weakness, incoordination, dyspnea, and in some cases, subcutaneous emphysema of the neck.<sup>65,561,763</sup> Some animals had a white or bloody nasal discharge. Experimental infections with some viruses were milder or asymptomatic, suggesting that co-infections may have increased the severity of the illness.<sup>65</sup> Clinical signs and mortality were reported only in harbor seals (*Phoca vitulina*) during one H10N7 outbreak, although gray seals (*Halichoerus grypus*) also had serological evidence of infection.<sup>564,813</sup>

An influenza virus was isolated from a diseased pilot whale, which had nonspecific signs including extreme emaciation, difficulty maneuvering and sloughing skin.<sup>763</sup> Whether this virus was the cause of the disease or an incidental finding is uncertain.<sup>528</sup> Other influenza viruses were isolated from whales that had been hunted, and were not linked with illness.<sup>814</sup>

## **Influenza B**

There is little information about the effects of influenza B viruses, if any, on mammals other than humans. One early field report suggested that an influenza-like outbreak in swine might have been caused by viruses acquired from humans, based on serology and the timing of the illness, which occurred concurrently with a human influenza B outbreak.<sup>155</sup> cited in <sup>156</sup> A follow-up study found that pigs inoculated with influenza B virus developed elevated temperatures, and some animals had mild respiratory signs of sneezing and serous nasal discharge; however, the clinical signs were overall mild

or absent.<sup>156</sup> In a recent study, some experimentally infected pigs similarly developed a transient fever, lasting 1-3 days, and minor lesions consistent with influenza were detected at necropsy.<sup>149</sup> Ponies inoculated with influenza B viruses sometimes had a fever for 1-3 days, and one animal developed nonspecific, self-limiting signs of illness including sweating, listlessness and unusually heavy breathing.<sup>571</sup> Influenza B infections have also been reported in some stranded seals.<sup>65</sup>

## **Influenza C**

Respiratory signs were reported in pigs and dogs inoculated with influenza C viruses. The pigs had nasal discharge and slight dyspnea, without fever.<sup>577</sup> Two pigs recovered quickly, but two others had clinical signs for 10 days. The dogs developed conjunctivitis and nasal discharge, which persisted in most animals for more than 10 days.<sup>579</sup> Experimentally infected rats, hamsters, ferrets and nonhuman primates did not become ill.<sup>580,581</sup>

## **Influenza D (Novel livestock-associated influenza C virus)**

Whether influenza D viruses cause any illnesses is still uncertain. These viruses have been recovered from apparently healthy cattle; however they were also found in some clinical samples from cattle with respiratory signs.<sup>2,4-6,355</sup> Influenza D viruses were originally detected in a herd of pigs exhibiting respiratory signs that resembled influenza, and they have since been found in other pigs with similar signs.<sup>1,5</sup> Neither pigs nor ferrets developed clinical signs or gross lesions after experimental inoculation.<sup>1</sup>

## **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.<sup>52,815</sup> 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.<sup>49,51,815</sup> 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).<sup>51</sup> However, the gross lesions in some outbreaks may not fit the classical pattern,<sup>815</sup> and birds that die peracutely may have few or no lesions.<sup>49,51,815</sup> Lesions reported from fatal cases in other species of birds vary.<sup>393,395,396,425,816</sup>

### **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.<sup>49,51</sup> Lesions (e.g., hemorrhagic

ovaries, involuted and degenerated ova) may be observed in the reproductive tract of laying hens, and the presence of yolk in the abdominal cavity can cause air sacculitis and peritonitis.<sup>51</sup> A small number of birds may have signs of acute renal failure and visceral urate deposition.<sup>49</sup>

Reproductive lesions, with peritonitis in some cases, were the only lesions reported in turkeys infected with pandemic H1N1 virus.<sup>504</sup>

## **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.<sup>16,19-21,24,26-28,41,65,172,561,679,680,763,817</sup> Concurrent bacterial infections, common in naturally infected animals, can result in more extensive damage to the lungs.<sup>14,41</sup> Lower respiratory tract lesions were reported in some animals infected with 2009 pandemic H1N1 virus.<sup>68,70,533</sup>

Some viruses have caused severe illnesses resulting 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.<sup>26-28,79,817</sup> Severe hemorrhagic bronchointerstitial pneumonia was reported in most fatal cases of canine H3N2 influenza in dogs in Asia (although few necropsies were done),<sup>794</sup> and dogs inoculated with this virus had pneumonia with consolidation, edema and hemorrhages.<sup>81,82,84,794</sup> 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,<sup>521</sup> although more typical influenza lesions were reported from other cases in cats.<sup>68,70</sup> Influenza-related pneumonia in harbor seals is characterized by necrotizing bronchitis and bronchiolitis and hemorrhagic alveolitis.<sup>763</sup> The lungs were hemorrhagic in a whale infected with influenza virus,<sup>763</sup> although the lesions could not be definitively attributed to this virus.<sup>528</sup>

## **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.<sup>57,58,60,103,112,114,715</sup> Bloody nasal discharge, severe pulmonary congestion and edema, and congestion of the spleen, kidney and liver were reported in a naturally infected dog.<sup>63</sup> Pulmonary lesions including interstitial pneumonia have been noted in some experimentally infected pigs,<sup>106</sup> while others had mild to minimal gross lesions.<sup>115</sup>

