

Avian Influenza

Fowl Plague, Grippe Aviaire

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Importance

Avian influenza viruses are contagious, highly variable viruses that are widespread in birds. Wild birds in aquatic habitats are thought to be their primary natural reservoirs, but some viruses are adapted to circulate in poultry.¹⁻⁹ Avian influenza viruses are divided into two groups, based on their virulence for gallinaceous poultry. Most are designated low pathogenic avian influenza (LPAI) viruses, as they usually circulate subclinically or cause only mild illnesses unless exacerbated by other factors. A certain subset of LPAI viruses, however, can sporadically develop into highly pathogenic avian influenza (HPAI) viruses, which are extremely virulent in chickens and turkeys.¹⁰ 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.^{2,11,12}

Avian influenza viruses sporadically infect mammals as well.^{12,17-43} While many human cases seem to be mild or subclinical, two currently circulating viral lineages are of higher concern. One is an H5N1 HPAI lineage that arose in Asia in the late 1990s, remained established in poultry in some countries, and has spread widely since that time, including in wild birds. Although human infections with H5N1 and its descendants (e.g., H5N6, H5N8 and H5N2 HPAI viruses) remain rare, they have cumulatively caused more than 900 cases, approximately half fatal, in the last 25 years.⁷¹⁹ The second lineage of concern is an H7N9 LPAI virus that arose in China in 2013, continues to circulate in poultry there, and has generated more than one HPAI virus since 2017.^{14-16,657,728} These H7N9 viruses have been responsible for at least 1500 human clinical cases in China, most reported in the elderly and the majority caused by LPAI viruses.^{657,719} About 39% of the known cases were fatal. The Asian lineage H5 HPAI viruses and the H7N9 lineage in China do not seem to be capable of sustained person-to-person transmission, to date. However, in rare cases avian influenza viruses can become adapted to circulate in mammals. During the last century, such viruses have caused or contributed to at least three pandemics in humans, increased the diversity of swine influenza viruses in pigs, and produced one of the two canine influenza viruses now circulating among dogs.^{1,44-57}

Etiology

Avian influenza viruses are a large group of viruses that belong to the species influenza A virus (genus Alphainfluenzavirus, family Orthomyxoviridae) and have birds as their reservoir hosts. Influenza A viruses are classified into subtypes (e.g., H1N2) based on two variable surface proteins, the hemagglutinin (HA) and neuraminidase (NA). At least 16 hemagglutinins (H1 to H16), and 9 neuraminidases (N1 to N9) have been found in viruses from birds, potentially resulting in more than a hundred different subtypes, though some hemagglutinins (e.g., H14, H15) seem to be uncommon, or perhaps are maintained in host species or locations that are not usually sampled.⁷ The hemagglutinin and neuraminidase proteins are major targets for the immune response, and there is ordinarily little or no cross-protection between different HA or NA types.⁶⁹⁻⁷⁸

Influenza viruses change frequently, as the result of mutations and gene reassortment between viruses.⁷⁹ Mutations cause gradual changes in a virus's HA and NA genes, a process called 'antigenic drift.' Once a virus has circulated for a time in poultry or other birds, antigenic drift can produce numerous viral variants. If the hemagglutinin and neuraminidase proteins change enough, a host's existing immune responses against that virus may no longer be protective. Genetic reassortment, which results from "re-shuffling" the 8 viral gene segments when two different viruses infect a single cell, can result in more rapid changes. The introduction of a new HA and/or NA by genetic reassortment, which is called an 'antigenic shift,' may be sufficient for the virus to immediately evade the existing immunity in its host species.

Highly pathogenic and low pathogenicity avian influenza viruses

Avian influenza viruses are categorized into 'highly pathogenic' or 'high pathogenicity' (HPAI) viruses, which usually cause severe disease in chickens and turkeys, and 'low pathogenic' or 'low pathogenicity' (LPAI) viruses, which are

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generally much less virulent in all birds, including poultry. The technical definition of an HPAI virus was originally based on its ability to cause severe disease in intravenously inoculated young chickens in the laboratory. It was later expanded to include viruses with certain genetic features associated with HPAI viruses, i.e., the sequence at the HA cleavage site, which influences its distribution in the body.^{2,58} Due to the second part of this definition, it is possible for a virus to be technically considered HPAI but cause only mild signs in poultry.^{67,68} Many of these viruses are thought to be evolving from LPAI to HPAI when they are found.

HPAI viruses found in nature have always contained the H5 or H7 hemagglutinin, with a few rare (and arguable) exceptions.^{10,61-63} Laboratory experiments suggest that other hemagglutinins can be artificially engineered to become HPAI;⁶⁵ however, a genetic structure found in most naturally occurring H5 viruses and about half of H7 viruses seems to encourage their transition to HPAI.^{66,69} This structure was also found infrequently in H4, H6, H9, H10, and H16 viruses, opening the possibility that HPAI or HPAI-like transformation might be possible in these viruses.^{66,69} Consistent with this, there are reports of two H10 viruses that technically fit the HPAI definition in intravenously inoculated chickens, though they caused only mild illness in birds infected by the normal respiratory (intranasal) route; an H10 virus that affected the kidneys and had a high mortality rate even in intranasally inoculated young chickens; and an H4N2 virus, found in quail, that had a genetic signature characteristic of HPAI viruses but low virulence in experimentally infected chickens.^{62,64,66}

The Eurasian and North American lineages

There are two well-recognized lineages of avian influenza viruses, Eurasian and North American.⁷ As implied by their names, Eurasian lineage viruses primarily circulate among birds in Eurasia, and North American lineage viruses in the Americas. However, viruses can occasionally cross between these geographic regions, particularly where there is overlap between migratory flyways, such as in Alaska and Iceland.^{7,80-92,670} Limited information from Central and South America suggests that some of the viruses in this region are closely related to the North American lineage, but they may co-circulate with some viruses unique to South America.^{93-95,642} The viruses in New Zealand and Australia might be geographically isolated to some extent, though there is evidence of mixing with viruses from other areas.⁹⁶⁻⁹⁸

Species Affected

Avian influenza viruses are apparently capable of infecting most or all birds, though a given species is not necessarily susceptible to all individual viruses, and some birds may not develop clinical signs or shed viruses efficiently.^{2,27,72,146-147,149-151,165-190,663,699} A few subtypes seem to have a limited host range. H13 and H16 viruses have mainly been found in gulls and terns, and H14 viruses have

been detected rarely and only in a few species, i.e., a few ducks, sea ducks and a herring gull.^{7,80,84,112,120-126}

The vast majority of LPAI viruses are maintained in asymptomatic wild birds, particularly birds found in wetlands and other aquatic habitats.¹⁻⁹ Some species may maintain viruses long-term, while others might be spillover hosts. Infections seem to be especially common among some 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).^{1-3,5-9,46,84,89,109-113,631} The importance of other aquatic birds (e.g., sea ducks, herons and egrets) is still poorly understood, but some might be important hosts.^{9,114,115-117,633-634,645,664,699,718} Many studies have found that infections are usually sporadic or uncommon in terrestrial wild birds (birds that live on land, e.g., raptors, passerines) and concluded that they are not important virus reservoirs.^{8,9,127-136} However, a few recent studies described significant virus circulation in some terrestrial birds that gather in flocks and/or reside in tropical regions.^{129,135,614}

When LPAI viruses from wild birds are transferred to gallinaceous 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.^{4,10,12} Most HPAI viruses do not circulate in wild birds, although they may be isolated transiently near outbreaks in poultry.^{10,131} However, the Asian lineage H5N1 viruses and their reassortants (e.g., H5N8 viruses), which have been found repeatedly in wild birds, appear to be an exception. Rare reports of HPAI viruses found in wild birds without an obvious poultry origin include an unrelated H5N2 virus found in a few asymptomatic wild ducks and geese in Africa, an H5N3 virus isolated from an outbreak among terns in the 1960s, and an H7N1 virus that was isolated from a sick wild siskin (*Carduelis spinus*).^{27,32,108,138-164}

