

# Avian Influenza

*Fowl Plague, Grippe Aviaire*

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## Importance

Avian influenza viruses are highly contagious, extremely variable viruses that are widespread in birds. Wild birds in aquatic habitats are thought to be their natural reservoir hosts, but domesticated poultry and other birds can also be infected.<sup>1-9</sup> Most viruses cause only mild disease in poultry, and are called low pathogenic avian influenza (LPAI) viruses. Highly pathogenic avian influenza (HPAI) viruses can develop from certain LPAI viruses, usually while they are circulating in poultry flocks.<sup>10</sup> HPAI viruses can kill up to 90-100% of the flock, and cause epidemics that may spread rapidly, devastate the poultry industry and result in severe trade restrictions.<sup>2,11,12</sup> In poultry, the presence of LPAI viruses capable of evolving into HPAI viruses can also affect international trade.<sup>11</sup>

Avian influenza viruses can occasionally affect mammals, including humans, usually after close contact with infected poultry. While infections in people are often limited to conjunctivitis or mild respiratory disease, some viruses can cause severe illness. In particular, Asian lineage H5N1 HPAI viruses have caused rare but life-threatening infections, now totaling nearly 850 laboratory-confirmed cases since 1997,<sup>13</sup> and H7N9 LPAI viruses have caused more than 600 serious human illnesses in China since 2013.<sup>14-16</sup> Avian influenza viruses can also infect other species of mammals, sometimes causing severe or fatal disease.<sup>12,17-43</sup> In rare cases, avian influenza viruses can become adapted to circulate in a mammalian species. During the last century, such viruses have caused or contributed to at least three pandemics in humans, contributed to the diversity of swine influenza viruses in pigs, and also produced one of the two canine influenza viruses now circulating among dogs.<sup>1,44-57</sup>

## Etiology

Avian influenza results from infection by viruses belonging to the species *influenza A virus*, genus *influenzavirus A* and family Orthomyxoviridae. These viruses are also called type A influenza viruses. Influenza A viruses are classified into subtypes based on two surface proteins, the hemagglutinin (HA) and neuraminidase (NA). A virus that has a type 1 HA and type 2 NA, for example, would have the subtype H1N2. At least 16 hemagglutinins (H1 to H16), and 9 neuraminidases (N1 to N9) have been found in viruses from birds, while two additional HA and NA types have been identified, to date, only in bats.<sup>2,6,12,58-60</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>7</sup>

Avian influenza viruses 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 or LPAI by its ability to cause severe disease in intravenously inoculated young chickens in the laboratory, or by its possession of certain genetic features that have been associated with high virulence in HPAI viruses (i.e., the sequence at the HA cleavage site).<sup>2,58</sup> HPAI viruses usually cause severe disease in chicken and turkey flocks, while LPAI infections are generally much milder in all avian species. With rare exceptions, HPAI viruses found in nature have always contained the H5 or H7 hemagglutinin.<sup>10,61-63</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 that became infected by the respiratory (intranasal) route.<sup>62</sup> Another H10 virus also fit the HPAI definition; however, this virus affected the kidneys and had a high mortality rate in intranasally inoculated young chickens.<sup>64</sup> In the laboratory, the insertion of genetic sequences from HPAI viruses into non-H7, non-H5 viruses has created some viruses that are 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>65</sup> Recently, an H4N2 virus with a genetic signature characteristic of HPAI viruses was isolated from a flock of naturally infected quail.<sup>66</sup> This virus had the biological characteristics of a LPAI virus, with low virulence when inoculated into chickens.



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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>67,68</sup> Such 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.

## Antigenic shift and drift in influenza A viruses

The viral HA, and to a lesser extent the NA, are major targets for the immune response, and there is ordinarily little or no cross-protection between different HA or NA types.<sup>69-78</sup> Influenza A viruses are very diverse, and two viruses that share a subtype may be only distantly related. The high variability is 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>79</sup> Once these proteins have changed enough, 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>76,77</sup> and when two different viruses infect the same cell, gene segments from both viruses may be packaged into a single, novel virion. 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 avian influenza viruses) or originally came from different hosts (for instance, 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 existing immunity. After a subtype has become established in a species and has circulated for a time, antigenic shifts and drift can produce numerous viral variants.

## Avian influenza virus lineages

There are two well-recognized lineages of avian influenza viruses, Eurasian and North American.<sup>7</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>7,80-92</sup> Viruses in wild birds (or portions of viruses) are more likely to be transferred between hemispheres in the latter regions. 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>93-95</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>96-98</sup>

## Transfer of influenza viruses between species

Although influenza A viruses are adapted to circulate in a particular host or hosts, they can occasionally infect other species. In most cases, the virus cannot be transmitted efficiently between members of that species, and soon disappears.<sup>1,5,12,31,45,50,79,99-105</sup> On rare occasions, however, a virus continues to circulate in the new host, either "whole" or after reassorting with another influenza virus.<sup>45,46,50-55,57,102,106,107</sup> Some influenza A viruses have become adapted to circulate in pigs (swine influenza viruses), horses (equine influenza viruses), humans (human influenza A viruses) and dogs (canine influenza viruses). The ancestors of these viruses are thought to have originated in birds, either in the distant past or more recently.<sup>1-5,7,50,51,108</sup> Further information about virus transmission between species can be found in the 'Influenza' factsheet.

## Species Affected

### Wild birds

The vast majority of LPAI viruses are maintained in asymptomatic wild birds, particularly birds in wetlands and other aquatic habitats, which are thought to be their natural reservoir hosts.<sup>1-9</sup> Some species may maintain viruses long-term, while others might be spillover hosts. Infections are particularly common among members of the order Anseriformes (waterfowl, such as ducks, geese and swans) and two families within the order Charadriiformes, the Laridae (gulls and terns) and Scolopacidae (shorebirds).<sup>1-3,5-9,46,84,89,109-113</sup> However, infections may be uncommon in some members of these orders. Within the Laridae, viruses tend to occur more often in gulls than terns.<sup>9</sup> The prevalence of infection among wading birds (waders) is reported to be high in some areas, but low in others.<sup>92,97,109</sup> Aquatic species belonging to other orders occasionally have high infection rates, and might also be involved in the epidemiology of this disease.<sup>9,114,115; 116 cited in 115</sup> For instance, infections among seabirds seem to be particularly common in murre (*Uria* spp.).<sup>117</sup>

The most common influenza subtypes in wild birds may differ between species and regions, and can change over time.<sup>7,111,112,115,117-119</sup> Migrating birds, which can fly long distances, may exchange viruses with other populations at staging, stopover or wintering sites.<sup>7</sup> Virus diversity seems to be particularly high among charadriiform birds.<sup>7,109</sup> A few avian influenza subtypes seem to have a limited host range. Examples include H13 and H16 viruses, which have mainly been found in gulls and terns, and H14 viruses, which have been detected rarely and only in a few species (i.e., in a few ducks, sea ducks and a herring gull).<sup>7,80,84,112,120-126</sup> Such viruses may rarely (or never) be transferred to poultry.

LPAI viruses can also infect wild birds that live on land (terrestrial birds), such as raptors and passerines, but under ordinary conditions, infections seem to be uncommon in these species, and they are not thought to be important

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reservoirs.<sup>8,9,127-136</sup> Higher infection 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, with an especially high prevalence in Japanese White-eyes (*Zosterops japonicus*).<sup>129,135</sup> Similarly, a recent study from Central and West Africa detected influenza virus RNA in an unusually high percentage of passerine birds.<sup>137</sup>

HPAI viruses are not usually found in wild birds, although they may be isolated transiently near outbreaks in poultry.<sup>131</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>27,32,108,138-164</sup>

## Domesticated birds and mammals

When LPAI viruses from wild birds are transferred to poultry, the viruses may circulate inefficiently and die out; become adapted to the new host and continue to circulate as LPAI viruses; or if they contain H5 or H7, they may evolve into HPAI viruses.<sup>4,10,12</sup> Once a virus has adapted to poultry, it rarely re-establishes itself in wild birds.<sup>10</sup> HPAI and LPAI viruses have been found in many domesticated birds, including gallinaceous poultry and game birds, ducks, geese, ratites, pigeons and cage birds; however, some species seem to be more resistant to infection and/or illness than others.<sup>2,27,72,146,147,149-151,165-190</sup> For example, there are few reports of infections in psittacine birds, and pigeons appear to be relatively resistant to infection compared to poultry.

Avian influenza virus infections have been detected occasionally in numerous species of mammals. Some of these species include cats, dogs, pigs, horses, donkeys, mink, and various wild and captive wild mammals.<sup>12,20-35,37,40,43,99,191-204</sup> Ferrets can be infected experimentally with many viruses.

## Important viral lineages and susceptible species

Poultry can be infected by many different LPAI and HPAI viruses, belonging to multiple subtypes, but three viral lineages are currently of particular concern. Some of these viruses have also been reported in mammals.

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

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 very diverse.<sup>12,205-211</sup> Some variants of H5N1 differ in their virulence for mammals and/or birds.<sup>150,210,212</sup> HPAI H5N2, H5N5, H5N6 and H5N8 viruses, resulting from reassortment between Asian lineage H5N1 viruses and other avian influenza viruses, have been reported among poultry in Asia.<sup>213-219</sup> H5N8 viruses became widespread among birds in

Asia and Europe in 2014.<sup>158,220</sup> They reached North America in late 2014, and have reassorted with North American lineage viruses to produce unique variants of other subtypes such as H5N1 and H5N2.<sup>157,159-161,220-224</sup> (Unless otherwise specified, "Asian lineage H5N1 viruses" usually refers to the original viruses circulating in the Eastern Hemisphere, and not to reassortant viruses from North America that contain the North American lineage NA.)