## **Diagnostic Tests**

### ***Influenza A viruses***

Avian influenza viruses, their antigens and nucleic acids can be detected in respiratory and/or intestinal samples (e.g., cloacal swabs) from birds.<sup>50</sup> Samples from various internal organs are also tested in dead birds suspected of having HPAI.<sup>50,51</sup> Respiratory samples are usually taken from mammals (e.g., nasal or nasopharyngeal swabs from living animals, or lung tissue samples collected at necropsy).<sup>15-17,26,543,818</sup>

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 employed in most clinical cases. Avian influenza viruses are isolated in embryonated eggs,<sup>50</sup> while mammalian influenza viruses can be isolated in embryonated chicken eggs or cultured cell lines.<sup>14,17,543,818</sup> Both eggs and cell cultures can be used to maximize the recovery of some mammalian viruses.<sup>26,543</sup> Virus shedding is usually brief in mammals, and respiratory samples should be collected very soon after the onset of clinical signs.<sup>17,24,329,543,679,680</sup> Isolation of the H3N8 canine influenza virus from live dogs can be difficult.<sup>24,679,680</sup> A virus detected in culture can be identified as influenza A with agar gel immunodiffusion (AGID), antigen-detection ELISAs or other immunoassays, or by a molecular test such as RT-PCR.<sup>49,50</sup> 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.<sup>14,50,818</sup> Genetic tests to identify characteristic patterns in the HA (at its cleavage site) and/or virulence tests in young chickens are used to distinguish LPAI viruses from HPAI viruses.<sup>50,51</sup>

RT-PCR assays are often used to detect influenza viruses in clinical samples.<sup>13,14,17,18,50,51,329,543,818-820</sup> Real-time RT-PCR is the method of choice for the diagnosis of avian influenza in many laboratories,<sup>50,51</sup> and it is also one of the two most reliable techniques for diagnosing H3N8 canine influenza (the other is serology).<sup>26,821,822</sup> 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).<sup>13,14,17,18,26,50,329,543,818,819</sup> The sensitivity and uses of these tests can differ between species.<sup>26,50,822</sup>

Serological tests may be used for diagnosis and/or other purposes. In birds, serology can be valuable in surveillance; however, it is not very useful for diagnosing HPAI infections in highly susceptible birds, which usually die before any antibodies develop. Serological tests used in poultry include AGID, hemagglutination inhibition (HI) and ELISAs.<sup>50</sup> AGID tests and ELISAs that detect conserved influenza virus proteins can recognize all avian influenza subtypes, but HI tests are subtype specific. In mammals, influenza is sometimes diagnosed retrospectively with a rising antibody titer in paired serum



samples.<sup>16,18,24,329,543,821,823</sup> Single tests are occasionally helpful when pre-existing titers are absent or uncommon (e.g., canine influenza in some dog populations).<sup>26,823</sup> Serological tests employed in mammals include HI, and in some species, other tests such as single-radial hemolysis, ELISAs and virus neutralization.<sup>13,14,16,17,24,26,543,818,821</sup> Cross-reactivity between influenza viruses can sometimes be an issue. In addition, some studies have found that mammals infected by viruses adapted to other species may fail to develop antibodies to the viral HA, despite having antibodies to other viral proteins, such as the viral nucleoprotein.<sup>465,550</sup>

Tests that can distinguish infected from vaccinated animals (DIVA tests) may be used in some surveillance programs in birds.<sup>50,165,824</sup> DIVA tests are rarely available for mammalian influenza viruses; however, one ELISA was used with a canarypox-vectored vaccine during the 2007-2008 equine influenza virus eradication campaign in Australia.<sup>330,336,678</sup> Another DIVA ELISA, based on the NS1 influenza protein, has been suggested for possible use with inactivated vaccines in horses.<sup>329</sup>

## Influenza D viruses

Diagnostic testing for influenza D viruses is not yet standardized. Some investigators have reported that these viruses can be readily isolated in two mammalian cell lines.<sup>1,355</sup> Other researchers had variable success in recovering influenza D viruses with mammalian cell lines.<sup>4,5</sup> RT-PCR has been employed by several groups and serology was used during the initial studies in the U.S.<sup>1,2,4-6</sup>

## Treatment

Mammals with influenza are usually treated with supportive care and rest.<sup>13,16,18,49</sup> Antibiotics may be used to control secondary bacterial infections.<sup>13,16,18,23,49</sup> Antiviral drugs used in humans are not generally given to animals, although ferrets infected with human influenza viruses have been treated with amantadine.<sup>485</sup> (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 virus,<sup>73</sup> and some authors have speculated that they might be of use in valuable horses.<sup>52,825</sup> One issue with antiviral drugs is that the brief period when viruses are most susceptible (48 hours) has often passed by the time the animal is seen.<sup>26</sup> 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

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. Reporting

requirements for the various influenza viruses differ between countries, but HPAI viruses are generally reportable. 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.). Unusual mortality among wildlife should also be reported (to state, tribal or federal natural resource agencies in the U.S.<sup>826</sup>)

## Prevention

### Vaccines

Vaccines are available for avian, swine and equine influenza viruses, and in some countries, for H3N2 or H3N8 canine influenza viruses.<sup>7,13,15-18,26,49,51,329,336,543,827,828</sup> A poor match between the vaccine and virus can compromise protection.<sup>297</sup> In pigs, some combinations of swine influenza vaccines and poorly matched challenge viruses were reported to exacerbate disease, at least in a laboratory setting.<sup>91,829-831</sup>