Mammals

Infections with diverse avian influenza viruses have been reported sporadically in mammals including domesticated species such as pigs, cats, dogs, goats, cattle, and equids; farmed guinea pigs, foxes, mink and raccoon dogs (*Nyctereutes procyonoides*); and various free-living or captive wild mammals and marsupials, such as large felids, stone martens (*Mustela foina*), fishers, otters, wild mink, palm civets (*Chrotogale owstoni*), plateau pikas (*Ochotona curzoniae*), raccoons (*Procyon lotor*), skunks, bears, and Virginia opossums (*Didelphis virginiana*); as well as various marine mammals.^{1,12,20-35,37-38,40,43,99,191-204,231,276,277,283,285-287,291-296,703,709,717} Experimental infections with diverse subtypes have been established in these and other mammals, such as striped skunks (*Mephitis mephitis*) and cottontail rabbits (*Sylvilagus* sp.).^{1,31,280-282,284,286,288,289,290,629,687} Ferrets and laboratory mice (*Mus musculus*) are often used as models for avian influenza virus infections.²⁹⁷⁻³⁰⁵ Laboratory mice owe their suitability to a defective gene (Mx1), which increases their susceptibility compared to their wild-type

progenitors.³⁰⁶⁻³⁰⁸ While wild mice have also been inoculated with certain LPAI viruses and might sometimes be naturally infected, some evidence suggests they are probably not common hosts.^{306,309-311}

Most infections with avian influenza viruses in mammals are transient: the virus cannot be transmitted efficiently and soon disappears.^{1,5,12,31,45,50,79,99-105} On rare occasions, however, a virus continues to circulate in the new host, either “whole” or after reassorting with another influenza virus.^{45-46,50-55,57,102,106-107} Some established swine influenza viruses in pigs are wholly of avian origin or contain avian-origin gene segments, and one avian influenza virus recently became established in dogs as the H3N2 canine influenza virus.^{45-46,55,57,193,194,252,701} Equine influenza viruses are also thought to have originated in birds.⁶¹⁶

Important viral lineages and susceptible species

Three viral lineages currently circulating in poultry are of particular concern for both birds and mammals, including humans.

Asian lineage H5N1 avian influenza viruses and their reassortants (e.g., H5N2, H5N5, H5N6, H5N8)

The A/goose/Guangdong/1996 (‘Asian lineage’) H5N1 HPAI viruses first emerged among poultry in China in the late 1990s, and have become widespread and very diverse since then, with a number of lineages, sublineages and variants.^{12,205-211} These viruses, which can circulate in wild birds and may be transferred long distances during their annual migrations, have also reassorted with local Eurasian lineage LPAI viruses in Asia and Europe to generate additional subtypes of H5 HPAI viruses (e.g., H5N2, H5N3, H5N4, H5N5, H5N6, H5N8).^{158, 213-220,613,624,635,656,661,711} In some cases, there may be more than one reassortant with the same subtype. For example, Asian lineage H5N6 HPAI viruses that arose in East Asia circulate in chickens there, while Asian lineage H5N6 HPAI viruses recently described in wild birds in Europe are genetically different and seem to preferentially replicate in wild and domestic waterfowl.^{692,704,712} Some reassortants apparently disappear after a relatively short time, while others persist.

Eurasian H5N8 HPAI viruses reached North America via wild bird migration in late 2014 and reassorted with North American lineage viruses to produce new and unique H5N1 and H5N2 HPAI viruses.^{157,159-161,220-224} An H5N2 HPAI virus was isolated from a wild bird in Alaska in late summer 2016, suggesting possible maintenance in wild bird populations.⁶⁵⁴ New H5N1 variants, apparently unrelated to these earlier viruses, caused outbreaks in wild birds and poultry in North America in late 2021 and 2022.⁶⁷⁹⁻⁶⁸⁰ These viruses have continued to circulate and reassorted with other avian influenza viruses in the Americas, resulting in additional diversity.

Asian lineage H5 viruses are detected sporadically in mammals, including humans. H5N1 viruses have been found in a wide variety of mammals including pigs, cats, captive or free-living large felids, dogs, donkeys, farmed fur-bearing animals (mink, foxes, raccoon dogs), stone martens, wild red

foxes (*Vulpes vulpes*), palm civets, wild plateau pikas, wild mink (*Mustela vison*), river otters, raccoons, skunks, bears, Virginia opossums and marine mammals (seals, sea lions, dolphins), while serological evidence of possible infection/exposure has been reported in horses.^{12,17-37,229-231,618,639,677,686} While limited studies in Egypt and Pakistan detected no antibodies to H5N1 viruses in cattle, buffalo, sheep or goats, cattle could be experimentally infected with Eurasian H5N1 viruses isolated from cats, and infections with North American lineages of H5N1 viruses were recently reported in cattle and goats in the U.S.^{229,240} Additional species known to be susceptible to H5N1 viruses, based on laboratory experiments, include ferrets, some non-human primates and rabbits.^{17,27,31,34,108,151,192,212,232-240}

Other Asian lineage H5 HPAI viruses have not been circulating as long, but some of them are also known to infect mammals. An H5N8 HPAI virus caused clinical cases in a red fox, common seals (*Phoca vitulina*) and a juvenile gray seal (*Halichoerus grypus*) at a rehabilitation center in the U.K., and H5N8 viruses were found in the brains of three dead harbor seals found on the North Sea coast in Europe.⁶⁷⁶ Seropositive dogs were detected on some H5N8-virus infected farms in Asia, and experimental infections with H5N8 viruses have been established in dogs, cats and ferrets.^{242-244,727} H5N6 viruses were suspected in the deaths of a few cats in South Korea, and were also found in apparently healthy pigs in China.^{39,655,666} In addition, experimental infections were established in dogs.⁶⁶⁶ An H5N2 virus recovered from a sick dog in China could be transmitted from experimentally infected dogs to dogs, chickens and cats.⁴⁰⁻⁴² Cottontail rabbits and pigs were inoculated with North American H5N2 and H5N8 viruses from the 2014-2015 outbreaks; however, in pigs, virus replication appeared limited and further virus transmission absent.^{644,688}

Host range of Eurasian H9N2 (LPAI) avian influenza viruses

A Eurasian lineage of H9N2 (LPAI) viruses has become widespread among poultry in some areas, and like the Asian lineage H5 viruses, it has become very diverse.^{195,245-249,672} This lineage has occasionally been reported in wild birds including some terrestrial species, though there is currently no evidence they are spreading it.²⁴⁹⁻²⁵¹ H9N2 viruses have been found occasionally in pigs, and might sometimes cause clinical signs in this species, though they are not thought to circulate in swine populations.^{193-196,252-253,672} They have also been detected in farmed mink, dogs, and a horse, as well as humans, and serological evidence of infection was found in cats near live bird markets, farmed foxes and raccoon dogs, and performing macaques.^{35,43,204,254-256,672} Experimental infections have been established in pikas, dogs and cats, though virus replication was sometimes limited in the latter two species.^{202,204,257-259}

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Host range of the zoonotic H7N9 avian influenza viruses

A lineage of H7N9 LPAI viruses has been found among poultry in China since 2013.^{14,15,260-264} Control programs, including routine poultry vaccination, have suppressed, but not eliminated, this virus, and like other long-circulating poultry viruses, it has diversified considerably.^{266,657,728} This lineage has also produced HPAI viruses, which have been detected concurrently with LPAI viruses in poultry. One HPAI virus emerged in 2017, and at least one unrelated HPAI virus was found in 2019.^{657,724,728}

Among birds, infections with these viruses have mainly been reported in poultry, although LPAI viruses or their nucleic acids were also detected in pigeons, an asymptomatic tree sparrow (*Passer montanus*), and wild waterfowl.^{264,267-268} Experimental H7N9 LPAI virus infections were established in Japanese quail (*Coturnix japonica*), some domestic waterfowl, pigeons, parakeets (*Melopsittacus undulates*), and several species of passerines.^{241,270-272} Whether wild birds could play any role in spreading these viruses is uncertain.^{264,268,269}

Many human infections with H7N9 LPAI and HPAI viruses have been reported, mostly between 2013 and 2017, though the only report of a naturally occurring infection in other mammals, to date, is of virus isolation from the nasal secretions of a group of camels with mild respiratory signs (no other tests, including serology, were done). Experimental infections with H7N9 LPAI viruses were established in miniature pigs, ferrets, striped skunks, raccoons, cottontail rabbits, laboratory mice and cynomolgus macaques.^{273-275,630,687}

Zoonotic potential

Avian influenza infections are reported sporadically in people who are in close contact with birds, and volunteers were experimentally infected with H4N8, H6N1 and H10N7 viruses.³²⁸ Reports of zoonotic infections before the late 1990s were limited to conjunctivitis, mild illnesses or asymptomatic infections. The Asian lineage H5N1 viruses were the first viruses recognized to cause serious illnesses in people, but the H7N9 LPAI and HPAI viruses currently circulating in China have caused a number of severe or fatal cases, and there are rare reports of deaths from other subtypes.^{14-16,46,108,260-264,312-315,712,719}

Adaptation of an avian influenza virus to humans is possible, though rare, and some human pandemics were caused by partially or wholly avian viruses.^{1,44-46,48-49,355} Such viruses continue to circulate as human influenza viruses after the pandemic.