Whether wild birds can maintain Asian lineage H5 viruses for long periods (or indefinitely), or are repeatedly infected from poultry, is still controversial.<sup>143,148,155,225-227</sup> However, the evidence that wild birds can transfer H5N1 HPAI viruses and some of their reassortants (e.g., H5N8) to new geographic regions now appears strong.<sup>138,139,157-160,220,227</sup>

Asian lineage H5N1 HPAI viruses seem to have an unusually wide host range. These viruses can infect a wide variety of wild birds belonging to many different orders, including the Anseriformes and Charadriiformes.<sup>27,32,108,143-156</sup> Both clinical cases and asymptomatic infections have been described.<sup>27,152,155,164,228</sup> These viruses can also 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 nebulosus*), 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>12,17-37</sup> Serological evidence of infection or exposure has also been reported in horses and raccoons.<sup>20,229-231</sup> Experimental infections have been established in cats, dogs, foxes, pigs, ferrets, laboratory rodents, cynomolgus macaques (*Macaca fascicularis*) and rabbits.<sup>17,27,31,34,108,151,192,212,232-240</sup> In rodents, susceptibility may differ between species. One group found little or no evidence for productive infections in experimentally infected black rats (*Rattus rattus*), although they seroconverted.<sup>241</sup> Cattle could be experimentally infected with viruses isolated from cats,<sup>240</sup> but studies in Egypt detected no antibodies to H5N1 viruses in cattle, buffalo, sheep or goats, suggesting that these species are not normally infected.<sup>229</sup>

Some Asian lineage H5 reassortants, such as an H5N2 virus recovered from a sick dog in China, may be able to cause illness in mammals.<sup>40-42</sup> This H5N2 virus could be transmitted from experimentally infected dogs to dogs, chickens and cats.<sup>40-42</sup> There have been no reports of illnesses caused by Asian lineage H5N8 viruses in mammals, as of February 2016, although seropositive dogs were detected on some infected farms in Asia.<sup>242</sup> Initial laboratory experiments in ferrets and mice reported low to moderate virulence in these species, suggesting that the currently circulating H5N8 viruses may be less pathogenic for mammals than some H5N1 isolates.<sup>242-244</sup> H5N8 virus replication was inefficient in experimentally infected dogs,

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which developed no clinical signs, while cats were more likely to become infected, and had mild and transient signs.<sup>242</sup> Black rats inoculated with an H5N8 virus did not seroconvert or shed virus.<sup>241</sup> Asian lineage H5N6 viruses have been isolated from apparently healthy pigs in China.<sup>39</sup>

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

A Eurasian lineage of H9N2 (LPAI) viruses is currently widespread among poultry in some areas, and has become very diverse, with numerous reassortants, including some that share internal genes with H5N1 viruses.<sup>195,245-249</sup> H9N2 viruses have been detected in wild birds including some terrestrial species.<sup>249-251</sup>

H9N2 viruses have been found occasionally in pigs, and might sometimes cause clinical signs in this species.<sup>193-196,252,253</sup> They have also been detected in farmed mink<sup>204,254</sup> and dogs,<sup>35,43</sup> and serological evidence of infection was found in cats near live bird markets in China,<sup>255</sup> as well as in performing macaques in Bangladesh, and wild plateau pikas in China.<sup>202,256</sup> Dogs and cats could be infected experimentally with some isolates, although virus replication was limited in some studies.<sup>257-259</sup> Experimental infections were also established in mink and pikas.<sup>202,204</sup> H9N2 variants may differ in their ability to replicate in mammals and/or cause disease.<sup>247,248,253</sup> In one study, experimentally infected pigs shed two H9N2 isolates that originated in poultry; however, an H9N2 isolate from wild birds did not appear to replicate in swine.<sup>253</sup>

## Host range of the zoonotic H7N9 avian influenza viruses

An H7N9 LPAI virus, which has recently caused serious human outbreaks in China, circulates there in poultry.<sup>14,15,260-264</sup> This virus acquired some of its genes from H9N2 viruses.<sup>261,265</sup> It has diversified considerably since its introduction, and regionally distinct lineages now exist.<sup>266</sup>

Among birds, infections have mainly been found in poultry (and in environmental samples from poultry markets, farms and similar sites), although this virus or its nucleic acids were also detected in two pigeons, an asymptomatic tree sparrow (*Passer montanus*), and wild waterfowl.<sup>264,267,268</sup> Whether wild birds play any role in spreading this virus is uncertain.<sup>264,268,269</sup> Experimental infections have been established in Japanese quail (*Coturnix coturnix japonica*), several species of ducks, Embden geese, pigeons, zebra finches (*Taeniopygia guttata*), society finches (*Lonchura striata domestica*), house sparrows (*Passer domesticus*), tree sparrows, parakeets (*Melopsittacus undulatus*) and jungle crows (*Corvus macrorhynchos*).<sup>241,270-272</sup> Pigeons and Pekin ducks were relatively resistant to infection, and while quail transmitted this virus efficiently to other birds, pigeons and Pekin ducks did not.<sup>270,272</sup> Some passerine birds and parakeets shed high titers in oropharyngeal secretions in one study.<sup>271</sup> Another group found that jungle crows shed

low titers of an H7N9 virus, but no virus was recovered from tree sparrows despite seroconversion.<sup>241</sup>

There have been no reports of illnesses in mammals, as of February 2016, and no evidence of H7N9 infections was found among stray dogs living near live poultry markets.<sup>35</sup> In experimental studies, isolates from humans could infect miniature pigs, ferrets, laboratory mice and cynomolgus macaques.<sup>273-275</sup> At present, there have been no reports of infected pigs in China,<sup>264</sup> and one serological survey reported little or no evidence of exposure in this species.<sup>276</sup> No virus was recovered from experimentally infected black rats, although they seroconverted.<sup>241</sup>

H7N7 LPAI viruses that resemble these H7N9 viruses in some of their genes have also been identified among poultry in China, and might have the potential to infect mammals.<sup>265</sup>

## **Other avian influenza viruses reported in mammals**

Infections caused by other avian influenza viruses are reported sporadically in mammals. In addition to Asian lineage H5 and Eurasian H9N2 viruses, diverse subtypes (e.g., H4, H5N2, H6N6, H7, H10N5 and H11N2) have been isolated occasionally from pigs, especially in Asia, and antibodies to avian H3 viruses have also been found.<sup>99,193-195,197-201,276,277</sup> While many infections with avian influenza viruses are transient, some established swine influenza viruses are wholly of avian origin or contain avian-origin gene segments.<sup>45,46,55,57,193,194,252</sup> (The Swine Influenza factsheet has additional information about these viruses.) One avian H3N8 virus affected horses in China for a short time, starting in 1989, but did not persist long term.<sup>278,279</sup> An H10N4 virus was responsible for an epidemic in farmed mink in Europe,<sup>31</sup> and experimental infections with H3N8, H4N6, H5N3, H7N7, H8N4 and H11N4 avian influenza viruses have been established in this species.<sup>1,31</sup>

Cats have been infected experimentally with some LPAI viruses (H1N9, H6N4, and H7N3) from waterfowl, as well as with an H7N7 HPAI virus isolated from a fatal human illness.<sup>280-282</sup> Serological evidence of infection with H10N8 viruses was reported in dogs,<sup>283</sup> an H6N1 virus was isolated from a dog coinfecting with canine distemper virus,<sup>38</sup> and dogs were infected experimentally with an H6N1 LPAI virus.<sup>284</sup> Domesticated guinea pigs in South America had antibodies to H5 influenza viruses.<sup>285</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>231,286,287</sup> Raccoons could be infected experimentally with an avian H4N8 virus,<sup>286</sup> striped skunks (*Mephitis mephitis*) with H4N6 and H3N8 viruses, and cottontail rabbits with an H4N6 virus.<sup>288,289; 290 cited in 288</sup> A number of influenza viruses (H3N3, H3N8, H7N7, H4N5, H4N6 and H10N7), closely related to avian viruses, have

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been isolated from seals.<sup>1,31,203,291-293</sup> Similarly, H1N3, H13N2 and H13N9 viruses, most likely of avian origin, have been isolated from whales.<sup>1,31</sup> Antibodies to various subtypes, some maintained only in birds, have also been detected in seals, and in some cases, in sea lions, walrus (*Odobenus rosmarus*) or porpoises.<sup>31,291,294-296</sup>

Laboratory mice (*Mus musculus*) and ferrets serve as models for mammalian infections with influenza viruses, including avian influenza viruses.<sup>297-305</sup> Most laboratory mice have a defective gene (Mx1), which increases their susceptibility to influenza viruses compared to their wild-type progenitors.<sup>306-308</sup> However, one recent study suggested that wild *Mus musculus* mice may also be susceptible to experimental inoculation with certain LPAI viruses.<sup>306</sup> Wild house mice at the site of an H5N8 avian influenza outbreak in poultry had serological evidence of infection with influenza A viruses (either avian or mammalian), but confirmatory testing and identification of the serotype could not be done due to the low sample volumes, and the virus could not be detected directly.<sup>306</sup> Some other studies have found no evidence for influenza viruses in wild mice.<sup>309-311</sup>

## Zoonotic potential

The two most commonly reported avian influenza viruses from human clinical cases have been the Asian lineage H5N1 HPAI viruses, and recently, H7N9 LPAI viruses in China.<sup>14,15,46,108,260-264,312</sup> There are currently no reported human infections caused by Asian lineage H5N8 viruses, although four infections with H5N6 viruses have been detected in China since 2014.<sup>16,313-315</sup> Illnesses caused by other subtypes have also been reported sporadically, with documented clinical cases caused by H9N2 (Eurasian lineage), H6N1 and multiple H7 and H10 avian influenza viruses.<sup>101,108,291,316-337</sup> Whether these infections are truly less common than subtypes such as H5N1 is unclear: viruses that tend to cause milder illnesses (e.g., H9N2 viruses) are less likely to be identified than those causing severe disease. Serological surveys in some highly exposed populations suggest the possibility of low level exposure to HA types found in birds, including H4, H5, H6, H7, H9, H10, H11 and H12.<sup>195,328,338-354</sup> Human volunteers were also infected with some subtypes (e.g., H4N8, H10N7 and H6N1), and sometimes developed mild respiratory signs and other influenza symptoms.<sup>328</sup> Adaptation to humans is possible, though rare, and some previous human pandemics were caused by partially or wholly avian viruses.<sup>1,44-46,48,49,355</sup>