In birds, vaccine use may be complicated by the 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, birds may still become infected and shed viruses. This can prevent infected flocks from being recognized if good surveillance programs are not used simultaneously.<sup>51,832-834</sup> In addition, vaccination programs can place selection pressures on influenza viruses, which may encourage the evolution of vaccine-resistant isolates.<sup>835-838</sup> While avian influenza vaccines are used routinely in some regions, other countries (including the U.S.) restrict their use.<sup>49,50</sup> In some cases, avian influenza vaccines may 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.<sup>50,561,832</sup>

Influenza vaccines for animals are changed periodically to reflect the current subtypes and strains in the area, although antigenic drift tends to be lower than in human influenza viruses.<sup>13-15,329,336</sup> A multi-country surveillance program for equine influenza viruses recommends changes in vaccine strains.<sup>330,828</sup> 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,<sup>40,297</sup> 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 swine 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.<sup>15,39,52,54,57,59-61,63,67-69,74,103,112,300,510-520,534,561,733,839-841</sup>

Management measures such as all-in/all-out production can help prevent the introduction of viruses in new animals.<sup>14,15,46,52,54,287</sup> Isolation of newly acquired animals (or animals returning to a facility) and testing before release also decreases the risk that the rest of the herd or flock will become infected.<sup>18,300,329</sup> Isolating infected animals may help reduce transmission within a facility during an outbreak,<sup>13,840</sup> and quarantines (voluntary self-quarantine or government-imposed) reduce transmission between premises.<sup>13,15</sup> Management measures, such as resting horses, can help decrease the severity of the illness.<sup>7,13,14,46,287</sup>

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.

## Eradication

H5N1 viruses are normally eradicated by depopulating 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<sup>46,287</sup> or management measures.<sup>300</sup> 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 from infected horses).<sup>678,842</sup>

## Morbidity and Mortality

### Birds

Influenza virus exposures 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.<sup>56,361</sup> The reported prevalence of LPAI viruses among wild birds ranges from <1% to more than 40%, typically with much higher rates in birds from aquatic environments than terrestrial species.<sup>188,193,356,358-360,363,366,367,372,373,377,843,844</sup> Currently, surveillance suggests that carriage of H5N1 HPAI viruses in wild bird populations without unusual mortality events is rare.<sup>428,845</sup> The prevalence of influenza viruses in poultry differs between nations, but confinement-raised commercial poultry in developed countries are generally free of LPAI and HPAI viruses.<sup>49</sup>

LPAI viruses usually cause mild illnesses or asymptomatic infections in poultry, including chickens, turkeys and ducks, but the outbreak can be more severe when there are concurrent infections or other exacerbating factors.<sup>48,50,51</sup> Chicken and turkey flocks infected with HPAI viruses have high cumulative morbidity and mortality rates, which may approach 90-100%.<sup>51,53</sup> HPAI viruses can cause mild or severe disease in other species, and domesticated or wild waterfowl are often mildly

affected.<sup>370,405-412</sup> 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).<sup>7,14,52,62,120,121,392,393,398,845,846</sup> Some H5N1 HPAI outbreaks, such as one at Qinghai Lake, China in 2005, have killed thousands of wild birds.<sup>847</sup> Wild bird deaths have also been associated with some Asian lineage H5 reassortants, such as H5N8 viruses, in Asia and North America, although these viruses have also been detected in apparently healthy wild birds.<sup>219,221,224,226,386,387,401,402,404</sup>

### Mammals

Mammalian influenza viruses differ in prevalence in their host species. Some viruses are very common. For example, a number of studies have reported that approximately 20-60% of domesticated pigs have antibodies to swine influenza viruses, with lower rates in feral swine and wild boar.<sup>7,14,46,93,142,300,503,538,818</sup> In contrast, North American H3N8 canine influenza viruses are currently uncommon in pets, possibly because virus shedding is low and transmission between these animals is inefficient.<sup>26,848,849</sup> However, these viruses are more prevalent where dogs are in close contact, such as kennels and animal shelters.<sup>849-851</sup>

During outbreaks, influenza viruses can spread rapidly in fully susceptible, exposed populations. Morbidity rates of 60-90% or higher have been reported in some naïve horse populations during equine influenza epidemics,<sup>7,13,20,21</sup> and infection rates may approach 100% during canine H3N8 virus outbreaks in kennels.<sup>25,26</sup>

In healthy mammals, uncomplicated infections with host-adapted equine and swine viruses are usually associated with low mortality rates and rapid recovery from the acute stage of the illness, although signs such as a cough may linger.<sup>7,13-21,329</sup> However, the severity of the illness can vary with the dose and strain of virus, and host factors such as young age, pre-existing immunity (or maternal antibodies), stressors such as transport and concurrent illnesses, and secondary bacterial infections.<sup>14,16,18,20,39-42,543</sup> More severe clinical signs have also been reported in pregnant mares close to parturition.<sup>42</sup>