Geographic Distribution

LPAI viruses are cosmopolitan in wild birds, although the circulating viruses differ between regions.^{1,7,93,96} Control programs in developed nations usually exclude these viruses from commercial, confinement-raised poultry.³ However, they may still be found in other birds, such as backyard flocks or live poultry markets.³ Eurasian lineage H9N2 LPAI

viruses are endemic in poultry in parts of Asia, the Middle East and Africa,^{356-359,672} with sporadic reports of their presence in poultry flocks, wild birds or game birds in Europe.^{250,360-361} The zoonotic H7N9 LPAI viruses remain endemic in poultry in mainland China, but they have not been reported from other regions, other than imported cases in people who had visited China.^{14-15,362-363}

HPAI viruses are eradicated from domestic flocks whenever possible, but the circulation of Asian lineage H5 viruses in wild birds has made outbreaks more common in formerly HPAI-free countries.^{12,157-158,220-221,613,624,635,656,661,711} Asian lineage H5N1 HPAI viruses remain endemic in poultry in certain countries in Asia and the Middle East.⁶³⁵ Other subtypes of this lineage, particularly H5N6 and H5N8 HPAI viruses, are also common in poultry in parts of Asia, and have been seen in Africa.^{613,656,698,712} Diverse subtypes of Asian lineage H5 HPAI viruses are seen periodically in wild birds in Eurasia, North America and Antarctica, and can spread to poultry flocks.^{12,158,220,613,624,635,654,656,661,679-680,711}

Transmission

Avian influenza viruses are shed in the feces and respiratory secretions of birds, but the relative amount of virus in these two locations varies with the virus and host species.^{1,2,58,79,369-370} Aquatic birds, such as waterfowl, usually shed large amounts of virus in the feces, and fecal-oral transmission is usually the most important route in these birds (fecal-cloacal transmission might also be possible).^{7,150,371-372} However, a few waterfowl LPAI viruses are spread predominantly by respiratory transmission, as are some viruses transferred to these birds from gallinaceous poultry (e.g., Asian lineage H5N1 HPAI viruses).^{150,172,373-375,628} Respiratory spread might also be important in some terrestrial wild birds, while contaminated carcasses are thought to be a significant source of exposure for raptors.^{7,133,699}

In poultry flocks, avian influenza viruses can spread by both the fecal-oral route and aerosols. Respiratory transmission tends to predominate among LPAI viruses, but fecal shedding can also be important in some instances.⁶⁷² Fomites can be important in transmission, and flies might act as mechanical vectors.^{2,4,376-377} The possibility of wind-borne transmission of HPAI viruses between farms was suggested by one study, but has not been conclusively demonstrated.³⁷⁸ Avian influenza viruses have sometimes been found in the yolk and albumen of eggs from chickens, turkeys and quail infected with HPAI viruses, as well as on their shells.^{379-385,705} It might also be possible for birds to shed LPAI viruses in eggs, but the current evidence suggests this is very rare, if it occurs at all.^{379,386,625}

Transmission of avian influenza viruses to mammals

Mammals, including humans, are usually infected with avian influenza viruses during close contact with infected birds or their tissues, though indirect contact via fomites (including contamination of feed with avian feces) is also

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thought possible.^{12,15,23,25-26,29-30,33,191,233,390-400} Respiratory transmission is likely to be important, and the eye may act as an additional entry point.^{274,303,305,401-402} Laboratory experiments provide evidence for oral transmission, and a few Asian lineage H5N1 HPAI virus infections in animals, and rare cases in humans (e.g., two cases reported after eating uncooked duck blood), were linked to eating raw tissues from infected birds.^{22,23,25-26,29-30,33,233,235-236,393,398-399,403-404}

Mammals usually shed avian influenza viruses in respiratory secretions. Fecal shedding has also been reported occasionally in humans and some experimentally infected mammals, though its significance is still uncertain.^{29,235-239,257,407-412,708} and there are reports of Asian lineage H5N1 HPAI viruses in the urine of mammals.³¹ Some avian influenza viruses can be shed in milk. Avian influenza viruses typically do not seem to spread readily between mammals.^{17,26,191,233,235,237,242,253,316-318,321} However, limited host-to-host transmission has occasionally caused clusters of infections or larger outbreaks.^{1,15,26,31,40-42,193-195,199,233,235,291-292,321,362,391-392,394-397,414-423,716,730} In humans, Asian lineage H5 HPAI viruses and the Chinese H7N9 viruses have infrequently been transmitted to other people, typically family members, during close contact.^{15,362,391-392,394-397,417-423} A ferret model suggested that some viruses might infect to the fetus if high viremia occurs during a systemic infection, and viral antigens and nucleic acids were found in the fetus of a woman who died of an Asian lineage H5N1 HPAI virus infection.⁴⁰⁵⁻⁴⁰⁶

Survival of influenza viruses in the environment

Environmental survival of avian influenza viruses is influenced by the initial amount of virus; temperature and exposure to sunlight; presence of organic material; pH and salinity (viruses in water); relative humidity (on solid surfaces or in feces); and possibly the viral strain.^{387-388,425-440,633} Some viruses may remain viable for several weeks to several months or more in the laboratory, when suspended in distilled water or sterilized environmental water, especially under cold conditions.^{425-426,428-430} However, the presence of natural microbial flora or other physical, chemical or biological factors in natural aquatic environments may considerably reduce their survival, and at some temperatures, viruses in natural water sources may remain viable for only a few days (or less) to a few weeks.^{429-431,434,442-443,633} Freeze-thaw cycles might increase inactivation in cold climates.⁴³³

Some anecdotal field observations stated that LPAI viruses can survive for at least 44 or 105 days under unspecified conditions,⁴²⁵ while laboratory studies under controlled conditions report varying survival times depending on the substrate. In feces between 15°C (59°F) and 35°C (95°F), LPAI or HPAI virus persistence ranged from < 1 day to 7 days, depending on factors such as the moisture content and protection from sunlight, while two studies at 4°C (39°F) reported survival of at least 30-40 days, and two other reports found it ranged from < 4 days to 13 days.^{388,432,434,436,440-441,444} 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); and for at least 2 weeks at 4°C if the relative humidity was low; 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.^{388,432,445} Some groups have reported prolonged survival on feathers: at least 6 days at room temperature in one study, and 15-30 days at 20°C (68°F) and 160-240 days at 4°C in another report.^{441,445,722} Other studies reported virus persistence for up to 13 days in soil (4°C), 20 to > 50 days in poultry meat at 20°C; up to 5-6 months in poultry meat at 4°C,⁴ 3 days (20°C) to 20 days (4°C) in liver, and 15 days in allantoic fluid at 37°C (99°F).^{427,432,438,722} 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 diverse environmental samples, live virus could only be isolated from one water puddle.⁴⁴⁶

Disinfection

Influenza A viruses are susceptible to a wide variety of disinfectants including sodium hypochlorite, 60-95% ethanol, quaternary ammonium compounds, aldehydes (glutaraldehyde, formaldehyde), phenols, acids, povidone-iodine and other agents.^{79,425,447-450} They can also be inactivated by heat of 56-60°C (133-140°F) for a minimum of 60 minutes (or higher temperatures for shorter periods), as well as by ionizing radiation or extremes of pH (pH 1-3 or pH 10-14).^{79,388,425,447,449} One report suggested that the zoonotic H7N9 viruses in China might be more stable than some other viruses at 50°C.⁴⁵¹

Infections in Animals

Incubation Period

The incubation period in birds is often a few hours to a few days; however, there are reports of longer periods in some species including turkeys and ostriches.^{2,3,79,609,702} The incubation period for avian influenza viruses in mammals is also thought to be short, and might sometimes be as little as 1-2 days.⁴⁰³