## Geographic Distribution

LPAI viruses are cosmopolitan in wild birds, although the specific viruses differ between regions.<sup>1,7,93,96</sup> While LPAI viruses were also common among poultry at one time, control programs in developed nations now usually exclude these viruses from commercial, confinement-raised poultry.<sup>3</sup> Even where such control programs exist, LPAI viruses may be present in backyard flocks, live poultry markets and similar sources.<sup>3</sup> Eurasian lineage H9N2

viruses are currently widespread among poultry in parts of Asia and the Middle East.<sup>356-359</sup> They have been detected in wild birds in Europe, where they also caused a few outbreaks in poultry flocks, and were isolated from game birds.<sup>250,360,361</sup> The zoonotic H7N9 LPAI viruses causing outbreaks in mainland China have not been reported from other regions, with the exception of imported cases in travelers.<sup>14,15,362,363</sup>

HPAI viruses are eradicated from all domesticated birds, whenever possible, and developed countries are usually HPAI-free. Asian lineage H5N1 HPAI viruses are currently considered to be endemic among poultry in a few nations in Asia and the Middle East, with outbreaks occurring at times in other countries in the Eastern Hemisphere.<sup>12</sup> These H5N1 viruses can also be found in wild birds in Eurasia,<sup>27,143,145-148,150,226,227,364,365</sup> but have not been detected in the Americas, Australia or New Zealand, as of February 2016.<sup>27,80-86,366,367</sup> Asian lineage HPAI H5N8 viruses were widely reported in Asia and Europe in 2014, and reached North America (the Pacific Northwest region) in late 2014.<sup>157,220,221</sup> In North America, these viruses have reassorted with North American lineage viruses to generate unique viruses of other subtypes such as H5N1 and H5N2 (e.g., containing HA from the H5N8 virus and NA from a North American LPAI virus).<sup>157,221</sup> Whether the H5N8 viruses or any of these reassortants will persist in the Americas is still uncertain. Worldwide eradication of the Asian lineage H5 viruses is not expected in the near future.<sup>12,368</sup>

## Transmission

Avian influenza viruses are shed in the feces and respiratory secretions of birds, although the relative amount of virus can vary with the specific virus, host species and other factors.<sup>1,2,58,79,369,370</sup> The feces contain large amounts of virus in aquatic birds such as waterfowl, and the fecal-oral route is thought to predominate in wild bird reservoirs.<sup>7,150,371,372</sup> Fecal-cloacal transmission might also be possible, but respiratory transmission is ordinarily thought to play little or no role.<sup>7</sup> However, there are some exceptions. Some viruses that have adapted to gallinaceous poultry, such as recent isolates of Asian lineage H5N1 HPAI viruses, can be found in higher quantities in respiratory secretions than the feces, even in wild waterfowl.<sup>150,172,373,374</sup> There are also reports of a few LPAI viruses found mainly in respiratory swabs from wild waterfowl,<sup>375</sup> and respiratory spread might be important in some wild terrestrial birds.<sup>7,133</sup>

Once an avian influenza virus has entered a poultry flock, it can spread on the farm by both the fecal-oral route and aerosols, due to the close proximity of the birds. Fomites can be important in transmission, and flies may act as mechanical vectors.<sup>2,4,376,377</sup> The possibility of wind-borne transmission of HPAI viruses between farms was suggested by one study,<sup>378</sup> but has not been conclusively demonstrated. Avian influenza viruses have also been found

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in the yolk and albumen of eggs from chickens, turkeys and quail infected with HPAI viruses.<sup>379-385</sup> Although HPAI virus infected eggs are unlikely to hatch, broken eggs could transmit the virus to other chicks in the incubator. It might be possible for LPAI viruses to be shed in eggs, but the current evidence suggests this is very rare, if it occurs at all.<sup>379,386</sup>

How long birds remain contagious differs between avian species, and varies with the severity of the infection (chickens and turkeys infected with HPAI viruses die very soon after infection). Most chickens usually excrete LPAI viruses for a week, and a minority of the flock for up to 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>46,132,168,387-389</sup>

## **Transmission of avian influenza viruses to mammals**

People and other mammals are usually infected with avian influenza viruses during close contact with infected birds or their tissues, although indirect contact via fomites or other means is also thought to be possible.<sup>12,15,23,25,26,29,30,33,191,233,390-400</sup>

Respiratory transmission is likely to be an important route of exposure, and the eye may also act as an entry point.<sup>274,303,305,401,402</sup> A few H5N1 HPAI virus infections in animals, and rare cases in humans, have been linked to the ingestion of raw tissues from infected birds.<sup>22,23,25,26,29,30,33,233,393,398,399</sup> Housecats in an animal shelter might have become infected from contaminated avian feces, ingested while grooming.<sup>191</sup> Feeding experiments provide evidence that H5N1 viruses can enter the body by the oral route in cats, pigs, ferrets, mice, hamsters and foxes, and transmission has been confirmed in cats by direct inoculation of the virus into the gastrointestinal tract.<sup>22,30,233,235,236,398,403,404</sup> In humans, the strongest evidence for oral transmission is that two people became infected with an Asian lineage H5N1 virus after eating uncooked duck blood.<sup>398</sup> There are other human cases where ingestion probably occurred, but additional routes of exposure also existed.<sup>399</sup>

A ferret model suggested that some viruses might be transmitted to the fetus, when there is high viremia during systemic infections.<sup>405</sup> Viral antigens and nucleic acids were also found in the fetus of a woman who died of an Asian lineage H5N1 infection.<sup>406</sup> Transplacental transmission seems much less likely with influenza viruses that replicate only in the respiratory tract.

## **Host-to-host transmission of avian influenza viruses in mammals**

Infected animals and people shed avian influenza viruses in respiratory secretions. Fecal shedding has been reported occasionally, although its significance is still uncertain.<sup>407,408</sup> Some avian influenza viruses that have been detected in feces include Asian lineage H5N1 HPAI viruses in humans and experimentally infected cats and foxes; H7N9 viruses in humans; and Eurasian H9N2 viruses in

experimentally infected dogs.<sup>29,235-239,257,409-412</sup> Most studies used PCR, and the presence of live influenza viruses in feces was confirmed by virus isolation in only rare instances. The source of these viruses is still uncertain, and could be swallowed respiratory fluids, but Asian lineage HPAI H5N1 viruses seem to be able to replicate in human intestinal tissues.<sup>413</sup> There are also reports of Asian lineage H5N1 HPAI viruses in the urine of some mammals.<sup>31</sup>

Sustained transmission of avian influenza viruses is a rare event in mammals, but limited host-to-host transmission has caused clusters of infections or outbreaks in animals (e.g., outbreaks caused by H10N4 and H9N2 viruses in mink and an H3N8 virus in horses).<sup>1,31,193-195,199,291,292,414</sup> H9N2 viruses did not seem to spread readily between pigs in one experiment, although these animals did shed virus.<sup>253</sup> Animal-to-animal transmission of Asian lineage H5N1 HPAI viruses was reported between tigers in one outbreak at a zoo, and experimentally between cats.<sup>26,233,235</sup> However, asymptomatic, naturally infected cats appeared to excrete these viruses only sporadically, and there was no evidence that they transmitted them to other cats.<sup>191</sup> In another study, there was no evidence for H5N1 virus transmission between small numbers of experimentally infected dogs and cats.<sup>237</sup> One experiment indicated that H5N1 viruses did not spread between pigs,<sup>17</sup> but recent evidence from Indonesia suggested that limited pig-to-pig transmission occurred within naturally infected herds.<sup>415</sup> Experimentally infected dogs were able to transmit one Asian lineage H5N2 virus to dogs, chickens and cats.<sup>40-42</sup> In contrast, no dog-to-dog transmission was observed for an Asian lineage H5N8 virus, and little or no transmission occurred in experimentally infected cats despite virus shedding.<sup>242</sup>

While most infected people do not seem to transmit avian viruses to others, including family members,<sup>316-318,321</sup> Asian lineage H5N1 HPAI viruses are capable of person-to-person transmission in rare instances,<sup>394-397</sup> and one H7N7 HPAI virus was found in a few family members of poultry workers in the Netherlands.<sup>321,416</sup> Likewise, the H7N9 virus in China does not appear to spread readily between people, but human-to-human transmission was suspected in a few family clusters and one case of suspected nosocomial transmission in a hospital.<sup>15,362,391,392,417-423</sup> Close, unprotected contact, seems to be necessary to transmit any of these viruses.<sup>394-397,420,421</sup> Sometimes person-to-person transmission can be difficult to distinguish from exposure to a common source of the virus (e.g., on fomites).

Some authors have also speculated about the possibility of virus transmission between mammals and birds in wild ecosystems, based on evidence from Qinghai Lake, China, where H5N1 viruses related to those previously found in wild plateau pikas<sup>192</sup> were isolated from dead migratory birds in 2009-2010, although this clade had not been found in wild aquatic birds at this location in 2007.<sup>424</sup> However, there was no serological evidence of exposure to H5 viruses in a recent study of plateau pikas in this area, despite evidence of exposure to H9 viruses.<sup>202</sup>

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## *Survival of influenza viruses in the environment*

Fecal-oral transmission of avian influenza viruses in birds may be facilitated by prolonged survival in some environments. The persistence of these viruses can be influenced by many factors such as 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>387,425-439</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>387,388,425,426,428,430,432,434,435,439-442</sup> Some viruses may survive for several weeks to several months or more in distilled water or sterilized environmental water, especially under cold conditions.<sup>425,426,428-430</sup> However, the presence of natural microbial flora may considerably reduce their survival in water, and at some temperatures, viruses may remain viable for only a few days (or less, in some environments) to a few weeks.<sup>429-431,434,443</sup> Other physical, chemical or biological factors in natural aquatic environments may also influence persistence.<sup>429,430,442,443</sup> Freeze-thaw cycles might help inactivate influenza viruses in cold climates.<sup>433</sup>

