

# A review of avian influenza in different bird species

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## Abstract

Only type A influenza viruses are known to cause natural infections in birds, but viruses of all 15 haemagglutinin and all nine neuraminidase influenza A subtypes in the majority of possible combinations have been isolated from avian species. Influenza A viruses infecting poultry can be divided into two distinct groups on the basis of their ability to cause disease. The very virulent viruses cause highly pathogenic avian influenza (HPAI), in which mortality may be as high as 100%. These viruses have been restricted to subtypes H5 and H7, although not all viruses of these subtypes cause HPAI. All other viruses cause a much milder, primarily respiratory disease, which may be exacerbated by other infections or environmental conditions. Since 1959, primary outbreaks of HPAI in poultry have been reported 17 times (eight since 1990), five in turkeys and 12 in chickens. HPAI viruses are rarely isolated from wild birds, but extremely high isolation rates of viruses of low virulence for poultry have been recorded in surveillance studies, giving overall figures of about 15% for ducks and geese and around 2% for all other species. Influenza viruses have been shown to affect all types of domestic or captive birds in all areas of the world, but the frequency with which primary infections occur in any type of bird depends on the degree of contact there is with feral birds. Secondary spread is usually associated with human involvement, probably by transferring infective faeces from infected to susceptible birds. © 2000 Elsevier Science B.V. All rights reserved.

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## 1. Aetiology

A disease capable of causing extremely high mortality in infected fowls was first defined in 1878 and was known as ‘fowl plague’. The causative organism of this disease was shown to be an ultra-filterable agent, i.e. a ‘virus’, as early as 1901, but it was not until 1955 that the relationship of this and other milder viruses isolated from birds with

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mammalian influenza A viruses (first isolated in the 1930s) was demonstrated (Schafer, 1955). Only type A influenza viruses are known to cause natural infections of birds, but viruses of all 15 (H1–H15) haemagglutinin (HA) and all nine (N1–N9) neuraminidase (NA) influenza A subtypes in the majority of possible combinations have been isolated from avian species.

## **2. Avian influenza pathogenicity**

Influenza A viruses infecting poultry can be divided into two distinct groups on the basis of their ability to cause disease in chickens. The very virulent viruses cause ‘fowl plague’, now termed highly pathogenic avian influenza [HPAI], in which mortality may be as high as 100%. These viruses have been restricted to subtypes H5 and H7, although not all viruses of these subtypes cause HPAI. All other viruses cause a much milder, primarily respiratory disease designated low pathogenicity avian influenza [LPAI], which, nevertheless, may be exacerbated by other infections or environmental conditions resulting in a much more serious disease.

The haemagglutinin glycoprotein for influenza viruses is produced as a precursor, HA0, which requires post translational cleavage by host proteases before it is functional and virus particles are infectious (Rott, 1992). The HA0 precursor proteins of avian influenza viruses of low virulence for poultry have a single arginine at the cleavage site and another at position –4. These viruses are limited to cleavage by host proteases such as trypsin-like enzymes and thus restricted to replication at sites in the host where such enzymes are found, i.e. the respiratory and intestinal tracts. HPAI viruses possess multiple basic amino acids [arginine and lysine] at their HA0 cleavage sites either as a result of apparent insertion or apparent substitution (Vey et al., 1992; Wood et al., 1993; Senne et al., 1996a) and appear to be cleavable by a ubiquitous protease[s], probably one or more proprotein-processing subtilisin-related endoproteases of which furin is the leading candidate (Stieneke-Grober et al., 1992). These viruses are able to replicate throughout the bird, damaging vital organs and tissues which results in disease and death (Rott, 1992). Typical cleavage site amino acid sequences for H5 viruses of high and low virulence are shown in Table 1.

As discussed above, HPAI has been recognised for well over 100 years and it seems clear that for the first third of the 20th century the virulent disease was endemic in some countries and occurred fairly regularly in others (review Alexander, 1987). Since the first report of an HPAI outbreak caused by a virus of H5 subtype, in 1959 (Pereira et al., 1965), primary outbreaks of HPAI in poultry have been reported 17 times, five in turkeys and 12 in chickens (Table 2). Nine were caused by influenza A viruses of H7 subtype and eight by viruses of H5 subtype; eight (four of each subtype) have occurred since 1991. Most of the 17 outbreaks have shown very limited spread, some, such as that in England in 1991 (Alexander et al., 1993), being self-limiting to a single flock of birds. However, in the USA in 1983 (Eckroade and Silverman-Bachin, 1987), Mexico in 1994 (Villarreal and Flores, 1998) and Pakistan in 1995 (Naeem, 1998) the disease became widespread infecting many flocks, causing enormous losses both economically and in the number of birds that died or were slaughtered as part of control policies.