Clinical Signs

Low pathogenic avian influenza

LPAI viruses usually cause subclinical infections or mild illnesses, which can be exacerbated by concurrent infections or poor husbandry, in poultry and other birds.^{2,3,70,180,264,270-271,460} Common clinical signs during outbreaks in chickens and turkeys include disorders of egg laying (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.^{2,3,70,383,452-460} The diseases caused by the Eurasian H9N2 and H7N9 viruses are generally consistent with these descriptions; however, some reports suggested that certain H9N2 variants might be more virulent,^{359,464-465,672} and the

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H7N9 viruses caused high mortality (75%) in some experimentally infected turkeys while being mild in chickens.⁷⁰⁰ There are infrequent reports of other LPAI viruses with higher virulence, such as an H10 virus isolated from waterfowl that affected the kidneys and had a 50% mortality rate in some intranasally inoculated chickens.⁶⁴

Clinical signs, if any, are generally similar in game birds (e.g., quail, pheasants, guinea fowl, partridges), pigeons and cage birds, but neurological signs and elevated mortality were reported in guinea fowl (*Numida meleagris*) infected with an H7N1 virus.^{241,264,267,271,461,464,668} Domestic ducks and geese are often infected subclinically, although there may be mild signs such as sinusitis.^{3,180} Free-living wild birds mostly appear to be asymptomatic,^{7,114,115,121,116 cited in 115,371} but a few reports described subtle effects such as decreased weight gain, behavioral effects or transient increases in body temperature.^{84,462-463,638}

HPAI viruses in birds

HPAI viruses usually cause a systemic illness with a low survival rate in chickens and turkeys.^{1,2,165} Common clinical signs include marked depression, anorexia, coughing, sneezing, sinusitis, blood-tinged oral and nasal discharge, diarrhea, neurological signs, ecchymoses on the shanks and feet, and edema and cyanosis of the unfeathered skin on the head, comb, wattle and/or snood.^{2-4,10,58,79,165-166,170,383,467-470} Egg production decreases or stops, and depigmented, deformed and shell-less eggs may be produced. Some birds may die suddenly with few or no preceding signs. Because a virus can be defined as HPAI based on its genetic composition alone, on rare occasions these viruses have been found in flocks that are only mildly ill.^{58,67} There have also been recent reports of some Asian lineage H5 viruses in Europe that caused mild or minimal signs, with a low prevalence of infection and low mortality rates, in poultry.

Outbreaks in gallinaceous game birds can be severe, with nonspecific signs, diarrhea, neurological signs and/or sudden death, but milder or minimal signs were reported in some flocks.^{166-168,461,659} The illness is variable in ostriches. These birds sometimes have few or no signs other than bilirubinuria (green urine syndrome), whether they are infected with HPAI or LPAI viruses, though more severe cases with neurological signs, mucosal hemorrhages, tracheitis and other syndromes have also been seen.^{183,185-189,152,241,609,648} Pigeons are thought to be relatively resistant to most HPAI viruses. Reports of overt illness in this species described nonspecific signs, neurological signs, greenish diarrhea or sudden death.^{10,132,474}

Domestic and wild waterfowl tend to be mildly affected, though domestic flocks can have respiratory signs (e.g., sinusitis), diarrhea, corneal opacity, occasional cases with neurological signs, and increased mortality. Certain Asian lineage H5 HPAI viruses are an exception to this pattern, and can cause severe acute disease with neurological signs and high mortality in both domestic and wild waterfowl.^{2,10,79,141,146-147,149-151,172-173,471-473} Some of these viruses are also reported to cause serious illnesses in various

captive or free-living wild birds, with occasional reports of high mortality and combinations of nonspecific signs, neurological disease, respiratory signs, greenish diarrhea and/or sudden death.^{10,32,127,132,138-139,144-145,147,149-153,158,161-163,173,221,223,228,241,474-486,611,622,649-650,663,667,696,707} Some of these reports described outbreaks where one or more species suffered severe effects, while others were apparently unaffected.³² Information about the effects of other HPAI viruses on wild birds is limited, but an H5N3 HPAI virus caused high mortality among South African terns in the 1960s, and an H7N1 HPAI virus caused conjunctivitis, apathy and anorexia, with a high mortality rate, in captive canaries (*Serinus canarius*) that had been exposed to a sick wild siskin.^{140,142}

Mammals infected with Asian lineage H5 viruses

Asian lineage H5 HPAI viruses have been found sporadically in mammals. Reported syndromes range from asymptomatic infections or mild respiratory signs to neurological signs and severe systemic illnesses. The viruses involved are diverse, and only a few cases have been described in most species.

Both symptomatic and subclinical infections have been reported in H5N1 virus-infected felids. Some severely-affected cats had respiratory signs (dyspnea, oculonasal discharge), blindness/ chorioretinitis, and/or neurological signs, while others were found dead, with one cat apparently well 24 hours earlier.^{24,25,29} Fatal illnesses with conjunctivitis and severe respiratory signs were described in experimentally infected cats.^{233,235,237,403,488} However, cats at an animal shelter that had been exposed to an H5N1 virus-infected swan were infected subclinically.¹⁹¹ Likewise, some captive large felids infected with H5N1 viruses died with respiratory signs (e.g., dyspnea, nasal discharge), high fever, vomiting and/or neurological signs,^{22-23,26,31,37,618,639} but zoo felids in one outbreak had much milder signs, with lethargy and a reduced appetite for up to a week, and recovered.³² The detection of antibodies to H5 viruses in cats and captive tigers also suggests the possibility of mild or asymptomatic infections.^{18,229,255,533-534,691,729}

Few serious illnesses have been documented in H5N1 virus-infected dogs. One dog that had eaten infected poultry developed a high fever, with panting and lethargy, and died the following day.³⁰ However, serological and virological evidence of infection was also found in live stray dogs in China during this time.³⁵ Furthermore, while some intranasally inoculated dogs developed clinical signs (fever, anorexia, conjunctivitis, mild respiratory signs and/or diarrhea), more severe respiratory signs, with a single death, were only reported in dogs inoculated directly into the trachea.^{34,237,238,488,666}

Respiratory signs were seen in a dog infected with an Asian lineage H5N2 HPAI virus, and this virus caused mild respiratory signs in experimentally infected dogs.^{40,42} One cat exposed to these dogs developed respiratory signs and conjunctivitis, but four other cats became subclinically infected.⁴¹ Asian lineage H5N6 HPAI viruses were thought

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to be the cause of death in three cats that died a few days after developing sudden onset of salivation, lethargy, convulsions, and bloody nasal and/or oral discharges.^{655,666} Dogs inoculated with an Asian H5N6 virus had only mild respiratory signs (sneezing, nasal discharge), while their contacts remained asymptomatic.⁶⁶⁶ Another study reported few or no clinical signs in dogs inoculated with an Asian lineage H5N8 virus, while cats had mild and transient signs, including fever and marginal weight loss.²⁴²

Reports of infected herds, as well as evidence from experimental infections, suggest that pigs infected with Asian lineage H5N1, H5N6, H5N8 and H5N2 HPAI viruses usually remain asymptomatic or have only nonspecific signs and/or mild respiratory disease.^{17,36,39,229,236,415,644} An 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.^{20,229} The role of the H5N1 virus in this outbreak was unclear, as the affected donkeys responded well to antibiotics.

A North American H5N1 virus was recently detected in a number of cattle herds and one group of goats. The clinical cases in the goats, which were fatal and affected only newborn animals, were characterized by neurological signs and occurred in animals that had been in close contact with infected poultry. Some infected cattle were asymptomatic, while others usually had mild clinical signs that sometimes included fever, lethargy, decreased appetite, mild respiratory signs (e.g., increased respiratory secretions), abnormal bowel movements and a drop in milk production. Some affected cattle had signs of mastitis and abnormal milk, which was reported to be thickened and creamy-yellow in appearance, similar to colostrum, in at least one herd where no other agents were detected. Affected cattle usually recover completely within a few weeks. However, some cats fed milk from sick cattle developed severe illnesses with a high case fatality rate.

Mild illnesses caused by Asian lineage H5 viruses are unlikely to be observed in free-living wild species. Reports of serious or fatal illnesses from H5N1 viruses include a number of animals that were found dead, but also neurological signs in various free-living or captive terrestrial and marine wildlife, as well as some reports of respiratory signs or nonspecific signs of illness.^{31,33,677,686} There are few descriptions of cases caused by other H5 viruses, but a juvenile red fox, which was being treated for mange at a wildlife rehabilitation center in the U.K., became infected with an H5N8 virus and died shortly after developing malaise and inappetence.⁶²⁶ Seals infected during this outbreak had signs ranging from lymphadenopathy alone to fatal neurological signs.⁶²⁶ Three wild harbor seals (*Phoca vitulina*) found dead in Europe had high levels of an H5N8 virus in the brain.⁶⁷⁶ Cottontail rabbits experimentally infected with North American isolates of H5N2 or H5N8 viruses remained asymptomatic.⁶⁸⁸

Mammals infected with other subtypes

Many avian influenza viruses seem to cause respiratory signs or subclinical infections in most infected mammals.