In feces, some anecdotal field observations stated that LPAI viruses can survive for at least 44 or 105 days, but the conditions were not specified.<sup>425</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>388,432,434,436,440,441,444</sup> At 4°C (39°F), some viruses survived for at least 30-40 days in two studies,<sup>434,440</sup> but they remained viable for times ranging from less than 4 days to 13 days in two recent reports.<sup>432,441</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>388</sup> and for at least 2 weeks at 4°C if the relative humidity was low;<sup>432</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>445</sup> Survival was longer on feathers than other objects in two reports: at least 6 days at room temperature in one study,<sup>445</sup> and 15 days at 20°C (68°F) and 160 days at 4°C in another report.<sup>441</sup> Some viruses persisted for up to 13 days in soil (4°C),<sup>432</sup> for more than 50 days (20°C) or 6 months (4°C) in poultry meat (pH 7),<sup>427</sup> and for 15 days in allantoic fluid held at 37°C (99°F).<sup>438</sup> Exposure to direct sunlight greatly reduced virus survival.<sup>432</sup> Environmental sampling in Cambodia suggested that virus persistence 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>446</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>79,425,447-450</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>79,388,425,447,449</sup> A recent report suggested that influenza A viruses may differ in thermostability at 50°C, and that the zoonotic H7N9 viruses in China may be more stable than some other viruses at this temperature.<sup>451</sup>

## Infections in Animals

### Incubation Period

The incubation period in poultry can be a few hours to a few days in individual birds, and up to 2 weeks in the flock.<sup>2,3,79</sup> A 21-day incubation period, which takes into account the transmission dynamics of the virus, is used for an avian population in the context of disease control.<sup>2</sup> The incubation period for avian influenza viruses in mammals is also thought to be short, and might be as little as 1-2 days in some cases.<sup>403</sup>

## Clinical Signs

### *Low pathogenic avian influenza*

LPAI viruses usually cause subclinical infections or mild illnesses in poultry and other birds.<sup>2,180,264,270,271</sup> Decreased egg production, misshapen eggs, decreased fertility or hatchability of the eggs, respiratory signs (sneezing, coughing, ocular and nasal discharge, swollen infraorbital sinuses), lethargy, decreased feed and water consumption, or somewhat increased flock mortality rates may be seen in chickens and turkeys.<sup>2,3,70,383,452-460</sup> Illnesses exacerbated by factors such as concurrent infections or young age can be more severe.<sup>3,58,180,461</sup> Viruses with higher virulence might also exist. One unusual H10 virus isolated from waterfowl affected the kidneys and had a 50% mortality rate in some intranasally inoculated chickens.<sup>64</sup>

Some gallinaceous game birds (e.g., quail, pheasants, guinea fowl, partridges) infected with LPAI viruses have been asymptomatic, while others had clinical signs including lethargy, respiratory signs such as sinusitis, conjunctivitis, decreased egg production and diarrhea.<sup>461</sup> One study reported neurological signs and elevated mortality in guinea fowl (*Numida meleagris*) infected with an H7N1 virus.<sup>461</sup> High mortality has been seen in young ostriches in some outbreaks; however, a virus isolated from one outbreak caused only green diarrhea in experimentally infected young birds.<sup>183</sup> Domesticated waterfowl (e.g., ducks and geese) are often infected subclinically, although there may be mild signs such as sinusitis.<sup>3,180</sup>

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Wild birds infected with LPAI viruses usually have few or no obvious clinical signs,<sup>7,371</sup> even during some epidemics among young birds at breeding colonies.<sup>114,115,121; 116 cited in 115</sup> However, subtle effects (e.g., decreased weight gain, behavioral effects or transient increases in body temperature) have been described in some cases.<sup>84,462,463</sup>

The H9N2 viruses currently circulating among poultry in the Eastern Hemisphere appear to be relatively virulent, and may cause significant respiratory signs and malaise in chickens, including experimentally infected birds that are not co-infected with other pathogens.<sup>464,465</sup> Both broilers and layers can be affected by these viruses.<sup>359,464,465</sup> Although quail are usually mildly affected by most other LPAI viruses, clinical signs were reported in some H9N2 outbreaks and in experimentally infected birds.<sup>359,464,466</sup> One H9N2 virus caused severe clinical signs in experimentally infected quail, and mild signs in jungle fowl, while house sparrows developed respiratory signs, and crows (*Corvus splendens*) had mild or no signs.<sup>464</sup> The zoonotic H7N9 LPAI viruses in China have caused only mild or asymptomatic infections in poultry and experimentally infected birds including poultry, jungle crows, parakeets and most songbirds.<sup>241,264,267,270,271</sup> A house sparrow became ill with lethargy and loose droppings and died during one experiment, and one zebra finch died without clinical signs, but these deaths might not have been caused by the virus.

## HPAI viruses in birds

HPAI viruses usually cause severe illness in chickens and turkeys, and few birds in infected flocks typically survive.<sup>1,2,165</sup> Marked depression, decreased feed and water intake, and other systemic, respiratory and/or neurological signs are often seen, but no signs are pathognomonic, and sudden death can also occur.<sup>2-4,10,58,79,165,166,170,383,467-470</sup> Commonly reported signs include coughing, sneezing, sinusitis, blood-tinged oral and nasal discharges, ecchymoses on the shanks and feet, edema and cyanosis of the unfeathered skin on the head, comb and wattle (and snood in turkeys), and diarrhea. Egg production decreases or stops, and depigmented, deformed and shell-less eggs may be produced. Because a virus can be defined as highly pathogenic based on its genetic composition alone, HPAI viruses may rarely be found in chicken or turkey flocks that have mild signs consistent with low pathogenic avian influenza.<sup>58,67</sup>

HPAI virus infections can be asymptomatic, mild or severe in other birds, including gallinaceous birds other than chickens and turkeys.<sup>1,2,7,27,32,58,79,127,140,142,144,145, 147,149,150,152,153,165-168,180,183,187-189</sup> Nonspecific clinical signs (e.g., anorexia, lethargy), neurological signs, diarrhea and sudden death have been reported in gallinaceous game birds, but milder or minimal signs were seen in some flocks.<sup>166-168,461</sup> Domesticated waterfowl tend to be mildly affected, but respiratory signs (e.g., sinusitis), diarrhea, corneal opacity, occasional cases with neurological signs, and increased mortality may be seen, and some Asian

lineage H5N1 HPAI viruses can cause severe acute disease with neurological signs and high mortality rates.<sup>2,79,146,147,149-151,172,173,471-473</sup> Pigeons are also thought to be relatively resistant to illness, although there have been reports of sporadic deaths and rare outbreaks, with clinical signs that included neurological signs, greenish diarrhea and sudden death.<sup>10,132,474</sup> Some pigeons that were experimentally infected with H5N1 viruses remained asymptomatic, while others became moderately to severely ill.<sup>10,132,474</sup>

There is limited information about avian influenza viruses in ostriches, but HPAI viruses may not necessarily be more pathogenic than LPAI viruses in this species.<sup>183,185-189</sup> The clinical signs tend to be mild in adult ostriches, and more severe in young birds less than 6 months of age, which can develop nonspecific signs (e.g., depression), dyspnea; green urine, diarrhea or hemorrhagic diarrhea, with increased mortality.<sup>183,188-190</sup> Elevated mortality reported in some outbreaks in ostriches, pigeons and other relatively resistant birds might be caused by concurrent infections and other complications.<sup>188,474</sup>

Studies in experimentally infected wild birds, and observations in captive and free-living wild birds, suggest that some species can be severely affected by Asian lineage H5N1 HPAI viruses, while others may have much milder signs or shed viruses asymptotically.<sup>32,127,144,145,147,149-153,173,228,241,475-477</sup> During one H5N1 outbreak at a wildlife rescue center, some birds died without preceding clinical signs, while others developed anorexia, extreme lethargy, dark green diarrhea, respiratory distress and/or neurological signs, with death often occurring within 1-2 days.<sup>32</sup> Some species at the facility did not seem to be affected. Neurological signs, varying from mild to severe, have been documented in a number of experimentally infected wild birds including some species of ducks, geese, gulls, house finches, jungle crows and budgerigars, as well as in naturally or experimentally infected raptors.<sup>149,152,173,228,241,478-483</sup> Respiratory and nonspecific signs were reported in experimentally infected common reed buntings (*Emberiza schoeniclus*).<sup>484</sup> Other experimentally infected birds, such as zebra finches, tree sparrows and brown-eared bulbuls (*Hypsipetes amaurotis*), had high mortality rates, but only nonspecific signs of depression and anorexia, or sudden death.<sup>152,241</sup> Starlings, pale thrushes (*Turdus pallidus*) and some species of ducks were mildly affected or unaffected, while house sparrows developed severe clinical signs in one study, and remained asymptomatic in another.<sup>149,152,153,484</sup>

Asian lineage H5N8 viruses have also been associated with wild bird die-offs in some countries, and these viruses and/or their reassortants have been detected in wild birds including sick, dead and apparently healthy waterfowl, and sick or dead birds in several other orders including raptors.<sup>138,139,158,161-163,221,223,485</sup> In some cases, the virus appeared to have affected the brain and the kidneys.<sup>138</sup> Experimental infections with one H5N8 isolate were asymptomatic in mallards, and either fatal or asymptomatic



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in Baikal teal (*Anas formosa*)<sup>486</sup> One of four experimentally infected tree sparrows and 2 of 4 jungle crows also died, but the remaining birds had no clinical signs although they sometimes shed virus.<sup>241</sup> Pigeons near an outbreak in North America did not have antibodies to H5 viruses, and most experimentally infected pigeons had limited susceptibility to this virus.<sup>487</sup> Individual variability was also noted in this study, with the virus replicating more readily in one bird.