Table 1

Amino acid sequences at the HA0 cleavage site of H5 influenza viruses in relation to their virulence for chickens<sup>a</sup>

Virus	Amino acids at HA0 cleavage site
H5 viruses low pathogenicity	
Various sources >100 isolates	-PQRETR*GLF-
H5 viruses high pathogenicity	
1994/5 Mexican isolates (H5N2)	-PQRKRKTR*GLF-
Chicken/Scotland/59 (H5N1)	-PQRKKR*GLF-
Tern/S. Africa/61 (H5N3)	-PQRETRRRQKR*GLF-
Chicken/Pennsylvania/1370/83 (H5N2)	-PQKKKR*GLF-
Turkey/England/50-92/91 (H5N1)	-PQRKRKTR*GLF-
HK/156/97 (H5N1) [human]	-PQRETRRRKKR*GLF-
ck/HK/97 (H5N1)	-PQRETRRRKKR*GLF-
Poultry/Italy/97 (H5N2)	-PQRRRKKR*GLF-

<sup>a</sup> Data taken from Genbank or viruses sequenced at VLA, Weybridge. Arginine (R) and lysine (K) are basic amino acids.

### 3. Host range and current situation

#### 3.1. Wild birds

The first reported isolation of an influenza virus from feral birds was the HPAI H5N3 subtype virus obtained in 1961 from common terns (*Sterna hirundo*) in South Africa (Becker, 1966), but it was not until the mid-1970s that any systematic investigation of influenza in feral birds was undertaken. These revealed the enormous pools of influenza viruses now known to be present in the wild bird population.

Table 2

Reported HPAI isolates from poultry since 1959

A/chicken/Scotland/59 (H5N1)
A/turkey/England/63 (H7N3)
A/turkey/Ontario/7732/66 (H5N9)
A/chicken/Victoria/76 (H7N7)
A/chicken/Germany/79 (H7N7)
A/turkey/England/199/79 (H7N7)
A/chicken/Pennsylvania/1370/83 (H5N2)
A/turkey/Ireland/1378/83 (H5N8)
A/chicken/Victoria/85 (H7N7)
A/turkey/England/50-92/91 (H5N1)
A/chicken/Victoria/1/92 (H7N3)
A/chicken/Queensland/667-6/94 (H7N3)
A/chicken/Mexico/8623-607/94 (H5N2)
A/chicken/Pakistan/447/94 (H7N3)
A/chicken/NSW/97 (H7N4)
A/chicken/Hong Kong/97 (H5N1)
A/chicken/Italy/330/97 (H5N2)

Although about 90 species from some 12 of the 50 Orders of birds have yielded influenza viruses (Stallknecht, 1998), the number, variety and widespread distribution of influenza viruses has been far greater in waterfowl, Order Anseriformes, than in other birds. In the surveys listed by Stallknecht and Shane (1988) a total of 21,318 samples from all species resulted in the isolation of 2317 (10.9%) viruses. Of these samples 14,303 were from birds of the Order Anseriformes and yielded 2173 (15.2%) isolates. The next highest isolation rates were 2.9 and 2.2% from the Passeriformes and Charadriiformes, respectively and the overall isolation rate from all birds other than ducks and geese was 2.1%. Each year waterfowl congregate in huge flocks, usually on lakes, before migratory flights are undertaken. Data from the 3-year study by Hinshaw et al. (1980) on ducks congregating on lakes in Alberta, Canada prior to their southern migration showed that influenza virus isolation rates from juvenile ducks may exceed 60%.

Stallknecht (1998) stressed the differences reported in the gene pools of influenza viruses in different species of wild birds, especially between the Anseriformes and Charadriiformes (Kawaoka et al., 1988). In particular, of the H subtypes most often isolated from gulls and shorebirds, H9 has rarely been reported in ducks and geese and H13 never.

HPAI viruses have been isolated rarely from feral birds and, apart from tern/S. Africa/61, when they have, it has usually been in the vicinity of outbreaks of HPAI in poultry or geographically and chronologically close to known outbreaks in poultry. This is keeping with the theory that the proposed mechanism for the emergence of HPAI viruses occurs only after the viruses have crossed from feral birds to poultry (Perdue et al., 1998).