LPAI viruses of diverse subtypes have been isolated occasionally from pigs.^{99,193-195,197-201,276-277} Generally, these outbreaks resemble swine influenza, with respiratory signs or subclinical virus circulation, and little or no mortality. Pigs experimentally infected with a variety of LPAI viruses from North America, Asia or Europe did not develop any overt clinical signs, except mild transient anorexia in some cases.^{273,610,629,647} Avian influenza virus (H9N2, H10N4) outbreaks in mink were characterized by respiratory signs of varying severity, accompanied by elevated mortality in some but not all outbreaks.^{1,31,204} An avian H3N8 virus epidemic among horses in China resembled equine influenza.²⁷⁸⁻²⁷⁹ Mortality was initially high (20-30%), but subsequently became minimal.

Few or no clinical signs were seen in cats inoculated with an H7N7 HPAI virus isolated from a fatal human case, an H9N2 poultry virus or several LPAI viruses from waterfowl.^{258,280-281} One H7N2 LPAI virus caused an outbreak among cats at three animal shelters in New York.^{636,674} Approximately 500 of the cats developed mild to moderate upper respiratory signs (coughing, sneezing, nasal discharge) and recovered fully, though the virus caused severe pneumonia in an elderly cat with underlying health conditions, which was euthanized. Cats that were experimentally infected with this virus had very mild signs, with one animal developing a fever and another cat sneezing extensively on a single day.⁶³⁶

One group isolated 13 H9N2 viruses from sick and healthy dogs in China, but whether these viruses were responsible for the clinical signs was unclear.⁴³ Dogs inoculated with an H9N2 virus developed respiratory signs in one study, but they remained asymptomatic or had only a mild fever in two other reports.^{257-258,259}

Various influenza A viruses, apparently of avian origin, have been associated with outbreaks of pneumonia or mass mortality in seals.^{1,101,203,489,490,709} The clinical signs in some outbreaks included weakness, incoordination, dyspnea, subcutaneous emphysema of the neck, and in some cases, a white or bloody nasal discharge.^{31,291,489} Experimental infections with these viruses were milder or asymptomatic, suggesting that co-infections may have increased the severity of the illness.³¹ An influenza virus was also isolated from a diseased pilot whale, which had nonspecific signs including extreme emaciation, difficulty maneuvering and sloughing skin.⁴⁸⁹ Whether this virus was the cause of the disease or an incidental finding is uncertain.⁴¹⁴ Other avian influenza viruses were isolated from whales that had been hunted, and were not linked with illness.⁴⁹¹

The H7N9 viruses in China were found in nasal swabs from a group of camels with mild respiratory signs of cough and nasal discharge. H7N9 LPAI viruses also caused respiratory signs in experimentally infected ferrets and skunks, while nonspecific signs (fever, reduced appetite,

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lethargy) and nasal discharge were seen in some individual raccoons and rabbits, and cynomolgus macaques developed a fever.^{273-274,643,687} Experimentally infected miniature pigs remained asymptomatic.²⁷³ Few or no clinical signs were seen in raccoons experimentally infected with an H4N8 virus.²⁸⁶

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

Low pathogenic avian influenza in birds

Lesions in LPAI virus-infected poultry may include rhinitis, sinusitis, and congestion and inflammation in the trachea, but lower respiratory tract lesions such as pneumonia usually occur only in birds with secondary bacterial infections.^{2,3} 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.² A small number of birds may have signs of acute renal failure and visceral urate deposition.³ Marked pancreatic hemorrhages were seen in turkeys experimentally infected with Chinese H7N9 LPAI viruses, but this is unusual.⁷⁰⁰

Highly pathogenic avian influenza in birds

The lesions in HPAI virus-infected chickens and turkeys are variable and resemble those found in other systemic avian diseases.^{471,492} Classically, they include edema and cyanosis of the head, wattle and comb; excess fluid (which may be blood-stained) in the nares and oral cavity; edema and diffuse subcutaneous hemorrhages on the feet and shanks; and petechiae on the viscera and sometimes in the muscles.^{2,3,492} There may also be other abnormalities, including hemorrhages, edema and/or congestion in various internal organs including the lungs, as well as severe airsacculitis and peritonitis.² Birds that die peracutely may have few or no lesions,^{2,3,492} and the gross lesions in some outbreaks may not fit the classical pattern.⁴⁹²

Similar internal lesions may be seen in other birds, though some lesions common in chickens and turkeys, such as cyanosis and hemorrhagic lesions in unfeathered skin, may be absent or less prominent.^{145,149,152,188,228,493,609,622,648,652,667,696,707} Necrotic lesions in the pancreas appear to be common in wild or domestic birds infected with Asian lineage H5 HPAI viruses.^{652,461} Some birds infected with these viruses also had encephalitis and/or meningitis.^{609,648}

Avian influenza viruses in mammals

Some mild to fatal infections in mammals are limited to the respiratory tract, with gross lesions that may include bronchitis, tracheitis, and congestion, consolidation, edema and/or emphysema of the lungs.^{17,236,293,666,687,709} However, some viruses, particularly Asian lineage H5 HPAI viruses, can cause systemic disease, with hemorrhagic lesions on various internal organs, multifocal hepatic necrosis, pancreatic necrosis, and enlargement and/or congestion of other internal organs including the spleen, kidney and liver.^{23-25,29-30,233,235,403,626,655} Lesions have also been reported sometimes in the brain.⁶²⁶ The lesions in many infected cattle

in North America appear to be limited to mastitis, with grossly firm mammary glands, though some acutely ill animals have also had gastrointestinal lesions (e.g., evidence of dehydration and reduced ruminal fermentation, small abomasal ulcers, shallow linear erosions of the intestinal lining).

Diagnostic Tests

Avian influenza viruses, their nucleic acids and antigens can be found in oropharyngeal, tracheal and/or cloacal swabs (or, if necessary, feces) from live birds.^{58,370} Immature feathers have also been proposed for sampling.⁴⁹⁴ The optimal samples can depend on the specific virus, species of bird and other factors. Samples from internal organs (e.g., trachea, lungs, air sacs, intestine, cecal tonsils, spleen, kidney, brain, liver and heart) are collected in dead birds suspected of highly pathogenic avian influenza.^{2,58}

Diagnostic tests should be validated for the avian species; some tests that are useful in chickens and turkeys may be less reliable in other birds.^{58,132,185} RT-PCR tests can detect influenza viruses directly in clinical samples, and real-time RT-PCR is the diagnostic method of choice in many laboratories.^{2,58,495} ELISAs including rapid tests are available for viral antigens.^{58,495} Due to the limitations of antigen detection tests, however, the World Organization for Animal Health (OIE) recommends that they be used to identify avian influenza only in flocks and not individual birds.⁵⁸

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

Serology can be valuable for surveillance and demonstrating freedom from infection, but chickens, turkeys and some other birds infected with HPAI viruses often die before developing antibodies.⁵⁸ Serological tests used in poultry include AGID, hemagglutination inhibition (HI) and ELISAs.⁵⁸ AGID 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.^{58,72,496}

Mammals

Tests to detect the virus directly, such as RT-PCR, virus isolation and immunohistochemistry, are used to diagnose clinical cases in mammals. While respiratory samples are likely to be useful in many animals, the presence of virus in

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different tissues may vary. For instance, cattle with H5N1 HPAI viruses in mammary glands and milk may or may not have any evidence of these viruses in other internal organs. Serology has been employed in surveillance; however, tests differ in their ability to detect antibodies to avian influenza viruses, and they have rarely been thoroughly evaluated in uncommonly tested species, such as wildlife.⁶⁸⁹ This may result either in false positives (e.g., due to cross-reactions with other viruses) or false negatives. There are reports of infected mammals developing detectable antibodies to other viral proteins (e.g., the nucleoprotein) but not the hemagglutinin.^{38,497}

Treatment

Poultry flocks infected with HPAI viruses are normally 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. Treatment for sick animals is usually symptomatic and supportive; antiviral agents used for influenza in humans are not prescribed for animals in most countries. Administering such drugs (e.g., amantadine) to sick birds might contribute to drug resistance.^{623,726}

Control

Disease reporting

Reporting requirements depend on the specific virus, host species and country, but HPAI viruses and LPAI viruses that contain H5 or H7 are often nationally notifiable.¹¹ In the U.S., state or federal veterinary authorities should be informed immediately of these viruses. Some states may have additional LPAI virus reporting requirements. Unusual mortality among wild birds might indicate the introduction of an HPAI virus, and should be reported to state, tribal or federal natural resource agencies in the U.S.⁴⁹⁹ Veterinarians in other countries should follow their national and/or local guidelines.