Information about the effects of other HPAI viruses on wild birds is limited. Wild waterfowl infected with most viruses seem to be resistant to clinical signs,<sup>10,141,150</sup> but an H5N3 HPAI virus caused high mortality among South African terns in the 1960s.<sup>140,142</sup> A wild siskin naturally infected with an H7N1 HPAI virus was ill, and the same virus caused conjunctivitis, apathy and anorexia, with a high mortality rate, in captive canaries (*Serinus canarius*) that had been exposed to this bird.<sup>142</sup>

## **Mammals infected with Asian lineage H5N1 viruses**

Asian lineage H5N1 HPAI viruses have caused fatal disease, as well as milder illnesses or asymptomatic infections, in mammals. A few clinical cases have been described, at most, in each species. Both symptomatic and subclinical infections have been reported in felids. One cat had a fever, depression, dyspnea, convulsions and ataxia, and a few infected housecats were found dead.<sup>24,25,29</sup> One of the latter cats was apparently well up to 24 hours before its death. Fatal illnesses with conjunctivitis and severe respiratory signs were described in experimentally infected cats.<sup>233,235,237,403,488</sup> Asymptomatic infections were reported in housecats in an animal shelter that had been accidentally exposed to a sick, H5N1-infected swan.<sup>191</sup> Some captive tigers and leopards died with clinical signs of respiratory distress, serosanguineous nasal discharge, high fever and neurological signs.<sup>22,23,26,31,37</sup> In another outbreak, captive lions, tigers, leopards and Asiatic golden cats were lethargic and had decreased appetites (without respiratory signs) for 5-7 days, but recovered.<sup>32</sup>

A dog that had eaten infected poultry developed a high fever, with panting and lethargy, and died the following day.<sup>30</sup> However, serological and virological evidence of infection has also been found in stray dogs in China during routine surveillance.<sup>35</sup> Most experimentally infected dogs remained asymptomatic or had relatively mild signs such as fever (which was transient in some studies), anorexia, conjunctivitis and/or diarrhea.<sup>34,237,238</sup> More severe respiratory signs (cough, labored breathing), with one fatal infection, were reported only in dogs inoculated directly into the trachea.<sup>34</sup> A study that infected both dogs and cats found that the cats were more susceptible and developed severe clinical signs, while dogs were likely to have few or no signs despite shedding virus.<sup>488</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 (e.g., mild

respiratory disease and anorexia).<sup>17,36,229,236,415</sup> Fever, respiratory and/or neurological signs, as well as sudden death, have been reported in a handful of cases in other species.<sup>20,31,33</sup> One H5N1 virus was isolated from donkeys during a respiratory disease outbreak in Egypt, and a subsequent investigation detected antibodies to these viruses in healthy donkeys and horses in that country.<sup>20,229</sup> The role of the H5N1 virus in this outbreak was unclear, as the affected donkeys responded well to antibiotics. Fatal respiratory disease, possibly with diarrhea, was reported in H5N1 virus-infected raccoon dogs, while captive palm civets had neurological signs, with evidence of interstitial pneumonia, encephalitis and hepatitis at necropsy, and a wild stone marten was found with neurological signs.<sup>31,33</sup>

## **Mammals infected with other Asian lineage H5 viruses**

Respiratory signs were seen in a dog infected with an Asian lineage H5N2 HPAI virus in China, and this virus caused mild respiratory signs in experimentally infected dogs.<sup>40,42</sup> One cat exposed to these dogs developed respiratory signs and conjunctivitis, but four other cats seroconverted without clinical signs.<sup>41</sup> One study reported no clinical signs and inefficient virus replication in dogs inoculated with an Asian lineage H5N8 virus, while cats had mild and transient signs, including fever and marginal weight loss.<sup>242</sup>

## **Mammals infected with other subtypes**

Infections with influenza A viruses, apparently of avian origin, have been associated with outbreaks of pneumonia or mass mortality in seals.<sup>1,101,203,489,490</sup> The clinical signs in some outbreaks included weakness, incoordination, dyspnea and subcutaneous emphysema of the neck.<sup>31,291,489</sup> A white or bloody nasal discharge was seen in some animals. Experimental infections with these viruses were milder or asymptomatic, suggesting that co-infections may have increased the severity of the illness.<sup>31</sup> An influenza virus was also isolated from a diseased pilot whale, which had nonspecific signs including extreme emaciation, difficulty maneuvering and sloughing skin.<sup>489</sup> Whether this virus was the cause of the disease or an incidental finding is uncertain.<sup>414</sup> Other viruses were isolated from whales that had been hunted, and were not linked with illness.<sup>491</sup>

There are only a few reports of naturally acquired or experimental infections in other mammals, except in animal models for human disease (ferrets and mice). An H10N4 virus caused respiratory signs (sneezing, coughing, and nasal and ocular discharges) and elevated mortality in mink during an outbreak in Europe.<sup>1,31</sup> An H9N2 virus outbreak among mink in China was characterized by mild respiratory signs, with no reported deaths.<sup>204</sup> One group isolated 13 H9N2 viruses from sick and healthy dogs in a study from China.<sup>43</sup> Some of these dogs had clinical signs that could be consistent with influenza virus infections, but other infected dogs had signs likely to be unrelated.<sup>43</sup> Dogs inoculated with an H9N2 virus developed clinical signs, including

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coughing, sneezing and nasal discharge, in one study,<sup>257</sup> but they remained asymptomatic or had only a mild fever in two other reports.<sup>258,259</sup> Experimentally infected cats did not become ill.<sup>258</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>280,281,286</sup>

No natural infections with the zoonotic H7N9 LPAI viruses in China have been reported, as of February 2016, and experimental inoculation of this virus resulted in fever alone in cynomolgus macaques and asymptomatic infections in miniature pigs.<sup>273</sup>

## Post Mortem Lesions [Click to view images](#)

### *Low pathogenic avian influenza in birds*

Poultry infected with LPAI viruses may exhibit rhinitis, sinusitis, congestion and inflammation in the trachea, but lower respiratory tract lesions such as pneumonia usually occur only in birds with secondary bacterial infections.<sup>2,3</sup> Lesions (e.g., hemorrhagic ovary, involuted and degenerated ova) may also be observed in the reproductive tract of laying hens, and the presence of yolk in the abdominal cavity can cause air sacculitis and peritonitis.<sup>2</sup> A small number of birds may have signs of acute renal failure and visceral urate deposition.<sup>3</sup>

### *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>471,492</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>2,3,492</sup> There may also be other abnormalities, including hemorrhages and/or congestion in various internal organs including the lungs, as well as severe airsacculitis and peritonitis (caused by yolk from ruptured ova).<sup>2</sup> However, the gross lesions in some outbreaks may not fit the classical pattern,<sup>492</sup> and birds that die peracutely may have few or no lesions.<sup>2,3,492</sup>

Variable lesions have also been reported in other gallinaceous birds.<sup>461</sup> Necrotic lesions in the pancreas (multiple foci of parenchymal discoloration) are common in quail and partridges infected with some HPAI viruses.<sup>461</sup> There may also be splenomegaly with parenchymal mottling, renal lesions, hemorrhages in internal organs and skeletal muscles, and pulmonary lesions (consolidation, edema, congestion and hemorrhages). However, some lesions seen in chickens and turkeys, such as cyanosis and hemorrhagic lesions in unfeathered skin, may not be as prominent in other gallinaceous birds.

In ostriches infected with avian influenza viruses, the gross lesions are usually hepatitis and peritonitis, with other secondary lesions.<sup>188</sup> Petechial hemorrhages, pancreatic

lesions (e.g., multifocal hemorrhagic necrosis), pulmonary congestion and edema, and additional gross lesions have been reported in other species of birds infected with HPAI viruses.<sup>145,149,152,228,493</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 consolidation and/or edema, pneumonia; hemorrhagic lesions in various internal organs; and in some cases, other lesions such as multifocal hepatic necrosis, hemorrhagic pancreatitis, or cerebral, renal and splenic congestion.<sup>23-25,29,233,235,403</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>30</sup> Pulmonary lesions including interstitial pneumonia have been noted in some experimentally infected pigs,<sup>17</sup> while others had mild to minimal gross lesions.<sup>236</sup>

## Diagnostic Tests

Avian influenza viruses can be detected in oropharyngeal, tracheal and/or cloacal swabs from live birds, with differing recovery rates from each site depending on the virus, species of bird and other factors.<sup>58,370</sup> Very small (pediatric) swabs can be valuable in small birds, but feces can be substituted if cloacal samples are not practical (e.g., cannot be collected without harming the bird).<sup>58</sup> A recent study, which examined experimentally infected birds, suggested that immature feathers may also be a useful sample.<sup>494</sup> Samples from internal organs (e.g., trachea, lungs, air sacs, intestine, spleen, kidney, brain, liver and heart) are also tested in dead birds suspected of having HPAI.<sup>2,58</sup> Diagnostic tests should be validated for the species of bird, and some tests that are useful in chickens and turkeys may be less reliable in other avian species.<sup>58,132,185</sup>

Virus isolation can be performed in all species, and can be useful for virus characterization. Avian influenza viruses are isolated in embryonated eggs, and can be identified as influenza A viruses with agar gel immunodiffusion (AGID), antigen-detection ELISAs or other immunoassays, or by a molecular test such as RT-PCR.<sup>3,58</sup> They can be subtyped with specific antisera in hemagglutination and neuraminidase inhibition tests, by RT-PCR, or by sequence analysis of the viral HA and NA genes.<sup>58</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>2,58</sup>

RT-PCR assays can detect influenza viruses directly in clinical samples, and real-time RT-PCR is the diagnostic method of choice in many laboratories.<sup>2,58,495</sup> Viral antigens can be detected with ELISAs including rapid tests.<sup>58,495</sup> Currently, the World Organization for Animal Health (OIE)

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recommends that antigen detection tests be used to identify avian influenza only in flocks and not in individual birds.<sup>58</sup>

Serology can be valuable for surveillance and demonstrating freedom from infection, but it is not very useful in diagnosing HPAI infections in highly susceptible birds, as they usually die before developing antibodies.<sup>58</sup> Serological tests used in poultry include AGID, hemagglutination inhibition (HI) and ELISAs.<sup>58</sup> AGID tests and ELISAs to detect conserved influenza virus proteins can recognize all avian influenza subtypes, but HI tests are subtype specific and may miss some infections. Cross-reactivity between influenza viruses can be an issue in serological tests. Tests that can distinguish infected from vaccinated birds (DIVA tests) should be used in surveillance when vaccination is part of a control program.<sup>58,72,496</sup>