### 3.2. Caged pet birds

Since 1975 when the first isolates from caged birds were recorded, isolates, from a variety of different countries, have been mainly of H4 or H3 subtypes. The majority of influenza viruses from caged birds come from passerine species and only rarely are psittacines infected. Although the presence of influenza viruses in birds held in quarantine is monitored continually in several countries around the world, there appears to have been periods, often lasting several years when no isolations have been made. These aspects are demonstrated by the isolations from captive caged birds in Great Britain shown in Table 3.

### 3.3. Ratites

The first isolations of influenza viruses from ratites were viruses of H7N1 subtype, but low pathogenicity in chickens, obtained as a result of an epizootic in ostriches in South Africa in 1991 in which high mortality was seen in young birds (Allwright et al., 1993). In 1994, influenza viruses of H5N9 were isolated from ostriches in South Africa and from emus and casowaries in the Netherlands after they had been rejected for importation into the USA following the isolation of an H5N9 virus from routine cloacal swabs (Koch, 1995). H5N2 subtype viruses were isolated from ostriches in Zimbabwe in 1995 and 1996

Table 3  
Isolations of influenza viruses from birds in quarantine in Great Britain

Date	Subtype	Number
1975	H4N6	29
1976–06.1977	H3N8	58
07.1977–1978		None
1979	H4N6	2
	H10N7	2
	H7N7	1
1980–06.1987		None
1987	H3N8	1
1988	H3N8, H3N6	5
	H4N6	4
1989	H3N8	2
	H4N2, H4N3, H4N6	19
	H7N7	1
1990	H4N3, H4N8	4
01.1991–06.1991	H4N1, H4N8	4
07.1991–04.1993		None
05.1993–08.1993	H4N6	4
08.1993–09.1997		None
10.1997	H4N6	9
10.1997–31.12.1998		None

and also in ostriches imported into the Netherlands and Denmark in 1996. In Denmark the isolations were associated with 146/506 deaths within 23 days of importation, however the virus was of low pathogenicity for chickens (Jorgensen et al., 1998). Virus of H9N2 was isolated from ostriches in South Africa in 1995. In USA, influenza viruses have been isolated from rheas and emus and Panigrahy and Senne (1998) list the following subtypes from such birds H3N2 in 1992, H4N2, H5N2, and H7N1 in 1993, H4N6, H5N9 and H10N4 in 1994, H7N3 in 1995 and H7N3 and H10N7 in 1996. All these were of low virulence for chickens.

### 3.4. Domestic poultry

During 1994–1999, infections of poultry with influenza viruses of H9 subtype have been noticeably common. Outbreaks due to H9N2 subtype occurred in domestic ducks, chickens and turkeys in Germany during 1995–1996 (Werner, 1998) and 1998, in chickens in Italy in 1994 (Papparella et al., 1995) and 1996 (Fioretti et al., 1998), in pheasants in Ireland in 1997 (Campbell, 1998), in ostriches in South Africa in 1995, in turkeys in the USA in 1995 and 1996 (Halvorson et al., 1998) and in chickens in Korea in 1996 (Mo et al., 1998). While outbreaks with H9N3 subtype virus were reported in China in 1994 (Yingjie, 1998). More recently, H9N2 viruses have been isolated in association with widespread and serious disease problems in commercial chickens in Iran and Pakistan.

### *3.4.1. Chickens*

In the second half of the 20th century, reports of influenza infections of chickens have been relatively rare in comparison to infections of domestic turkeys or ducks despite the much higher populations of chickens throughout the world. For example in the USA, despite frequent influenza epizootics in turkeys in some states, only three outbreaks in chickens were recorded between 1964 and 1982 (Pomeroy, 1982).

Despite the low incidence of influenza infections of chickens throughout the world, 12 of the 17 primary outbreaks of HPAI since 1959 were in chickens and significant spread occurred in Pennsylvania and neighbouring states in the USA during 1983–1984 and in Mexico and Pakistan in 1994–1995.

The outbreaks in Pennsylvania began in April 1983 and were associated with isolations of H5N2 influenza viruses which were of low pathogenicity in laboratory tests. This virus spread to flocks throughout Pennsylvania between April and September 1983, causing mild to severe respiratory disease and egg production problems in layers, but mortality was low, usually 0–15% (Eckroade et al., 1984). However, in October 1983 outbreaks of the disease with clinical signs of classical HPAI and high mortality were reported. Viruses from these outbreaks were also typed as H5N2 but were confirmed by laboratory tests as highly pathogenic (Eckroade et al., 1984). Despite the implementation of a stamping out policy, control proved difficult and it was not until 1st July 1984 that the final outbreak was confirmed, in Virginia. The outbreaks had resulted in the slaughter of more than 17,000,000 birds, with compensation and other costs in excess of US\$ 60,000,000.