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 domestic or wild birds and contaminated fomites including water sources.^{4,5,46,79,471} All-in/ all-out flock management is helpful in poultry, and birds should not be returned to the farm from live bird markets or other slaughter channels.⁴ Birds added to established flocks can be quarantined and tested. To reduce the risk of reassortment between human and avian influenza viruses, people are encouraged to avoid contact with birds while suffering flu symptoms.⁴⁵

Some countries use avian influenza vaccines to suppress illness and reduce virus circulation in poultry flocks, or to protect valuable species such as zoo birds from highly virulent viruses.^{51,58,291} Most vaccines are produced for chickens, but some have also been validated for use in turkeys.^{168,503} Their efficacy may differ in other species.⁸ By suppressing clinical signs, vaccination can mask the

introduction of a virus, unless there is a good surveillance program to detect asymptomatic infections.^{2,179,507,51-519} It can also promote the emergence of vaccine-resistant isolates.^{515,517,520-521} Thus, 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.

Avian influenza viruses can be eradicated by depopulation of infected flocks, followed by cleaning and disinfection, typically combined with movement controls, quarantines, and perhaps vaccination.⁴⁷¹ Insect and rodent control is recommended, though their importance as mechanical or biological vectors is still unclear.^{632,637,710} Mammals should be kept from contact with potentially infected birds and should not be fed any of their tissues. Any mammals that become ill should be isolated.

Morbidity and Mortality

Birds

Influenza virus infections 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.^{9,113,631} Reported infection rates with LPAI viruses in different species and environments range from < 1% to 40% or more, and seroprevalence from < 1% to > 90%.^{8,9,84,89,110-116,119,128-129,134-135,522-525,634,699,718} These rates are generally higher in aquatic than terrestrial species. In temperate climates, LPAI virus prevalence is reported to rise in late summer staging areas before migration, when bird densities are high and young hatch-year birds have not yet developed immunity.⁵²⁶ Conversely, seasonal changes appear to be limited in tropical wetlands of Africa, where young birds may be present year-round and birds aggregate more gradually as wetlands dry out.⁶³¹

In endemic regions, avian influenza viruses tend to re-emerge in poultry during the colder months.⁵²⁷⁻⁵²⁸ LPAI viruses are relatively common in poultry in the absence of control programs, while HPAI outbreaks were historically uncommon. However, the dissemination of Asian lineage H5 HPAI viruses by migratory wild birds has elevated the risk of outbreaks. Some epidemics in Europe (e.g., 2017-2018 H5N6) mainly affected wild birds, while other viruses (e.g., 2016-2017 H5N8) were often transferred to poultry.⁶⁹² Outbreaks in poultry and wild birds have decreased significantly in Europe since October 2023, compared to the past, perhaps due to increased immunity among wild birds and/or a change in the composition of the circulating viruses, though other factors such as underreporting are also possible.

LPAI viruses usually cause mild illnesses or asymptomatic infections in birds, including chickens and turkeys, but outbreaks can be more severe when there are concurrent infections or other exacerbating factors.^{2,58,180} HPAI viruses, in contrast, have cumulative morbidity and mortality rates that may approach 90-100% in chickens and turkeys.^{2,12} Most HPAI viruses spread rapidly though the flock, and any birds that survive are usually in poor condition, though there are reports of milder and more

limited outbreaks, including some caused by Asia lineage H5 viruses.^{529-530,620}

Morbidity and mortality rates in other domestic and wild species are variable. Some birds, such as waterfowl, are minimally affected by many HPAI viruses, with few or no deaths, but mortality may approach 100% in others.^{10,32,132,149,152-153,165-171,175,183,185-189,461,484} Some Asian lineage H5N1 viruses and reassortants can be highly virulent even in waterfowl, and their introduction may be heralded by unusual deaths among wild birds (e.g., swans in Europe, crows in Pakistan).^{1,32,46,138-139,144-145,147,150,154,158,161-163,221,223,364-365,471,485,531} Certain individuals within a species also seem to be more susceptible, sometimes but not always due to factors such as age or comorbidities.^{241,487,663,699}

Mammals

Pigs seem to be infected fairly regularly by avian influenza viruses from birds, often with only minor consequences even when the virus is an Asian lineage H5 HPAI virus.^{1,5,17,19,36,39,46,99,151,193-195,197-201,253,415,644} Studies often report antibodies to avian viruses in < 1% to 5% of the pigs sampled, though higher rates have also been seen, including in reports from impoverished areas where pigs are fed scraps that may include dead bird carcasses.^{17,36,99,193-195,197-201,229,276-277,415,532}

Clinical cases in other mammals seem to be sporadic and uncommon, typically with one to a few cases reported at a time.^{7,28,31,33,626,677,686} A few avian influenza outbreaks have been documented in mink, cats, horses, cattle, goats and marine mammals. In 1984, an H10N4 virus affected 33 mink farms in Sweden, with nearly 100% morbidity and 3% mortality.^{1,31} An H9N2 outbreak among mink in China was milder, with no elevated mortality, and some additional farms with no history of outbreaks had seropositive mink.^{204,254} An outbreak caused by an H7N2 LPAI virus at three New York animal shelters affected approximately 500 cats, mostly with mild to moderate respiratory signs,^{636,674} and an H3N8 virus caused an extensive epidemic among horses in China in 1989.²⁷⁸⁻²⁷⁹ The latter virus circulated for a few years in horses before disappearing. Mortality was initially around 20-30%, but later became minimal.

The Asian lineage H5 HPAI viruses, which are widespread, have caused a number of clinical cases in mammals, with some of the most severe illnesses reported in cats and other felids.^{23-26,29,31-32,37,191,233,235,488,618,639,655} Both Eurasian and North American reassortant viruses can cause severe as well as mild cases in mammals. Reports that compared experimental infections in cats and dogs found that cats appeared more likely to develop severe clinical signs from an H5N1 virus, and they were more readily infected with an H5N8 virus though the symptoms were mild.^{242,488,727} Nevertheless, serological studies suggest that asymptomatic or mild cases are possible in both species. Reported seroprevalence to various avian influenza viruses, including H5 viruses, ranges from < 2% to 45% in dogs and from < 2% to 73% (the latter a very small sample of 11 cats in Thailand) in cats, though most studies in both species found antibodies

in less than 5% of the animals sampled.^{18,30,34-35,43,229,237-238,255,283,488,533-534,690,729}

In 2024, a number of cattle herds in the U.S. were found to be infected with Asian lineage H5N1 viruses. While the virus appears to have been introduced into some herds via wild birds, some evidence suggests it may have also spread between cattle in close contact at dairies. The means of virus spread in these animals has not yet been established, but live viruses have been found in milk, and viral nucleic acids were detected in nasal swabs from cattle with respiratory signs. In some Texas herds, cases appeared to peak about 4–6 days after the first signs of illness were observed, then diminished over the next 2 weeks, with most cows subsequently returning slowly to regular milking. Approximately 10-15% of the herd was usually affected, with clinical cases most common in multiparous cows during middle to late lactation. Other outbreaks in the Americas included one H5N1 outbreak in a goat herd exposed to sick poultry; mass deaths among sea lions infected with H5N1 viruses in Peru during an outbreak among seabirds; and the detection of H5N1 viruses in a number of stranded seals in North America during outbreaks in wild birds.