The H3N8 canine influenza virus has followed this pattern of generally high morbidity and low mortality, except during the initial outbreaks in racing greyhounds, when severe and fatal cases were common.<sup>22-27</sup> Several papers have reported severe H3N2 canine influenza virus outbreaks in Asia, with a case fatality rate of 50% in two small case series in pets; case fatality of 25% in dogs and 40% in cats during one explosive outbreak at an animal shelter; and morbidity and mortality rates of 77% and 23%, respectively, in dogs, and 47% and 22%, respectively, in cats, at another animal shelter.<sup>76,81,86,554</sup> However, clinical cases were reported to be relatively mild after an H3N2 virus was introduced to the U.S., and the case fatality rate was low: news reports indicated that,

as of May 2015, there were approximately 8 confirmed deaths in more than 1500 cases in dogs.<sup>800</sup> The reason for this discrepancy is not clear, although serological studies of dogs and cats in Asia also suggest that a significant number of animals there might have been infected without severe clinical signs.<sup>85,86,88,246,443,555,558,795-799</sup>

## Viruses acquired from other species

Few generalizations can be made about influenza viruses acquired from other species; however, pigs seem to be infected fairly regularly by viruses from birds and humans, often with only minor consequences even when the virus belongs to the Asian lineage of H5N1 HPAI viruses.<sup>7,14,15,27,46,94,95,104,106,109,115,129,142,144,252,430,431,438,452,524,533,576,721,852</sup> The consequences of infection with these H5N1 viruses have varied widely in other mammals. Infections in cats and other felids ranged from asymptomatic to fatal, while dogs generally appear to be less severely affected than cats, and sporadic deaths have been reported in other species such as raccoon dogs, palm civets, and a mink.<sup>57-65,103,110,112,114-117,211,246,429,712,792</sup> Experimental infections in various species, likewise, varied from subclinical or mild to severe and fatal,<sup>110,115,116,429,434</sup> and some studies have reported antibodies to H5 viruses in some cats, dogs, horses, donkeys and pigs tested in Asia or Egypt.<sup>65,104,106,107,430,431,443,721,799</sup> Taken together, 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 from other species,<sup>7,65,74,75,441,534,801</sup> and two recently published studies suggest that H9N2 avian influenza viruses might be a concern on mink farms in China.<sup>441,442</sup> While morbidity rates in influenza virus-infected mink can approach 100%, mortality rates have differed between outbreaks, and were probably influenced by co-infections and other factors.<sup>7,65,74,75,441,534,801</sup> During one extensive and severe outbreak caused by a avian H10N4 virus, the morbidity rate was nearly 100% and the mortality rate was 3%.<sup>7,65</sup> In contrast, an H9N2 avian influenza virus and an H3N2 swine influenza virus caused few or no deaths.<sup>75,441</sup>

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.<sup>7,562</sup> Explosive epidemics in seals are thought to be exacerbated by high population densities and unseasonably warm temperatures, as well as co-infections.<sup>65,763</sup>

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.<sup>67-73,510-514,517,518,520,522,523,527</sup> In one outbreak at a cat colony, half of the cats had clinical signs, and 25 of the 90 cats died.<sup>521</sup> 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 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.<sup>732,798</sup> Infections with this virus have also stimulated renewed research into the possibility that dogs and cats may be infected with other human influenza viruses. A number of surveys have found that only a few animals (< 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.<sup>333,492,732,796,798,853-863;731 cited in 732</sup>

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, with little or no mortality in subsequent years.<sup>13,19</sup>

## 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 1-4 days.<sup>7,11,31,37,47,864,865</sup> Most zoonotic infections caused by swine and avian influenza viruses also seem to become apparent soon after exposure (e.g., within 5 days for most North American H3N2 swine influenza viruses and Asian lineage H5N1 HPAI viruses), although the incubation period for some H5N1 cases might be as long as 8-17 days.<sup>203,207,612,707,725,726,866,867</sup>

## Clinical Signs

### Seasonal human influenza

Uncomplicated infections with human influenza A viruses (including pandemic H1N1 virus) or influenza 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.<sup>7,9-12,31</sup> Intestinal signs (vomiting, nausea, diarrhea, abdominal pain), otitis media and febrile seizures can also occur, especially in children, and dehydration is a particular concern in very young patients.<sup>9,10,30,31,868</sup> 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.<sup>7,9,30,31</sup>

More severe respiratory syndromes, including pneumonia, are possible,<sup>9,11,12,30,31</sup> and deterioration can occur rapidly in these cases.<sup>35,869</sup> Severe primary viral pneumonia and/or acute respiratory distress syndrome, as well as multiple organ failure and other serious syndromes, occurred in a small percentage of cases during



the 2009-2010 pandemic, and affected an unusually large number of children and young adults.<sup>32,38,44,47,865,869-871</sup> Influenza can 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.<sup>32,35,37,38,45,871-873</sup> Other possible complications include various neurological syndromes including encephalitis, myositis (e.g., benign acute childhood myositis), rhabdomyolysis and myocarditis.<sup>11,30,139-141,868</sup> 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.<sup>31</sup>

Influenza C virus infections 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.<sup>7,129-138,157</sup> Fever was a common symptom in some studies,<sup>132,134-136</sup> but a study of young adults in Finland found that most had mild upper respiratory signs without fever.<sup>138</sup> Neurological signs have been reported in a few cases, and included seizures/unconsciousness in an infant, and drowsiness and hemiparesis in a child.<sup>136,874</sup>

