

# 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.

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



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# Highly Pathogenic Avian Influenza

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 murres (*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