Infections in Humans

Incubation Period

The incubation period for Asian lineage H5N1 HPAI and H7N9 LPAI/ HPAI virus infections is estimated to be about 3-5 days in most cases, with a range of 1-13 days in H7N9 virus infections, and up to 8 and possibly 17 days in H5N1 virus infections.^{205,209,391,418-419,537,538,708}

Clinical Signs

Asian lineage H5 HPAI viruses

Many documented infections with Asian lineage H5N1 HPAI viruses, which often affect younger people, have been severe.^{12,108,328} Common initial signs are 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.^{205,209,539} Respiratory signs are not always present at diagnosis; two patients from Vietnam had acute encephalitis and no obvious respiratory involvement.⁵⁴⁰ Similarly, a patient from Thailand initially exhibited only fever and diarrhea.⁵⁴⁰ Lower respiratory signs (e.g., chest pain, dyspnea, tachypnea, sometimes with blood-tinged sputum) often develop soon after the onset of the illness.^{205,209} Most patients with lower respiratory involvement deteriorate rapidly, and serious complications including heart failure, kidney disease, encephalitis and multiorgan dysfunction are common in the later stages.^{205,209,539}

Milder cases have been reported occasionally, particularly among children, some of whom had symptoms consistent with childhood respiratory illnesses and recovered without antiviral treatment.^{328,541,615} Several mild cases were

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also described during recent poultry outbreaks in Europe and North America, though it is possible that the use of antiviral drugs influenced their course. In one case, a man in his 80s, who had been exposed to infected birds in the U.K., was prescribed prophylactic oseltamivir and remained asymptomatic.⁶⁷¹ A man in his 40s in the U.S. had no symptoms except fatigue,⁶⁷⁸ while two people exposed to infected dairy cattle in the U.S. only developed self-limited conjunctivitis and another person had mild upper respiratory signs. Family members of these individuals did not become infected. At least some H5N1 reassortants in the Americas can, however, also cause severe illness. Two cases with severe respiratory signs and systemic illnesses were reported in 2023, one in a previously healthy 53-year-old man in Chile and the other in a 9 year old child exposed to sick poultry in Ecuador.

Most reported illnesses caused by Asian lineage H5N6 HPAI viruses, to date, occurred in older adults, but clinically resembled cases caused by H5N1 viruses, with a high case fatality rate.^{313-315,612,641,658,692,721} Rare H5N6 cases documented in children included mild illnesses in a few young children but also a fatal case in an obese 9-year-old.^{313-315,612,617,658,692-693,721,725} As of May 2022, no reports of illnesses caused by H5N8 viruses have been published, though there are a few reports of virus isolation and/or the detection of nucleic acids in nasal swabs from asymptomatic poultry workers, and a few people seroconverted in paired serum samples.⁶⁸²

Zoonotic H7N9 LPAI viruses in China

A number of clinical cases caused by H7N9 viruses have been reported in China, most often in older people.^{14,15,260,411,542,545} The illnesses caused by LPAI viruses and the 2017 HPAI viruses appear to be clinically similar.⁷²³ The most common symptoms have been fever and coughing, and a minority of patients had diarrhea and vomiting, but conjunctivitis seems to be uncommon.^{537,545} Many patients have deteriorated rapidly, developing severe pneumonia with dyspnea and/or hemoptysis, frequently complicated by acute respiratory distress syndrome and multiorgan dysfunction.^{412,537,544-545} Concurrent bacterial and/or fungal infections (including ventilator-associated pathogens) were identified in some patients, and may have contributed to the clinical picture.^{412,537,708} There are, however, also a few reports of uncomplicated cases with mild upper respiratory signs or fever alone, especially in children.^{260,418,537,543,545-546} Serological surveys and case investigations also indicate the possibility of undiagnosed asymptomatic infections or mild cases.^{354,411,537,547-550}

Other avian influenza viruses

Illnesses caused by H9N2 viruses have mainly been reported in children, including infants.^{108,328-334,675,706} Most of these cases were 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. More severe respiratory illnesses have been reported occasionally, including one case in a 17-month-old child initially thought to have a respiratory

syncytial virus infection.⁶⁷⁵ All young patients to date, including a 3-month-old infant with acute lymphoblastic lymphoma, made an uneventful recovery. Acute, influenza-like upper respiratory signs or asymptomatic infections were also seen in some adults ranging in age from their 20s to 80s, though one 32-year-old developed pneumonia and a severely immunocompromised 47-year-old woman had respiratory failure.^{334,672} Two deaths occurred in adults with underlying medical conditions.⁷¹⁹

Conjunctivitis and/or mild to moderate upper respiratory signs have been reported in many people infected with various H7 LPAI or HPAI viruses, an H10N7 virus and some other subtypes.^{101,291,319-327,336,708} One mild clinical case occurred in a person exposed to H7N3-virus infected cats during an outbreak at an animal shelter, where serological testing of shelter employees and adopters also found significant antibody titers in one of 121 shelter workers.^{674,653} Human volunteers infected with H4N8, H10N7 and H6N1 viruses sometimes developed mild respiratory signs and other symptoms that resembled human influenza.³²⁸

However, there are also a few reports of serious illnesses. One H7N7 HPAI virus, which caused only mild symptoms in most people, resulted in fatal acute respiratory distress syndrome and other complications in a previously healthy person, while an H7N4 LPAI virus caused serious pneumonia in a 68-year-old woman with underlying comorbidities, and an LPAI H7N2 virus caused severe pneumonia in a person infected with both HIV and a member of the *Mycobacterium avium* complex.^{318,321,640} Severe lower respiratory tract disease, progressing in some cases to multiple organ failure and septic shock, was seen in three people, ranging in age from 55 to 75 years, infected with H10N8 viruses in China.^{316,335} Two of these cases were fatal despite treatment, though the youngest patient recovered with intensive care and antiviral drugs. An H10N3 virus caused severe pneumonia in a young person in China.⁶⁸³ More recently, an elderly woman with chronic illnesses who became coinfecting with an H10N5 virus and a seasonal human H3N2 virus in China became seriously ill. A 20-year-old woman infected with an H6N1 virus in China developed a persistent high fever, cough and dyspnea, with radiological evidence of lower respiratory tract disease, but made an uneventful recovery after treatment with oseltamivir and antibiotics.³¹⁷

Diagnostic Tests

The assays used to diagnose avian influenza virus infections in people are similar to those in animals.^{12,209,264} Commercial rapid diagnostic test kits for routine influenza diagnosis might detect some viruses; however, these tests are optimized for human influenza viruses, and their sensitivity for avian influenza viruses can be much lower.^{12,553-558} Testing that identifies the presence of an influenza A virus, but does not detect the hemagglutinins in human influenza viruses, might indicate a novel, possibly zoonotic, virus.¹² Specific tests for novel influenza viruses are generally performed by state, regional or national public health

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laboratories, and in some cases by reference laboratories capable of handling dangerous human pathogens such as H5N1 HPAI viruses.^{12,209} RT-PCR tests are available for Asian lineage H5N1 HPAI viruses as well as the zoonotic H7N9 viruses in China.^{209,418,551-552}

Serology is mainly employed in research, but it may occasionally be useful for retrospective diagnosis of a clinical case.³⁹⁰ Tests used for avian influenza serology in humans include the microneutralization assay, which is the most commonly used test, and other assays such as hemagglutination inhibition.^{209,328,554,559} Serology is not always reliable: titers to avian viruses in people may be low and sometimes decay quickly, especially in mild illnesses, and some people with virologically confirmed cases do not seem to seroconvert.^{324,327,560,617} Conversely, some titers may be caused by cross-reactivity with human influenza viruses.