## Mammals

Tests such as RT-PCR and virus isolation have been used to diagnose clinical cases in mammals, and serological tests have been employed in surveillance. Some animals infected with avian influenza viruses may fail to develop antibodies to the viral HA, despite having antibodies to other viral proteins (e.g., the viral nucleoprotein).<sup>38,497</sup>

## Treatment

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

## Control

### Disease reporting

A quick response is vital for containing avian influenza outbreaks, and in some cases, for minimizing the risk of zoonotic transmission. In addition to national notification requirements, HPAI viruses and LPAI viruses that contain H5 or H7 must be reported to the OIE by member nations.<sup>498</sup> Veterinarians who encounter or suspect a reportable disease should follow their country-specific guidelines for informing the proper authorities (state or federal veterinary authorities in the U.S. for diseases in animals). Unusual mortality among wild birds should also be reported (e.g., to state, tribal or federal natural resource agencies in the U.S.<sup>499</sup>)

### Prevention

The risk of introducing a virus to poultry or other birds can be reduced by good biosecurity and hygiene, which includes preventing any contact with other domesticated or wild birds, mechanical vectors and fomites including water sources.<sup>4,5,46,79,471</sup> All-in/ all-out flock management is helpful in poultry flocks, and birds should not be returned to the farm from live bird markets or other slaughter channels.<sup>4</sup> To help prevent reassortment between human

and avian influenza viruses, people are encouraged to avoid contact with birds while suffering flu symptoms.<sup>45</sup>

Avian influenza vaccines include both traditional inactivated whole virus vaccines and newer recombinant vectored vaccines.<sup>500-502</sup> Most vaccines are produced for chickens, although they may be validated for use in turkeys, and their effectiveness can differ in other species.<sup>168,503</sup> In addition to suppressing clinical signs, some vaccines are capable of increasing resistance to infection, and decreasing virus excretion and transmission.<sup>146,168,177,178,369,504-514</sup> However, clinical protection is not necessarily correlated with reduced virus shedding, and some birds can become infected even in the best-case scenario.<sup>179,515-517</sup> Thus, vaccination can mask infections if good surveillance programs are not used simultaneously.<sup>2,507,518,519</sup> Vaccination can also place selection pressures on influenza viruses, which may encourage the emergence of vaccine-resistant isolates.<sup>515,517,520,521</sup> In different countries, vaccines may either be used routinely to protect poultry flocks, as an adjunct control measure during an outbreak, or to protect valuable species such as zoo birds from highly virulent viruses such as H5N1.<sup>58,291,518</sup> Vaccination in the U.S. is restricted and requires the approval of the state veterinarian, and in the case of H5 and H7 vaccines, USDA approval.

During outbreaks, HPAI viruses are normally eradicated by depopulation of infected flocks, combined with other measures such as movement controls, quarantines and perhaps vaccination.<sup>471</sup> Insect and rodent control, disposal of contaminated material, and thorough cleaning and disinfection are also important.

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

## Morbidity and Mortality

### Birds

Exposure to influenza viruses and shedding patterns among wild birds are complex and likely to reflect their exposure to different habitats, as well as gregariousness and other social factors, and pre-existing immunity.<sup>9,113</sup> Reported infection rates with LPAI viruses range from <1% to more than 40%, and seroprevalence rates from <1% to greater than 95%, typically with much higher rates in birds from aquatic environments than terrestrial species.<sup>8,9,84,89,110-113,115,119,128,129,134,135,522-525</sup> Some studies have reported that infection rates are higher in young birds than adults (e.g., young egrets and herons at breeding colonies or young ducks).<sup>84,110,114-116</sup> LPAI virus prevalence can also be higher during certain seasons, such as in late summer staging areas before migration, when bird densities are high and young “hatch year” birds have not yet developed immunity.<sup>526</sup> Currently, surveillance suggests that carriage of H5N1 HPAI viruses in wild bird populations without unusual mortality events is rare.<sup>227,364</sup>

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The prevalence of influenza viruses in poultry differs between nations, but commercial, confinement-raised poultry in developed countries are usually free of both LPAI and HPAI viruses.<sup>3</sup> Even in these regions, LPAI viruses may be present in backyard flocks, live poultry markets and similar sources.<sup>3</sup> HPAI outbreaks are uncommon under ordinary conditions, while LPAI outbreaks tend to occur more often. However, the continued presence of Asian lineage H5 HPAI viruses in poultry elevates the risk of outbreaks throughout the world. These H5N1 viruses tend to reemerge during colder seasons in endemic areas.<sup>527,528</sup>

Avian influenza differs in severity, depending on the species of bird as well as the virus. LPAI viruses usually cause mild illnesses or asymptomatic infections in birds, including chickens and ducks, but outbreaks can be more severe when there are concurrent infections or other exacerbating factors.<sup>2,58,180</sup> High mortality is occasionally seen in young ostriches infected with either LPAI or HPAI viruses, although adult birds seem to be only mildly affected by both.<sup>10,183,185-189</sup>

HPAI viruses usually cause high and rapidly escalating mortality in chicken and turkey flocks, with cumulative morbidity and mortality rates that may approach 90-100%.<sup>2,12</sup> Some reports suggest that Asian lineage H5N8 viruses might spread somewhat more slowly through chicken flocks than H5N1 viruses, and that the clinical presentation may be somewhat less severe.<sup>529,530</sup> Any birds that survive an HPAI outbreak are usually in poor condition and do not begin laying again for several weeks. Morbidity and mortality rates can sometimes approach 100% in other domesticated and wild birds, as well; however, susceptibility varies greatly, and certain species such as waterfowl tend not to be severely affected.<sup>32,132,149,152,153,165-171,175,461,484</sup> Some Asian lineage H5N1 viruses cause severe illness even in waterfowl, and the introduction of these viruses may be heralded by unusual deaths among wild birds (e.g., swans in Europe and recently crows in Pakistan).<sup>1,32,46,144,145,147,150,154,364,365,471</sup> Thousands of wild birds were killed in some outbreaks, such as one at Qinghai Lake, China in 2005.<sup>531</sup> Wild bird deaths have also been associated with some Asian lineage H5 reassortants, such as H5N8 viruses, in Asia.<sup>138,139,158,161-163,221,223,485</sup>

## Mammals

Pigs seem to be infected fairly regularly by avian influenza viruses from birds, often with only minor consequences even when the virus belongs to the Asian lineage of H5N1 HPAI viruses.<sup>1,5,17,19,36,39,46,99,151,193-195,197-201,253,415</sup> Low levels of exposure have been reported for H5N1, H9N2 and other subtypes in some endemic areas, with seroprevalence to these viruses typically ranging from < 1% to 5% and occasionally higher, and virus detection rates of <1% to 7.5% in pigs during H5N1 outbreaks among poultry.<sup>17,36,99,193-195,197-201,229,276,277,415,532</sup> Some studies reporting higher seroprevalence to H5N1 viruses examined

pigs in poor neighborhoods where they are fed dead bird carcasses and other organic remains, and in one Egyptian study, 8 of 11 positive samples came from a single herd.<sup>36</sup>

H5N1 HPAI virus infections reported in housecats and large zoo felids ranged from asymptomatic to fatal, while experimentally infected cats exhibited severe disease with high mortality.<sup>23-26,29,31,32,37,191,233,235,488</sup> No seropositive cats were found in parts of Austria and Germany where these viruses had been found in wild birds, but low titers were detected in 8% of 25 cats in Egypt, and 73% of 11 cats in an unpublished study from Thailand.<sup>18,229,533</sup> Recently, a survey of more than 900 healthy cats in northeastern China reported that approximately 2% had antibodies to H5N1 viruses, using the HI test, but no sera reacted in a confirmatory microneutralization assay.<sup>534</sup> Another large survey, which examined 700 stray cats, found that a very small number of sera (3 cats) reacted to H5N1 viruses in both serological assays, and larger numbers of cats (18) had antibodies to H9N2 viruses.<sup>255</sup>

Several avian influenza viruses have been reported in dogs, although in some cases, there may be little information about the consequences of infection. While there is one report of a fatal H5N1 HPAI case in a dog, experimental infections have been mild or symptomatic in this species, except when the inoculation method bypassed normal upper respiratory defense mechanisms.<sup>30,34,237,238,488</sup> Surveys reported antibodies to H5N1 viruses in 25% of dogs during outbreaks in Thailand, 4% of 25 dogs in Egypt (low titers), and 1% of stray dogs in live markets and on poultry farms in China, with virological confirmation of infection from 2 dogs in China by PCR.<sup>18,35,229</sup> Eurasian lineage H9N2 viruses have also been isolated from dogs,<sup>43</sup> and surveys in China reported seroprevalence rates to these viruses that ranged from <5% (with evidence of infection in 0.4% of dogs by RT-PCR) to 20-45% in various canine populations.<sup>35,43</sup> There is also serological evidence of exposure to H10N8 viruses in few feral dogs living near poultry markets, but whether this virus causes illness in dogs is not known.<sup>283</sup>

The effects of Asian lineage H5N1 HPAI viruses on equids are still uncertain, but surveys from Egypt reported that approximately 25% of donkeys and horses were seropositive.<sup>20,229</sup> Fatal infections with these viruses have been reported occasionally in other species such as raccoon dogs, palm civets and mink, but little more is known.<sup>27,28,31,33</sup> Other avian influenza viruses have caused outbreaks in mink. In 1984, an H10N4 virus affected 33 mink farms in Sweden, with a morbidity rate of nearly 100% and mortality rate of 3%.<sup>1,31</sup> However, an H9N2 outbreak among mink in China was reported to be mild, with no elevated mortality.<sup>204</sup> Mink on some other Chinese farms also had antibodies to H9N2 viruses.<sup>204,254</sup> The severity of influenza in mink is thought to be influenced by co-infections and other factors.<sup>1,31,100,104,535,536</sup>

## Infections in Humans

### Incubation Period

Most zoonotic infections caused by Asian lineage H5N1 HPAI viruses seem to become apparent within approximately 5 days, although the incubation period for some cases may be as long as 8 and possibly 17 days.<sup>205,209</sup> Estimates of the mean incubation period for the zoonotic H7N9 viruses have varied from 3 days (in two analyses, which considered large numbers of cases) to 5-6 days, with a range of 1-13 days.<sup>391,418,419,537,538</sup>

