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# History of highly pathogenic avian influenza

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**Summary**

The most widely quoted date for the beginning of the recorded history of avian influenza (AI) is 1878, when researchers first differentiated a disease of poultry (initially known as fowl plague but later renamed highly pathogenic avian influenza) from other diseases with high mortality rates. Current evidence indicates that highly pathogenic AI (HPAI) viruses arise through mutation after low pathogenicity AI viruses of H5 or H7 subtype are introduced into poultry. Between 1877 and 1958, a number of epizootics of HPAI occurred in most parts of the world. From 1959 to 1995, the emergence of HPAI viruses was recorded on 15 occasions, but losses were minimal. In contrast, between 1996 and 2008, HPAI viruses emerged at least 11 times and four of these outbreaks involved many millions of birds.

Events during this recent period are overshadowed by the current epizootic of HPAI due to an H5N1 virus that has spread throughout Asia and into Europe and Africa, affecting over 60 countries and causing the loss of hundreds of millions of birds. All sectors of the poultry population have been affected, but free-range commercial ducks, village poultry, live bird markets and fighting cocks seem especially significant in the spread of the virus. The role of wild birds has been extensively debated but it is likely that both wild birds and domestic poultry are responsible for its spread.

Even without these H5N1 outbreaks, the period 1995 to 2008 will be considered significant in the history of HPAI because of the vast numbers of birds that died or were culled in three of the other ten epizootics during this time.

**Keywords**

Avian influenza – Definition – H5N1 – Highly pathogenic avian influenza virus – History – Nomenclature – Outbreaks – Virulence.

## Introduction

Since 2003, the spread across Asia and into Europe and Africa of an H5N1 avian influenza (AI) virus, which is virulent for poultry and other birds, and capable of infecting humans causing serious disease and often death, has attracted the attention of many scientists and the media. There has been a tendency by those new to the field to treat avian influenza in general as a new disease, about which little is known in terms of epidemiology, transmission and control. Even before the emergence of the H5N1 virus, possibly because of the rarity of outbreaks of the highly pathogenic disease, either through ignorance or complacency, in many countries or poultry production sectors, proven measures for preventing introduction and spread had never been put in place or had been allowed to lapse.

As a result, the recent accounts of outbreaks of highly pathogenic AI (HPAI) viruses, including the H5N1 virus, that have spread and caused serious disease problems, bear a remarkable similarity to those describing outbreaks that occurred half a century ago or more.

Much can be learnt from the accounts of previous disease outbreaks, especially about spread and prevention. For those involved in disease control, including trading restrictions, an understanding of how and why definitions arose and the origins of the current nomenclature is essential. It is the objective of this review to cover the history of HPAI, explaining how the disease and its causative viruses were first recognised and defined, and briefly outlining the outbreaks that have occurred since its first recognition as a specific disease.

# Recognising the disease

The earliest and most widely quoted date for the beginning of the recorded history of AI is 1878, referring to the paper by Perroncito (79), in which the author described a disease with high flock mortality that was affecting chickens and other poultry in Italy at that time. This disease was later to be known as 'fowl plague' and, subsequently, HPAI. It seems unlikely that this was the first occurrence of the disease and throughout the history of the domestication of poultry there have been reports of high flock mortality, but the importance of the paper by Perroncito was that it was the first to distinguish between this disease and bacterial diseases, such as fowl cholera. This, in turn, meant that, for the first time, diagnoses of HPAI could be made with any accuracy at all.

Despite the description by Perroncito, diagnosis of poultry diseases with high mortality remained confused into the 20th Century. Numerous different names, listed in detail by Kaleta and Rülke (48), were used to describe disease outbreaks that were most likely HPAI. Eventually, the term 'fowl plague', probably first used by Beaudette in 1925 (19), was accepted and used primarily to describe disease caused by what is now recognised as virulent influenza A viruses of H7 subtype. Later, at the First International Symposium on Avian Influenza, held in 1981 in Beltsville, Maryland, United States of America (USA), it was recommended that the term 'highly pathogenic avian influenza' be used (16) to describe the disease caused by influenza A viruses of any subtype that fulfilled the specified virulence criteria.

It is worth noting that, some 50 years after the description by Perroncito, sufficient confusion existed in the diagnosis of 'fowl plague' that many workers initially considered that Newcastle disease, first described in 1926 (37, 55), was just another form of HPAI and not a new disease, as claimed by Doyle (37). Doyle (38) responded to this view with a thorough demonstration that the two diseases were caused by different viruses, which, with the work by Burnet and Ferry (25), closed the argument. Nevertheless, it is highly possible that the 1926 outbreaks of Newcastle disease were not the first (5), and the presence of another disease capable of causing extremely high flock mortality in susceptible poultry may have added to the difficulties in diagnosis.

# Recognising the viruses

The virus responsible for HPAI or 'fowl plague' was the second (after foot and mouth disease) to be identified as an ultra-filterable agent (i.e. able to pass through ceramic filters that removed bacteria and yeasts). This demonstration is usually credited to Centanni and Savonuzzi in 1901 (30), although Wilkinson and Waterson (119) point to similar findings by contemporaneous workers.