## Avian influenza infections in humans

### Asian lineage H5N1 HPAI viruses and reassortants

Most infections with Asian lineage H5N1 HPAI viruses have been severe.<sup>53,108,237</sup> 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.<sup>203,207,875</sup> Lower respiratory signs tend to develop soon after the onset of the illness.<sup>203,207</sup> Most patients deteriorate rapidly, and serious complications including multiorgan dysfunction are common in the later stages.<sup>203,207,875</sup> Milder cases have been reported occasionally, particularly among children.<sup>237,876</sup> Rapid treatment with antiviral drugs may have been a factor in some mild cases;<sup>877-879</sup> however, at least one child with upper respiratory signs made an uncomplicated recovery after antibiotic treatment alone.<sup>876</sup>

Three infections with Asian lineage H5N6 HPAI viruses in older adults were severe, with fever and severe respiratory signs in at least two patients.<sup>232-234</sup> One of these cases was fatal; the other patient required mechanical ventilation but recovered after treatment with oseltamivir and antibiotics.<sup>233,234</sup> (Details of the third case have not been published.) A child infected with an H5N6 virus had a mild illness with prompt recovery.<sup>232-234</sup>

### Eurasian lineage H9N2 LPAI viruses

Most illnesses caused by H9N2 viruses have been reported in children and infants.<sup>108,235,237,238,241-244</sup> 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.<sup>108,235,237,238,241-244</sup> All of these patients, including a 3-month-old infant with acute lymphoblastic lymphoma,<sup>241</sup> made an uneventful recovery. Acute, influenza-like upper respiratory signs were also reported in two adults.<sup>243</sup> However, severe lower respiratory disease, which developed into respiratory failure, occurred in an immunocompromised woman who had serious underlying conditions.<sup>241</sup>

### H7N9 LPAI viruses in China

Most clinical cases caused by H7N9 viruses in China have been serious.<sup>231,258,262,695,880-882</sup> 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.<sup>696,866,883</sup> Diarrhea and vomiting were sometimes reported, but conjunctivitis was uncommon, and most patients did not have nasal congestion or rhinorrhea as the initial signs.<sup>866,884</sup>

A few uncomplicated cases were characterized by mild upper respiratory signs or fever alone, especially in children.<sup>258,725,866,881,884,885</sup> 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.<sup>258,866,881,885</sup> At least one asymptomatic infection has been reported in an adult.<sup>695,866</sup> Antibodies to H7N9 viruses in healthy poultry or live bird market workers suggest that some mild cases or asymptomatic infections might not have been diagnosed.<sup>609,882,886-888</sup>

### 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 H10N7 viruses.<sup>172,561,598,614,615,618,722,724,889-893</sup> One H7N7 HPAI virus, which caused only mild illness in most people, resulted in fatal acute respiratory distress syndrome and other complications in one otherwise healthy person.<sup>722</sup> 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.<sup>729</sup> 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.<sup>616</sup> She made an uneventful recovery after treatment with oseltamivir and antibiotics. Three older adults with H10N8 infections in China developed severe lower respiratory tract disease, progressing in some cases to multiple organ failure and septic shock, and two of these cases were fatal.<sup>617,730</sup>

## 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.<sup>7,14,98,99,286,293,498,584,586,591,593,595,597,702,706,707,894,895</sup> 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.<sup>707</sup> Most healthy people infected with these H3N2 viruses had a mild illness, although young children were sometimes hospitalized for dehydration.<sup>98,99,286,293,584,586,591,593,595,702,707,894</sup> The illness was also mild and flu-like in one cancer patient undergoing chemotherapy, who became infected with a European swine influenza virus.<sup>597</sup> Serological evidence suggests that mild or asymptomatic cases might occur sporadically among people who are occupationally exposed.<sup>7,14,159,337,599-604</sup>

Swine 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.<sup>99,286,585,588-590,595,596,702,707,896</sup> A few serious or fatal 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.<sup>7</sup>

## Diagnostic Tests

### Infections caused by influenza A and B viruses

A number of assays, similar to those used in animals, can diagnose influenza A and B infections in humans.<sup>31,897</sup> Upper respiratory samples are generally collected for routine seasonal influenza diagnosis, but samples from the lower respiratory tract are appropriate in some cases.<sup>53,207</sup> RT-PCR techniques are now the method of choice for detecting and subtyping human influenza viruses in many laboratories, due to their speed and sensitivity.<sup>897,898</sup> These tests can also be used for zoonotic influenza virus infections.<sup>207,725,899,900</sup> Virus isolation can be done, although traditional techniques take 3-14 days, and are too slow for the initial diagnosis and management of the case.<sup>45,897</sup> Some newer methods (e.g., shell vial-based culture techniques) are faster, if available.<sup>897</sup> Antigen-detection assays used in humans include immunofluorescence and immunoassays such as ELISAs.<sup>9,31,45,898</sup> 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, and

may not detect novel infections including zoonotic viruses.<sup>31,45,53,897,898,901,902</sup> 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.<sup>53</sup> 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 handling dangerous human pathogens such as H5N1 HPAI viruses.<sup>53,207</sup>

Resistance to antiviral drugs can be detected either with phenotypic tests or by gene-based testing to detect molecular markers of resistance.<sup>897</sup> The need to perform susceptibility testing depends on the composition of circulating viruses and the individual case.<sup>897</sup> These tests are available in a limited number of laboratories and take several days to perform.<sup>897</sup>