### Clinical Signs

#### Asian lineage H5N1 HPAI viruses

Most infections with Asian lineage H5N1 HPAI viruses have been severe.<sup>12,108,328</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>205,209,539</sup> Respiratory signs are not always present at diagnosis; two patients from Vietnam had acute encephalitis without symptoms to indicate respiratory involvement.<sup>540</sup> Similarly, a patient from Thailand initially exhibited only fever and diarrhea.<sup>540</sup> Lower respiratory signs (e.g., chest pain, dyspnea, tachypnea) often develop soon after the onset of the illness.<sup>205,209</sup> Respiratory secretions and sputum are sometimes blood-tinged.<sup>205</sup> Most patients deteriorate rapidly, and serious complications including heart failure, kidney disease, encephalitis and multiorgan dysfunction are common in the later stages.<sup>205,209,539</sup> Milder cases have been reported occasionally, particularly among children.<sup>328,541</sup>

#### Other Asian lineage H5 HPAI viruses

Three infections with Asian lineage H5N6 HPAI viruses in older adults were serious, with fever and severe respiratory signs in at least two patients.<sup>313-315</sup> One of these two cases was fatal; the other patient required mechanical ventilation, but recovered after treatment with oseltamivir and antibiotics (details of the third case have not been published).<sup>314,315</sup> A child infected with an H5N6 virus had a mild illness with prompt recovery.<sup>313-315</sup>

#### Eurasian lineage H9N2 LPAI viruses

Most illnesses caused by H9N2 viruses have been reported in children and infants.<sup>108,328-334</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>108,328-334</sup> All of these patients, including a 3-month-old infant with acute lymphoblastic lymphoma,<sup>334</sup> made an uneventful recovery. Acute, influenza-like upper respiratory signs were also reported in two adults, a 35-year-old woman and a 75-year-old man.<sup>330</sup> Severe lower respiratory disease, which developed into respiratory failure, was seen in a 47-year-old woman, who

had chronic graft vs. host disease and bronchiolitis obliterans after a bone marrow transplant, and was receiving immunosuppressive therapy.<sup>334</sup> She survived after treatment with antiviral drugs, antibiotics for pneumonia, and supportive care, but required long-term oxygen supplementation on discharge.

#### Zoonotic H7N9 LPAI viruses in China, 2013-2016

Most clinical cases caused by H7N9 viruses in China have been serious, to date.<sup>14,15,260,411,542,543</sup> The most common symptoms were fever and coughing, but a significant number of patients also had dyspnea and/or hemoptysis, and severe pneumonia (frequently complicated by acute respiratory distress syndrome and multiorgan dysfunction) developed in most laboratory-confirmed cases.<sup>412,537,544</sup> A minority of patients had diarrhea and vomiting, but nasal congestion and rhinorrhea were not common initial signs.<sup>537,545</sup> Conjunctivitis (which is a common sign with some other avian influenza viruses) and encephalitis were uncommon.<sup>545</sup> In most cases, patients deteriorated rapidly after the initial signs.<sup>537,545</sup> Concurrent bacterial infections were identified in some patients, and may have contributed to the clinical picture.<sup>412,537</sup>

A few uncomplicated cases were characterized by mild upper respiratory signs or fever alone, especially in children.<sup>260,418,537,543,545,546</sup> At least one asymptomatic infection has been reported in an adult,<sup>411,537</sup> and serological studies in poultry workers suggest the possibility of additional mild or asymptomatic cases.<sup>354,547-550</sup>

#### Other avian influenza viruses

Mild illnesses, with conjunctivitis and/or upper respiratory signs, have been reported in a number of people infected with various H7 LPAI or HPAI viruses and an H10N7 virus.<sup>101,291,319-327,336</sup> One H7N7 HPAI virus, which caused only mild symptoms in most people, resulted in fatal acute respiratory distress syndrome and other complications in one otherwise healthy person.<sup>321</sup> His initial symptoms included a persistent high fever and headache, but no signs of respiratory disease. The virus isolated from this case had accumulated a significant number of mutations, while viruses from most other infected individuals had not, and it also caused severe illness in experimentally infected ferrets and mice.<sup>305,321</sup> Severe illness (pneumonia) was also reported in a person infected with an LPAI H7N2 virus; however, he had serious underlying medical conditions, including HIV infection and infection with *Mycobacterium avium* complex.<sup>318</sup> This patient was hospitalized but recovered without antiviral treatment. A 20-year-old woman infected with an H6N1 virus in China developed a persistent high fever and cough, progressing to shortness of breath, with radiological evidence of lower respiratory tract disease.<sup>317</sup> She made an uneventful recovery after treatment with oseltamivir and antibiotics. Severe lower respiratory tract disease, progressing in some cases to multiple organ failure and septic shock, was reported in three people with H10N8 infections in China.<sup>316,335</sup> Two cases were fatal, one

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in a 73-year-old patient who had underlying health conditions, and another in a 75-year old. The third patient, who was 55 years of age, recovered after mechanical ventilation and treatment with various drugs including oseltamivir. The other two patients also received oseltamivir.

## Diagnostic Tests

Avian influenza viruses may be detected in samples from the upper and/or lower respiratory tract, depending on the site of the infection.<sup>12,209,264</sup> RT-PCR is usually the primary test for Asian lineage H5N1 HPAI viruses.<sup>209</sup> RT-PCR assays have also been published for the H7N9 influenza viruses causing outbreaks in China.<sup>418,551,552</sup> Virus isolation can be performed, but it is slower.<sup>553,554</sup> Antiviral resistance can be evaluated with phenotypic tests or gene-based testing to detect molecular markers of resistance, but these tests are available in a limited number of laboratories, and take several days to perform.<sup>554</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>12,209</sup>

During routine influenza diagnosis, testing that identifies the presence of influenza A, but does not detect the hemagglutinins in common human influenza viruses, might indicate a novel, possibly zoonotic, virus.<sup>12</sup> Commercial rapid diagnostic test kits used for seasonal human influenza virus infections may not detect avian influenza viruses.<sup>12,553-558</sup>

Serology is used for epidemiological studies, and occasionally for retrospective diagnosis of a case.<sup>390</sup> The microneutralization assay is considered to be the most reliable test for detecting antibodies to avian influenza viruses in humans,<sup>209,328</sup> although other serological tests (e.g. hemagglutination inhibition) have also been used.<sup>554,559</sup> No seroconversion occurred with some avian influenza viruses, even in virologically confirmed cases.<sup>324,327</sup> Seroconversion might also vary with the severity of the illness (and the test): although adults with severe illnesses caused by the H7N9 virus in China seroconverted, titers were low or absent in a few mild cases in children.<sup>560</sup>

## Treatment

Treatment for avian influenza may vary, depending on the severity of the case. In addition to symptomatic treatment, it can include various drugs, including antibiotics to treat or prevent secondary bacterial pneumonia, and antivirals.<sup>561,562</sup> Two groups of antiviral drugs – the adamantanes (amantadine, rimantadine), and neuraminidase inhibitors (zanamivir, oseltamivir, peramivir and laninamivir) – are effective against some influenza A viruses, but some of these drugs (peramivir and laninamivir) are not licensed in all countries.<sup>78,448,553,558,563-566</sup> Side effects including gastrointestinal and CNS effects are possible, particularly with some drugs.<sup>553,558</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>448,553,558,563-566</sup> Oseltamivir, which is the most widely used antiviral drug, appears to increase the chance of survival in patients infected with Asian lineage H5N1 and H7N9 viruses, particularly if it is given early.<sup>209,539,540,567,568</sup>

Antiviral resistance can develop rapidly in influenza viruses, and may even emerge during treatment.<sup>1,78,558,569</sup> At present, Asian lineage H5N1 HPAI viruses are usually sensitive to oseltamivir, and they are often (though not always) resistant to adamantanes.<sup>12,209,527,570</sup> Although resistance to zanamivir and oseltamivir has been reported, it is currently uncommon.<sup>12,209,527,570</sup> Likewise, the H7N9 LPAI viruses are often sensitive to oseltamivir, and all of the H7N9 isolates from humans have contained a mutation suggesting resistance to adamantanes.<sup>261,362,544</sup> Oseltamivir-resistant viruses of H7N9 viruses have been described.<sup>362,544</sup> One recent study documented low levels of resistance to neuraminidase inhibitors among avian influenza viruses in wild birds.<sup>571</sup>

## Prevention

Protective measures for zoonotic avian influenza viruses include controlling the source of the virus (e.g., eradicating HPAI viruses, closing infected poultry markets); avoiding contact with sick animals, animals known to be infected, and their environments; employing good sanitation and hygiene (e.g., hand washing); and using personal protective equipment (PPE) where appropriate.<sup>12,205,392</sup> While the recommended PPE can vary with the situation and risk of illness, it may include respiratory and eye protection such as respirators and goggles, as well as protective clothing including gloves.<sup>12,499,572</sup> The hands should be washed with soap and water before eating, drinking, smoking, or rubbing the eyes.<sup>499</sup>

Because HPAI viruses have been found in meat and/or eggs from several avian species.<sup>71,178,379-385,454,573-577</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>12,499,578</sup> Sanitary precautions and cooking methods recommended to destroy *Salmonella* and other poultry pathogens in meat are sufficient to kill avian influenza viruses.<sup>12</sup> Eggs should be cooked until the whites and yolks are both firm.<sup>12,499</sup> Wild birds should be observed from a distance, as they may be infected with some viruses, and hunters should not handle or eat sick game.<sup>499</sup> H5N1 vaccines for humans have been developed in the event of an epidemic, but are not in routine use.<sup>12,579</sup>

More detailed recommendations for specific groups at risk of exposure (e.g., people who cull infected birds, field biologists, and hunters) have been published by some national agencies, including the CDC, the Department of the Interior and U.S. Geological Survey National Wildlife Health Center in the U.S.,<sup>12,499,572,580</sup> and international

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agencies such as the World Health Organization. In some cases, recommendations may include antiviral prophylaxis (e.g., for people who cull birds infected with Asian lineage H5N1 HPAI viruses) and/or vaccination for human influenza to reduce the risk of reassortment between human and animal influenza viruses.<sup>12,45,540</sup> People who become ill should inform their physician of any exposure to avian influenza viruses.