In 1986 a virus similar to that responsible for the 1983–1984 outbreaks reappeared in five north-east states of the USA (Garnett, 1987). In each state the index cases were linked to live bird markets in New York City. A survey showed that in early 1986, 26 of 44 live bird markets in New York and 12 of 26 in New Jersey had birds which were positive for H5N2 virus (Garnett, 1987).

In Pakistan, the epizootic began in the northern part of the country (a wintering area for migratory birds) in December 1994 and spread to 156 of 286 farms in a 100 km radius affecting 2.2 million birds with mortality between 51–100% (Naeem, 1998). Virus isolates were identified as highly pathogenic avian influenza A viruses of H7N3 subtype. Nucleotide sequencing of the haemagglutinin cleavage site region of the HA gene indicated some variation in different isolates (Alexander et al., 1996). Vaccination and increased biosecurity programmes were implemented in the affected region of Pakistan and no outbreaks have been recorded since August 1995 (Naeem, 1998).

In Mexico, the episode of HPAI was more complicated and in some ways similar to the epizootic seen in Pennsylvania in 1983 (Webster and Kawaoka, 1988). Investigations of respiratory disease led to the isolation of avian influenza viruses in three states in May 1994; the viruses isolated were shown to be of H5N2 subtype, but had low pathogenicity for chickens (Campos-Lopez et al., 1996; Villarreal and Flores, 1998). Between June to December 1994, isolates of low pathogenicity H5N2 virus were obtained from poultry in 11 states. In January 1995, several flocks in the states of Puebla and Queretaro which had shown high mortality and lesions characteristic of HPAI (Senne et al., 1996b) were reported as infected with HPAI virus of H5N2 subtype. It seemed highly likely that the original virus of low pathogenicity had mutated to virulence, the mechanism by which this may have occurred is discussed below. The Mexican authorities applied policies of

depopulation, movement restrictions and vaccination to control both high and low pathogenicity viruses.

Eight HPAI outbreaks in backyard poultry flocks infected with H5N2 virus were reported in Italy in 1997–1998 (Fioretti et al., 1998; Capua et al., 1999).

Outbreaks of H5N1 HPAI occurred on three farms in Hong Kong during March–May 1997 with mortalities ranging from 70–100% (Claas et al., 1998) and subsequent spread to live bird markets in Hong Kong. As a result of the apparent spread of this virus to humans (Claas et al., 1998) the entire chicken population of Hong Kong of over one million birds was slaughtered.

Three HPAI outbreaks occurred in chickens in Australia during the 1990s, one in Victoria in 1992 (Forsyth et al., 1993), another in Queensland in 1995 (Westbury, 1998) and the third in New South Wales in 1997; each case was caused by a virus of H7 subtype the first two with N3 the third with N4. In all there have been five reported outbreaks in chickens in Australia all with H7 viruses. In each case the disease outbreaks were limited.

#### 3.4.2. *Turkeys*

Since 1963, when the first reported influenza isolation was made from turkeys, most of the major turkey-producing countries have had disease problems associated with influenza infections. Several distinct epizootiological patterns have been seen. In the USA, since 1964, influenza outbreaks in turkeys have been reported from 19 different states spread across the country. In the majority of these states, outbreaks have been sporadic and infrequent but in California and Minnesota, where turkey farms are heavily concentrated and situated on migratory waterfowl flyways, influenza virus infections have been seen more consistently. In Minnesota, influenza outbreaks in turkeys have occurred every year since 1966, occasionally reaching particularly severe proportions (Pomeroy, 1982; Halvorson et al., 1998). In 1995, two separate major outbreaks caused by LPAI viruses occurred in turkeys in the USA (Halvorson et al., 1998). One caused by virus of H7N3 subtype affected turkeys in Utah and was associated with about 40% mortality in 0- to 4-week-old birds. In most cases, mortality was associated with dual infections with *Escherichia coli* or *Pasteurella multocida*. The other outbreak occurred in Minnesota and was caused by virus of H9N2 subtype. During 1995, 178 turkey farms were infected resulting in the worst economic loss to influenza infections [approximately US\$ 6,000,000] recorded in one year in Minnesota (Halvorson et al., 1998). Inactivated vaccines were used to combat the disease outbreaks in both Utah and Minnesota.

In Canada, outbreaks were reported in turkeys every year between 1963 and 1971 but of the 69 outbreaks reported in Ontario between 1963 and 1980, only six were recorded during 1971 to 1980; this dramatic reduction was attributed to measures taken to prevent introduction once it was clear that initially wild birds were responsible (Lang, 1982).