Because people have antibodies to the subtypes found in circulating influenza viruses, serology is not generally useful for the routine diagnosis of seasonal influenza.<sup>31</sup> However, zoonotic influenza virus infections are occasionally diagnosed retrospectively by serology.<sup>703</sup> Although a rising titer must be seen for a definitive diagnosis, single titers may be helpful in some circumstances. Tests used to detect influenza virus antibodies in humans include hemagglutination inhibition, virus neutralization, enzyme immunoassays and complement fixation.<sup>897,903</sup> The microneutralization assay is considered to be the most reliable test for detecting antibodies to avian influenza viruses.<sup>207,237</sup> People infected with some avian influenza viruses did not seroconvert, even in virologically confirmed cases.<sup>614,724</sup>

### Infections caused by influenza C viruses

RT-PCR or culture can be used to diagnose influenza C.<sup>904,905</sup> It can be difficult to isolate these viruses in cell lines, and although they can be isolated in embryonated eggs, this technique is not widely available in diagnostic laboratories.<sup>905</sup>

## 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.<sup>32</sup>

Two groups of antiviral drugs – adamantanes (amantadine, rimantadine), and neuraminidase inhibitors (zanamivir, oseltamivir, peramivir and laninamivir) – are used to treat some cases of influenza.<sup>9,11,30,31,45,906,907</sup> Adamantanes are active against human influenza A viruses, while neuraminidase inhibitors can be used in both influenza A and influenza B infections.<sup>9,11,12,23,31,45,906,907</sup> 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.<sup>11,12,23,31,45,906,907</sup> 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 may also be employed for some milder cases of seasonal influenza.<sup>31,45,203,207,314,875,908</sup> There has been some debate about the benefits of oseltamivir for uncomplicated seasonal influenza in healthy patients.<sup>9,30,45,906,909-913</sup> The side effects of specific drugs vary, but can include gastrointestinal and CNS effects.<sup>31,45</sup>

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.<sup>7,9,30,31</sup> At one time, adamantanes were used most often to treat seasonal influenza in the U.S.; however, many H1N1, H3N2, and influenza B viruses had become resistant to these drugs by the 2006-2008 flu seasons.<sup>7,9,30,897,906,907</sup> After antiviral drug recommendations changed, seasonal H1N1 influenza viruses rapidly became resistant to oseltamivir, although many lost their resistance to adamantanes.<sup>897</sup> These H1N1 viruses co-circulated with adamantane-resistant, oseltamivir-sensitive H3N2 and influenza B viruses, complicating treatment decisions.<sup>897</sup> This pattern changed with the introduction of pandemic H1N1, and during the 2015-2016 influenza season, many of the circulating seasonal influenza viruses in the U.S., including pandemic H1N1, were resistant to adamantanes and sensitive to neuraminidase inhibitors.<sup>31</sup> There have also been reports of seasonal influenza A viruses resistant to both drug classes, and oseltamivir-resistant influenza B viruses have been found.<sup>897,914</sup>

Asian lineage H5N1 HPAI viruses and Chinese H7N9 LPAI viruses are usually sensitive to oseltamivir and resistant to adamantanes, at present, although this could change.<sup>53,207,259,640,883,915,916</sup> 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).<sup>917</sup> Another study found a high prevalence of amantadine resistance in some lineages of swine influenza viruses in North America.<sup>918</sup> Published reports suggest that neuraminidase resistance is currently uncommon among swine influenza viruses in the U.S. and Germany.<sup>918,919</sup>

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.<sup>897</sup>

## Prevention

Annual vaccines, usually given in the fall before the flu season (or as appropriate for local patterns of virus

circulation), are available for influenza A and B.<sup>7,9,268,920,921</sup> They contain the viral strains considered 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.<sup>31,276,922,923</sup> Immunization recommendations may differ between countries, although vaccination of some groups, such as the elderly, is consistently recommended.<sup>31,924</sup>

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.<sup>30,31,45,906</sup> The use of antiviral prophylaxis should be balanced against the risk of encouraging the emergence of drug-resistant strains.<sup>45</sup> 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.<sup>31,53,97,925</sup> To protect others, the mouth and nose should be covered when coughing or sneezing.<sup>31,97,925</sup> Recommendations on the use of face masks, respirators, gloves and other barrier precautions vary, and current setting-specific guidelines (e.g., for hospitals vs. the community) should be consulted.<sup>31,32,673</sup> 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.<sup>672,673,675,926-930</sup>

Additional measures that have been recommended during pandemics or outbreaks caused by novel viruses include avoidance of crowds and gatherings, cancellation of social events, and voluntary self-isolation of individuals who develop influenza-like signs (with the exception of necessities such as seeking medical care).<sup>925,931-936</sup>

## 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 hand washing; avoiding contact with sick animals or animals known to be infected; and employing personal protective equipment where appropriate (for instance, when working with infected birds or swine).<sup>53,97,203,704</sup> While zoonotic infections are usually acquired during close contact with animals,<sup>53,97</sup> aerosolized viruses may be present in confined areas such as production barns, where large numbers of swine are concentrated.<sup>676,677</sup> Because HPAI viruses have been found in meat and/or eggs from several avian species,<sup>164,418,660-666,778,937-941</sup> 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.<sup>53,826,942</sup> Swine influenza viruses can also be inactivated by cooking,<sup>97,943,944</sup> although these viruses are respiratory pathogens and are not likely to be present in retail meat.<sup>642</sup>