Treatment

Treatment sometimes includes antiviral drugs, as well as symptomatic and supportive treatment.^{78,448,553,558,561-566} Phenotypic tests or gene-based testing can evaluate a virus's susceptibility to antiviral agents, but these tests are available in a limited number of laboratories and take several days to perform.⁵⁵⁴ Thus, the initial choice of drug is often empirical. Oseltamivir and other neuraminidase inhibitors are generally used for Asian lineage H5N1 HPAI and Chinese H7N9 viruses, as these viruses are often (H5N1) or usually (H7N9) resistant to adamantanes.^{12,209,261,362,527,539,540,544,567-568,570,657} 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.^{448,553,558,563-566} Antiviral resistance can develop rapidly, sometimes emerging even during treatment.^{1,78,558,569}

Prevention

Preventive efforts for zoonotic avian influenza viruses include controlling the source of the virus (e.g., eradicating HPAI viruses, implementing measures to reduce transmission in live poultry markets); avoiding contact with sick animals and their environments; employing good sanitation and hygiene when around birds (e.g., hand washing before contacting mucous membranes, eating or drinking); and using personal protective equipment (PPE) where appropriate.^{12,205,392,499,673} While the recommended PPE differs, depending on 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.^{12,499,572} Certain cultural practices in some impoverished areas, such as keeping poultry inside the home to observe sick birds or to prevent theft or predation, or eating sick birds to prevent the loss of a valuable protein source, are likely to increase the risk of infection.⁶²⁷

Because HPAI viruses have been found in meat and/or eggs from several avian species,^{71,178,379-385,454,573-577} careful food handling practices are important when working with raw poultry or wild game bird products in endemic areas, and meat, eggs or other tissues should be completely cooked

before eating.^{12,499,578} Eating sick poultry or wild birds increases the risk of exposure during food preparation, and should be avoided.⁴⁹⁹ Milk from cows infected with Asian lineage H5 HPAI viruses can also contain live viruses, though they are destroyed by heat treatment (e.g., pasteurization). 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 and international agencies.^{12,499,572,580} In some cases, these recommendations may include antiviral prophylaxis, for instance in people who cull birds infected with Asian lineage H5N1 HPAI viruses.^{12,45,540} Vaccines for humans are not in routine use, but they have been developed for some avian influenza subtypes in the event of an epidemic.^{12,579,660} People who become ill should inform their physician of any exposure to avian influenza viruses.

Morbidity and Mortality

The consequences of infection with avian influenza viruses vary greatly. While many viruses seem to mostly cause conjunctivitis or mild respiratory illnesses, some appear more likely to cause severe disease. Like human influenza viruses, even less virulent avian influenza viruses can occasionally cause a serious clinical case, typically (though not invariably) in the elderly, very young children, and those with underlying illnesses.

H5N1 avian influenza

As of spring 2022, 863 laboratory-confirmed human infections with Asian lineage H5N1 HPAI viruses had been reported to the World Health Organization (WHO) since 1997.⁷¹⁹ Additional probable cases not included in this count may raise the total to around 900.⁶⁵¹ H5N1 HPAI viruses are, nevertheless, considered to affect humans only rarely: the large number of cases is attributed to the widespread circulation of these viruses for more than 2 decades, resulting in frequent human exposure in some countries. Most clinical cases have been seen in younger people with no predisposing conditions.²⁰⁹ The overall case fatality rate in known, laboratory-confirmed cases is estimated to be around 53-56%,^{582,719} though it appears to be lower in young children than adults, and there also seem to be significant differences between countries.^{13,16,312,539, 582,587,615} Case fatality rates as low as 28% have been reported during some time periods (e.g., 2006-2010) in Egypt, where many of the reported cases affect children.^{582,646,651}

Antibodies to H5N1 viruses and reports of seroconversion have been seen in some poultry-exposed populations, fueling speculation on the possibility of additional asymptomatic or mild infections.^{229,338-340,342-345,351-352,354,588-591,619,635,646,665,684,697} Most of these studies suggest that exposure is low (e.g., < 0.5-2%) in the general population, while seropositivity in poultry-exposed groups ranges from < 0.5% to 10% or higher, with a few reports of antibodies in > 40% of tested poultry workers or hospital staff in parts of Asia during active outbreaks. Rare virologically-confirmed asymptomatic or mild cases have also been recognized; however, only a few of these people

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had not received antiviral drugs, complicating the interpretation of these cases.^{328,541,586-587,593,671,678,708} Cross-reactivity with human influenza viruses in serological assays and, conversely, poor seroconversion to H5N1 viruses, might influence estimates of exposure, and the true prevalence of mild cases is still uncertain and controversial.⁶⁴⁶

Other Asian lineage H5 viruses

Asian lineage H5N6 HPAI viruses have become common in poultry in parts of Asia, resulting in occasional human infections.⁷¹² As of April 2022, 78 laboratory-confirmed cases and 32 deaths had been reported to the WHO, and sporadic cases continue to be reported.⁷¹⁹ Many of these cases, which often affected older adults, were severe.^{313-315,617,641} There are a few known mild illnesses in children, at least one of which was identified through a routine flu surveillance program in Laos; however, one fatal case was seen in an obese 9-year-old.^{313-315,612,617,658,692-693,721,725}

A different H5N6 HPAI virus found in Europe has not been linked to any human infections, as of 2022.⁷⁰⁴

H7N9 avian influenza

Approximately 1500 laboratory-confirmed illnesses caused by H7N9 viruses have been reported to WHO by China, as of April 2022.⁷¹⁹ They mainly occurred during the winter months from 2013 to 2017, with sporadic cases seen between winter outbreaks and after 2017.^{14,15,260-261,263,549,657,724} The number of cases reported each year varied, with 134 laboratory confirmed cases in spring 2013, 306 cases in 2013-14, 219 in 2014-15, 114 in 2015-16, and 447 in 2016-17.⁷¹⁵ A human case in 2019 was caused by a variant distinct from the 2017 strains, suggesting the development of resistance to the vaccines used to control infections in poultry.⁷²⁴ Both LPAI and HPAI viruses caused human cases in 2016-2107.⁶⁵⁷ The severity of these illnesses appeared to be similar, though the case fatality rate was slightly higher in the HPAI group (a much smaller number of patients in the HPAI group makes the significance of this finding difficult to assess).⁷²³

Most human cases were associated with live bird poultry markets, although some occurred on infected farms.^{15,264,390-392,549,594-596} 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.⁵⁴⁹ Elderly men were overrepresented among the cases 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.^{391,597}

Many of the reported cases were in older individuals, and the risk of serious illness and death increased significantly with age, while cases in children were often mild.^{15,260,264,391,411,537,542-543,550,618,694-695,712} Concurrent

diseases or other comorbidities were noted in many patients, although serious cases and fatalities also occurred in previously healthy individuals, including some who were

young or middle-aged.^{260,264,363,391,411,418,537,542,598,713} The overall case fatality rate in the cases reported to WHO is currently 39%.⁷¹⁹ However, serological studies have found some evidence of exposure in people with no history of illness, suggesting that some milder cases may be missed and the fatality rate is likely to be lower.^{354,547-549,685} The reported seroprevalence ranges from about 1% to 17% in poultry workers and live bird market workers, but appears to be much lower in the general population.^{354,547-549, 662,685,714,720}

Other avian influenza viruses

Many of the sporadic illnesses caused by other H7 LPAI or HPAI viruses, H9N2 LPAI viruses and various additional LPAI subtypes in healthy people have been mild.^{12,16,101,108,195,291,319-333,336,653,672,674-675,706,708} The few serious cases were mostly reported in those who are elderly and/or had underlying illnesses; nevertheless, there are rare reports of severe illnesses even in healthy young people.^{316-318,321,335,640,683} These cases may be unpredictable: one H7N7 HPAI virus caused a fatal illness in a healthy person while affecting others only mildly.³²¹

The possibility of additional unrecognized mild cases or asymptomatic infections is suggested by the occurrence of antibodies to H4, H5, H6, H7, H9, H10, H11 and H12 viruses, generally at a relatively low prevalence, in people who are exposed to poultry or waterfowl; seroconversion up to 4% among poultry workers during some H7 virus outbreaks; and rare seroconversion to H6, H7 and H12 viruses in prospective studies of adults with poultry exposure in Cambodia and rural Thailand.^{195,328,338-354,591,602-603,605-608,685} No symptomatic cases were identified in these prospective studies. Exposure to avian H1 and H3 viruses is also likely, but it can be difficult to distinguish from human influenza viruses by serology.

Internet Resources

[Canadian Food Inspection Agency \[CFIA\]. Notifiable Avian Influenza Hazard Specific Plan](#)

[Centers for Disease Control and Prevention, U.S. Avian Influenza](#)

[European Center for Disease Prevention and Control \(ECDC\). Avian Influenza](#)

[Public Health Agency of Canada. Pathogen Safety Data Sheets](#)

[The Merck Manual](#)

[The Merck Veterinary Manual](#)

[United States Department of Agriculture \(USDA\) Animal and Plant Health Inspection Service \(APHIS\)](#)

[USDA APHIS. Avian Health](#)

[United States Geological Survey \(USGS\). National Wildlife Health Center. Wildlife Health Bulletins.](#)

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[USGS Wildlife Health Bulletin #05-03 \(with recommendations for field biologists, hunters and others regarding contact with wild birds\)](#)

[World Health Organization. Influenza. Avian and Other Zoonotic](#)

[World Organization for Animal Health \(WOAH\)](#)

[WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals](#)

[WOAH Terrestrial Animal Health Code](#)

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