In Great Britain, influenza outbreaks in turkeys have been restricted to one or two isolated incidents in the years recorded, with the exception of 1979 when 16 farms were affected (Alexander, 1982). Of the 22 separate introductions recorded in turkeys in Great Britain between 1963 and 1993, 17 were on farms in Norfolk, a county that includes important 'stop-over' areas for migratory waterfowl.

In 1999, LPAI virus of H7N1 subtype caused serious widespread problems in turkey flocks in Northern Italy. As with other LPAI outbreaks, relatively high mortality was occasionally seen especially in young poults.

Compared to the frequency of isolations of influenza viruses of low pathogenicity from turkeys, HPAI virus infections have been rarely reported. Excluding spread to turkeys during the Pennsylvania epizootic, which affected mainly chickens, of the 17 reported isolations of HPAI since 1959 only five were primarily from turkeys (Table 2). Interestingly, only one has been reported in turkeys in North America where infections with LPAI viruses are common, in 1966 in Ontario, Canada; whereas four have been reported in the British Isles where infections with LPAI viruses are rare, three in the county of Norfolk in England (1963, 1979 and 1991) and one in Ireland (1983).

#### 3.4.3. Commercial ducks

The influenza status of commercial ducks in most countries is poorly understood or has not been investigated. When surveillance of commercial ducks has been undertaken, enormous pools of virus and many subtype combinations have been detected, especially from meat birds which are usually fattened on open fields. For example, Alexander (1982) reported the isolation of 32 viruses from 60 pools of cloacal swabs taken from ducks at slaughter. Studies in Hong Kong in the late 1970s and early 1980s isolating virus from carcasses at duck dressing plants or on duck farms indicated about 6% of the ducks were infected with influenza viruses of various subtypes (Shortridge, 1982).

HPAI virus was reported to be infecting duck flocks, in Ireland in 1983, no disease signs were seen and infection only established following virus isolation (Alexander et al., 1987).

#### 3.4.4. Other domestic poultry

Other commercially reared birds represent a very small proportion of domestic poultry in most countries. Some such birds (e.g. pheasants and geese) are reared under semi-wild conditions. Isolations of influenza viruses have been reported from muscovy ducks (*Cairinia moschata*), mallard ducks (*Anas platyrhynchos*), pheasants (*Phasianus* spp.), Japanese quail (*Coturnix coturnix japonica*), chukars (*Alectoris chukar*), guinea fowl (*Numida meleagris*), and various types of goose.

## 4. Comment

The present understanding of the ecology of influenza viruses in birds is that there are large pools of influenza A viruses covering all known subtypes in feral birds, especially ducks and geese. The outbreaks of both HPAI and LPAI in domestic poultry seem to be the result of introduction initially from feral birds. Despite the frequency with which influenza viruses are isolated from domestic poultry in some countries, in none is it considered that these viruses are enzootic in turkeys or chickens. Even when outbreaks occur regularly, such as in Minnesota, USA, the considerable variation in virus subtype, the differences in the number of outbreaks seen each year and the seasonal relationship of outbreaks all suggest that the influenza epizootics are brought about as a result of new



primary introductions. Most of the evidence obtained on the prevalence of influenza in different types of poultry and different geographical locations supports the view that the primary introduction is from feral birds. So that influenza viruses are most likely to infect poultry reared in a way that allows contact with feral birds, such as fattening ducks reared on fields or ponds, or turkeys and ostriches reared on range, especially when these are also situated on migratory waterfowl routes, and far less likely to occur in poultry reared in bird-proof confinement. This understanding also allows strategies for the prevention of introduction to poultry to be developed. However, in many countries practices likely to encourage wild birds to poultry farms, such as surface storage of drinking water, rearing mixed species on the same farm, failure to bird-proof food stores and even the construction of artificial ponds to attract waterfowl are still pursued.

When influenza viruses do move from feral birds to poultry, they may spread from flock to flock and farm to farm by a number of methods. Primarily, these consist of the mechanical transfer of infective faeces from infected to susceptible birds and inevitably there is human involvement in this transfer. Prevention of secondary spread after an initial outbreak can be achieved by good biosecurity procedures, especially control of movements of personnel and equipment to and from the premises. Where such practices are not enforced widespread distribution of the virus may occur with associated disease and economic losses. For viruses of H5 and H7 subtype large scale epizootics may also greatly increase the probability that HPAI viruses will emerge by mutation (Garcia et al., 1996).

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