More detailed recommendations for specific groups at risk of exposure, including the general public, have been published by some national agencies (e.g., the CDC, the Department of the Interior and U.S. Geological Survey National Wildlife Health Center in the U.S.,)<sup>53,97,826,945</sup> and international agencies such as the World Health Organization. In some cases, recommendations may include antiviral prophylaxis and/or vaccination for human influenza to reduce the risk of reassortment between human and animal influenza viruses.<sup>53</sup> Currently, the CDC recommends that people who are at elevated risk of complications with human influenza viruses avoid pigs and pig barns when attending fairs in North America, and that other people take precautions to reduce the risk of infection with swine influenza viruses.<sup>97</sup> 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, epidemic, or pandemic, or as sporadic cases.<sup>8</sup> Historical evidence suggests that pandemics occur every 10 to 40 years.<sup>7,11,14</sup> 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.<sup>7,9,946</sup> 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.<sup>920,921,947-949</sup>

Uncomplicated infections with seasonal influenza viruses are rarely fatal in most healthy people, although the morbidity rate can be high.<sup>7-12</sup> Approximately a third of influenza virus infections are thought to be asymptomatic.<sup>47</sup> Groups at higher risk for severe illness include the elderly; young children (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.<sup>9,11,12,30-38,43</sup> Obesity was first recognized as a risk factor during the 2009-2010 pandemic.<sup>31,43</sup>

Since 1968, H3N2 influenza A viruses have caused the most serious epidemics with the highest mortality rates.<sup>30,31</sup> Except after the introduction of a new virus, over 90% of influenza-related deaths occur in the elderly.<sup>30,268</sup> Morbidity and mortality rates usually increase during influenza A pandemics, sometimes

dramatically.<sup>7,9,14,31,46,53</sup> 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%.<sup>8</sup> 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<sup>950</sup>) usually becomes established in the population and circulates for years.<sup>7,8,14,124</sup> Influenza B viruses can cause epidemics, but they have not, to date, been responsible for pandemics.<sup>7</sup>

### 2009-2010 pandemic

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.<sup>37,951,952</sup> Overall, the pandemic H1N1 virus has caused relatively mild illnesses, and the estimated case fatality rate for this virus is less than 0.5%, with a number of estimates suggesting that it is less than 0.05%.<sup>37,47</sup> Nevertheless, an elevated number of patients developed viral pneumonia during this pandemic, and case fatality rates in younger age groups were higher than with seasonal influenza viruses.<sup>35,37,44,45,869,953</sup> 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.<sup>36,37</sup> The relative sparing of older populations appeared to result from immunity to similar, previously circulating viruses (pandemic H1N1 was antigenically very similar to the 1918 virus), and possibly other factors.<sup>33,36,47,954-957</sup> The concentration of severe illnesses mainly in younger, healthier age groups is thought to have contributed significantly to the low overall mortality rate, and many seriously ill patients recovered with hospitalization and intensive care.<sup>32,37</sup> However, older patients who became infected had an elevated risk of severe illness and death.<sup>47</sup>

The prevalence of pre-existing conditions among seriously ill children differed between studies, but predisposing conditions (e.g., asthma, immunosuppression, neurological diseases) were relatively common in some series.<sup>32,958,959</sup> Nevertheless, a significant number of serious or fatal cases were reported in healthy children or young adults.<sup>32,35,37,38,44,45,47,869,960,961</sup> Obesity and pregnancy were recognized as risk factors for more serious illness during this pandemic.<sup>31,43</sup> The impact of this virus was also greater in indigenous groups.<sup>33,37,47</sup> The reason is still uncertain, but might involve access to healthcare, concurrent illnesses, increased crowding or other factors.<sup>37,47</sup>

### Influenza C

Serological studies suggest that many people are exposed to influenza C viruses in childhood, although infections can continue to occur in adults.<sup>136-138,962-965</sup> One recent study from Scotland found two peaks of mild influenza C-related illness, one in children and a second in adults over the age of 45 years.<sup>157</sup> At one time, these viruses were thought to cause only sporadic cases of

influenza and minor localized outbreaks.<sup>7,9,129</sup> However, in 2004, a nationwide influenza C epidemic was reported in Japan.<sup>904</sup> 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.<sup>132</sup>

## Zoonotic swine influenza

The overall prevalence of swine influenza virus infections in humans is uncertain. While cross-reactivity to human influenza viruses may be an issue, serological studies suggest that some people who work with pigs have been exposed to swine influenza viruses.<sup>7,14,159,309,337,599-604,606,607,609,610,966,967</sup> 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.<sup>7,14,97-99,159,286,287,293,584-597,702,706,707,894-896</sup> Although 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.<sup>97</sup> Approximately one case was documented every 1-2 years in the U.S. at one time; however, this increased to 21 cases between 2005 and June 2011, 13 cases from August 2011 to April 2012, and 306 confirmed cases (mainly associated with fairs) in summer 2012.<sup>97-99</sup> 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 new reporting requirements may also play a role.<sup>96-99</sup>

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.<sup>98,99,286,293,584-586,588-591,593,595,596,702,707,894,896</sup> 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.<sup>98,99,286,293,584-586,588-591,593,595,596,702,707,894,896</sup>