## Morbidity and Mortality

### *H5N1 avian influenza*

Between 1997 and September 2015, there were nearly 850 laboratory-confirmed human infections with Asian lineage H5N1 viruses, which generally occurred as the result of close contact with poultry.<sup>16</sup> Illnesses caused by H5N1 viruses have been rare, overall; however, these viruses have been found in poultry (including small backyard flocks) for over a decade, resulting in high levels of human exposure. Increased numbers of human infections have been noted recently in Egypt, possibly due to the prevalence of certain viral strains.<sup>581</sup> Most patients with illnesses caused by H5N1 viruses have been young and had no predisposing conditions.<sup>209</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>13,16,312</sup> Likewise, a summary of confirmed, probable and suspected H5N1 cases documented worldwide between 2006 and 2010 found that 56% of these cases were fatal.<sup>582</sup> However, the case fatality rate differs between countries and groups of patients.<sup>539,582-586</sup> It is lower in young children than adults,<sup>582,586,587</sup> and in patients with milder symptoms at the time of diagnosis.<sup>587</sup> One study found that rhinorrhea was linked to improved survival, possibly because it was indicative of milder cases or upper respiratory disease.<sup>586</sup> Conversely, delays in antiviral (oseltamivir) treatment were associated with a worse prognosis.<sup>586</sup> The case fatality rate seems to be particularly low in Egypt, where 28% of confirmed, suspect and probable cases were fatal between 2006 and 2010, and the median age of patients was 6 years.<sup>582</sup> Their young age, which tends to be associated with early diagnosis, as well as treatment-related factors and the virulence of the circulating viruses, might be factors in the relatively high survival rate.<sup>582,586,587</sup>

Antibodies to H5N1 viruses have been reported in some poultry-exposed populations that have no history of severe H5N1 disease, fueling speculation on the likelihood of asymptomatic or mild infections.<sup>229,339,340,343,352,588-591</sup> Most studies have reported seroprevalence rates of 0% to 5%, with a few reporting higher levels, and a meta-analysis of studies published before 2012 suggests that the overall seroprevalence is approximately 1-2% or less.<sup>229,339,340,343,344,351,352,354,588-592</sup> Factors such as cross-reactivity with human influenza viruses in serological assays, or poor seroconversion to some avian viruses, might influence estimates of exposure, and the true prevalence of mild cases is still uncertain and controversial. Rare, laboratory

confirmed, asymptomatic or mild cases have also been recognized.<sup>328,541,593</sup> Rapid treatment with antiviral drugs might have been a factor in some of these cases; however, one child had only upper respiratory signs and made an uncomplicated recovery after antibiotic treatment alone.<sup>541,582,586,587</sup> Prospective studies from Nigeria and rural Thailand documented rare instances of seroconversion to H5 avian influenza viruses, but were unable to find virological evidence of any avian influenza viruses during influenza-like illnesses.<sup>338,340,342</sup> The occurrence of milder cases would be expected to lower the case fatality rate. However, it is possible that some severe cases have also been missed or attributed to other diseases; thus, the net effect of any undiagnosed cases is uncertain.

### *Other Asian lineage H5 viruses*

Three illnesses caused by Asian lineage H5N6 viruses in patients aged 49 years or older were severe; however, one infection in a child was mild.<sup>313-315</sup> One of the two published cases in the older adults was fatal; the other person recovered with intensive treatment.<sup>313,314</sup>

### *H7N9 avian influenza*

Approximately 680 laboratory-confirmed clinical cases, with at least 275 fatalities, have been caused by LPAI H7N9 viruses in China (or in travelers to China), as of September 2015.<sup>16</sup> They mainly occurred in three waves to date, the first consisting of approximately 130 cases 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>14,15,260,261,263,549</sup> This H7N9 virus is circulating subclinically in poultry, and human illnesses have mainly been associated with live bird poultry markets, although infected farms have also resulted in at least one human illness.<sup>15,264,390-392,549,594-596</sup> During the first wave, culling of live birds in wholesale markets, and closure of markets with cleaning and disinfection, were associated with declines in the number of human cases.<sup>392</sup> However, many live markets were not closed, or re-opened after being closed for a short period.<sup>261</sup> Significant environmental contamination with H7N9 viruses has since been reported in some new poultry slaughter and processing plants, which have replaced live bird markets or serve as an alternative in some areas.<sup>549</sup>

Many of the known clinical cases have occurred in older patients.<sup>542</sup> During the first wave, 55% of the patients were older than 59 years.<sup>391</sup> Elderly men were overrepresented in urban areas, particularly in locations where their traditional family roles result in increased exposure to retail live poultry, but men were not affected significantly more often than women in rural regions.<sup>391,597</sup> Most reported cases in adults (including young and middle-aged adults) have been serious, while many cases in children were mild.<sup>15,260,264,411,537,542,543</sup> Some cases may have been mitigated by prompt treatment with oseltamivir, but other mild cases occurred in people admitted to the hospital for observation alone, or were identified only after

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the person had recovered.<sup>260,537,543,546</sup> Analyses of cases to October, 2014 reported case fatality rates of approximately 36% to 48% in hospitalized, laboratory confirmed patients during the first two waves,<sup>15,260,264,550</sup> with the risk of death among hospitalized patients increasing significantly with age.<sup>260,550</sup> Concurrent diseases or predisposing causes have been reported in a significant number of patients (e.g., 45% of cases in the first wave), although serious cases and fatalities also occurred in previously healthy individuals.<sup>260,264,363,391,411,418,537,542,598</sup> Delayed treatment with antiviral drugs was also suggested as a possible factor in the high case fatality rate.<sup>537,545</sup>

The likelihood of additional, undiagnosed mild or asymptomatic infections is still being assessed. In the majority of cases, there was no virological evidence of exposure among patient contacts who developed influenza-like signs. Some of the known mild cases were identified through national virological sampling of people with influenza-like illnesses.<sup>260,264,543</sup> However, these samples are collected from people who visit primary care centers with influenza-like illnesses, and some cases could have been missed.<sup>543</sup> Some initial serological studies found no H7N9 reactivity among poultry market workers, healthcare staff, patient contacts and other populations.<sup>261,417,419,599-601</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>354,547-549</sup> These studies report that seroprevalence rates are low ( $\leq 1\%$ ) in the general population,<sup>547,548</sup> with one survey also documenting low seroprevalence in veterinarians (2%).<sup>354</sup> Although cross-reactivity with other H7 viruses that may circulate in poultry is possible, these surveys suggest that mild or asymptomatic infections may have occurred among poultry workers. As a result, some authors have suggested that the overall case fatality rate in all symptomatic cases might be as low as  $<1\%$  to 3%, if milder cases are also accounted for; however, such estimates currently have a high degree of uncertainty.<sup>260,550</sup>

## H9N2 avian influenza viruses

Clinical cases caused by Eurasian lineage H9N2 viruses have mainly been reported in children.<sup>12,16,108,195,328-333</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>334</sup> Many serological studies have found antibodies to H9N2 viruses in  $<1\%$  to 5% of poultry-exposed groups in endemic regions; however, a few studies have reported higher seroprevalence rates, including 9% of agricultural workers in Bulgaria, 11% of poultry workers and 23% of live bird market workers in China, 56% of live bird market workers in Hong Kong, and 48% of poultry workers in Pakistan.<sup>195,338-341,343,344,347,349,354,591,602,603</sup> A review and meta-analysis of the literature, which included

exposure to all H9N2 viruses worldwide in both Eastern and Western Hemispheres (i.e., not just the Eurasian lineage H9N2 viruses), reported a median seroprevalence of 5%, using the HI test.<sup>604</sup> For microneutralization assays, the median seroprevalence rate was 3% (range  $<1\%$  to 9%) if the cutoffs employed by the authors of each study were used, and 0.3% (range 0.1% to 1.4%) if these cutoffs were adjusted to those recommended by the World Health Organization. A prospective study of adults with poultry exposure in rural Thailand reported rare instances of seroconversion to H9 viruses, but the two people who seroconverted did not report being ill, and no avian influenza viruses were detected in other people who had influenza-like illnesses.<sup>338</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>101,291,319-326</sup> Mild signs were reported in poultry workers infected with an H10N7 virus in Australia,<sup>327</sup> but H10N8 viruses caused fatal infections in two elderly patients in China and a serious illness in a 55-year-old.<sup>316,335</sup> A young woman infected with an H6N1 virus in China had evidence of lower respiratory tract complications, but recovered with treatment.<sup>316,317</sup> The possibility of other, unrecognized infections may be suggested by the occurrence of antibodies to various subtypes, generally at a low prevalence, in people who are exposed to poultry or waterfowl.<sup>195,328,338,340,345-353,603,605-608</sup> Susceptibility (and/or seroconversion) might differ between viruses: 3.8% of poultry workers seroconverted during an H7N3 LPAI outbreak in Italy in 2003, but no seropositive individuals were identified in serum samples collected during H7N1 epidemics from 1999-2002.<sup>606</sup> Rare seroconversion to H6, H7 and H12 viruses was reported in prospective studies of adults with poultry exposure in Cambodia and rural Thailand, but no clinical cases were identified.<sup>338,353</sup>

## Internet Resources

Canadian Food Inspection Agency [CFIA]. Fact Sheet - Avian Influenza

<http://www.inspection.gc.ca/animals/terrestrial-animals/diseases/reportable/ai/eng/1323990856863/1323991018946>

CFIA Notifiable Avian Influenza Hazard Specific Plan

<http://www.inspection.gc.ca/english/animal/disemala/avflu/man/avflue.shtml>

Centers for Disease Control and Prevention. Avian Influenza

<http://www.cdc.gov/flu/avianflu/>



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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>

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\\_buletins/WHB\\_05\\_03.jsp](http://www.nwhc.usgs.gov/publications/wildlife_health_buletins/WHB_05_03.jsp)

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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