## Asian lineage H5 avian influenza viruses

Between 1997 and February 2016, Asian lineage H5N1 viruses were responsible for more than 800 laboratory-confirmed human infections, generally as the result of close contact with poultry.<sup>231</sup> Most patients were young and had no predisposing conditions.<sup>207</sup> The case fatality rate for all laboratory confirmed cases reported to WHO has consistently been about 59-60% in the last few years.<sup>231,611,968</sup> 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.<sup>875,877,879,969-971</sup> 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.<sup>877-879</sup> 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.<sup>431,609,620,621,623,629,972-976</sup> Rare, laboratory confirmed, asymptomatic or mild cases have also been recognized.<sup>237,876,977</sup> Recent prospective studies documented seroconversion in rare instances, but detected no clinical cases.<sup>619,621,622</sup>

Asian lineage H5N6 viruses have caused a few severe clinical cases in patients aged 49 years or older; however, one infection in a child was mild.<sup>232-234</sup>

## H7N9 avian influenza viruses in China

Approximately 680 laboratory-confirmed clinical cases, with at least 275 fatalities, have been caused by H7N9 LPAI viruses in China, as of September 2015.<sup>231</sup> They mainly occurred in three waves to date, the first between February and May 2013, the second from October 2013 to May 2014, and the third beginning in Fall 2015, with sporadic cases reported between outbreaks.<sup>258,259,261,262,888,978</sup> These viruses are circulating subclinically among poultry in China, and human cases have mainly been associated with live bird poultry markets; however, infected farms have also resulted in at least one human illness.<sup>263,264,612,703,704,888,979,980</sup> Most reported cases have been serious, except in children, who often (though not always) presented with mild illnesses.<sup>258,263,264,695,866,880,881</sup> Elderly people were overrepresented among the clinical cases, probably due to increased exposure and/or increased susceptibility.<sup>612,880,981</sup> As of October 2014, case fatality rates were approximately 36% to 48% in hospitalized, laboratory confirmed cases during the first two waves,<sup>258,264,882,978</sup> with the risk of death among hospitalized patients increasing significantly with age.<sup>258,882</sup> 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.<sup>258,264,612,641,695,725,866,880,982</sup>

The likelihood of additional, undiagnosed mild or asymptomatic infections is still being assessed, although few cases were detected during national virological sampling of people with influenza-like illnesses.<sup>258,264,881</sup> Some initial serological studies reported no H7N9 reactivity among poultry market workers, healthcare staff, patient contacts and other populations.<sup>259,726,983-986</sup> However, several surveys have now detected antibody titers to H7N9 viruses in up to 17% of poultry workers or live bird market workers, with two studies documenting recent increases in seroprevalence.<sup>609,886-888</sup> These studies report that seroprevalence rates are low ( $\leq 1\%$ ) in the general population,<sup>886,887</sup> with one survey also documenting low seroprevalence (2%) in veterinarians.<sup>609</sup>

Taking into account the serological studies, some authors have speculated that the overall case fatality rate might be as low as <1% to 3%, if milder cases are also accounted for.<sup>258,882</sup>

## ***Eurasian lineage H9N2 avian influenza viruses***

Clinical cases caused by H9N2 viruses have mainly been reported in children.<sup>53,108,231,235-238,242-244</sup> 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.<sup>241</sup> Serological studies suggest that exposure to H9N2 viruses may occur in some people who are exposed repeatedly to poultry in endemic areas,<sup>236,239,240,605,609,620,621,623,624,976,987-989</sup> and a prospective study of adults with poultry exposure in rural Thailand reported rare instances of seroconversion, although no clinical cases were detected.<sup>619</sup>

## ***Other avian influenza viruses***

With the exception of the H7N9 viruses in China, most reported infections with H7 viruses in healthy people have been mild, 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.<sup>172,561,615,722,724,889-893</sup> Mild signs were reported in poultry workers infected with an H10N7 virus,<sup>614</sup> but H10N8 viruses caused fatal infections in two elderly patients in China and a serious illness in a 55-year-old,<sup>617,730</sup> and a young woman infected with an H6N1 virus in China developed lower respiratory tract complications.<sup>616</sup> 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.<sup>236,237,239,240,600,619,621,625-629,631,988,990-992</sup>

## **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://healthycanadians.gc.ca/diseases-conditions-maladies-affections/disease-maladie/flu-grippe/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>
- The Merck Veterinary Manual  
<http://www.merckvetmanual.com/mvm/index.html>
- United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS).  
<https://www.aphis.usda.gov/aphis/home/>
- USDA APHIS. Biosecurity for the Birds  
<https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-disease-information/avian-influenza-disease/birdbiosecurity>
- United States Geological Survey (USGS). National Wildlife Health Center. List of Species Affected by H5N1 (Avian Influenza)  
[http://www.nwhc.usgs.gov/disease\\_information/avian\\_influenza/affected\\_species\\_chart.jsp](http://www.nwhc.usgs.gov/disease_information/avian_influenza/affected_species_chart.jsp)
- 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](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/](http://www.who.int/influenza/human_animal_interface/en/)
- World Organization for Animal Health (OIE)  
<http://www.oie.int>
- OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals  
<http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/>
- OIE Terrestrial Animal Health Code  
<http://www.oie.int/international-standard-setting/terrestrial-code/access-online/>

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