It is worth commenting on the difficulties facing virologists in the early 20th Century. There were no simple methods for propagating viruses other than infection of susceptible hosts; virus could not be easily detected and, as a consequence, diagnosis was difficult. It usually relied on the failure of vaccinated birds to succumb to challenge or the ability of recovered birds to resist challenge with known 'fowl plague' virus. It was not until 1934 that Burnet and Ferry (25) described the use of embryonated fowls' eggs to propagate fowl plague virus, even though Centanni had described the infection of embryonated eggs in 1902 (29). The ability of fowl plague virus to cause the agglutination of red blood cells – the property subsequently used to detect, identify and measure antibodies against AI viruses – was not demonstrated until 1943 (64).

So, for a considerable number of years in the history of AI, the only viruses recognised were 'fowl plague' virus isolates, which were considered to be essentially the same virus (all belonging to what is now called subtype H7) and not particularly related to swine or human influenza viruses, which had been first isolated in 1931 (94) and 1933 (101), respectively. This, and the lack of any uniform naming of isolates, often caused significant problems in later years as strains sent to other laboratories were often renamed, so that fowl plague virus (FPV) Weybridge and FPV Dobson became recognised strains, although their provenance is not clear. Even the origins of one of the most popular laboratory strains, Brescia 1902, are confusing. Petek (80) considered this strain to be a virus isolated in Italy in 1935 and not 1902, as generally thought. However, this becomes even more complicated, since Burnet and Ferry used the 'Brescia' strain in their work, described in 1934 (25), and refer to earlier workers using the same strain. Similarly, Pereira *et al.* (78) record that the classical strain A/FPV/Dutch/27 (H7N7) had been isolated in Indonesia before 1927, but the fact that there was an outbreak in the Netherlands in 1927 (44) casts some doubt on this origin.

However, in 1955, Schäfer (89) demonstrated that fowl plague viruses shared common internal antigens with known mammalian influenza A viruses, which Newcastle disease virus did not. This led to a taxonomy in which fowl plague viruses were grouped with the mammalian influenza viruses (13, 14). Shortly after this finding by Schäfer, an unusual virus that had been isolated from chickens in Germany in 1949 by Dinter (34), known as virus N, was shown to be an influenza virus too (87). This virus had been considered a variant fowl plague virus because it showed some minor relationship with fowl plague viruses in serological tests but did not kill inoculated adult chickens. Thus, virus N, or A/chicken/Germany/N/49 (H10N7) in the current nomenclature, represents the first isolation of a low pathogenicity AI (LPAI) virus, the vanguard of the enormous numbers of LPAI viruses to be isolated in the following 60 years.

Two viruses isolated from commercial ducks with sinusitis in 1956, one in Czechoslovakia (54), now named A/duck/Czechoslovakia/56 (H4N6), the other in England (14, 83), now named A/duck/England/56 (H11N6), were the next to be identified as AI viruses of low virulence. These viruses were shown to be distinguishable from each other, from fowl plague viruses and from virus N. These were probably not the first LPAI viruses from ducks, since Mitchell *et al.*, writing in 1967, recorded the isolation of a virus (of H10N7 subtype) from commercial ducks in Canada in 1952 (67).

As observed by Alexander *et al.* (9), the self-limiting outbreak of a highly pathogenic disease on a small chicken farm on the east coast of Scotland in 1959 was largely unreported. But this outbreak yielded an HPAI virus, now named A/chicken/Scotland/59 (H5N1), that was not antigenically related in haemagglutination inhibition tests to the 'fowl plague' viruses. Within two years, another HPAI virus, antigenically related in haemagglutination inhibition tests to chicken/Scotland/59, and now named A/tern/South Africa/61 (H5N3), was obtained from a large die-off of European common terns (*Sterna hirundo*) in South Africa (21, 88). The tern isolate was also the first AI virus to be isolated from wild birds.

As the number of known influenza viruses grew, the relationships between the isolates were shown to be increasingly complex. In a landmark publication in 1965, Pereira *et al.* (78) reported the results of examining eight available AI isolates by haemagglutination inhibition, complement fixation and virus neutralisation tests. These tests showed differences and similarities between the viruses that meant these eight viruses could be placed into at least four groups. The authors also discussed the importance of a clear nomenclature for influenza viruses.

Influenza A viruses continued to be isolated occasionally from poultry throughout the 1960s, especially from turkeys in North America and domestic ducks in Europe (for a detailed review, see 1). However, in the early 1970s, the understanding of pools and reservoirs of AI viruses was completely revolutionised by surveillance studies of wild birds, especially wild waterfowl. Studies on influenza reservoirs in animals had been suggested by the World Health Organization (WHO) as early as 1957 (49) but, although evidence of influenza viruses in wild waterfowl was obtained from serological studies (e.g. 40) during the 1960s, it was not until 1972 that surveillance studies based on virus isolation began to reveal the true numbers and diversity of influenza viruses in wild bird populations. In that year, AI viruses were isolated from shearwaters (*Puffinus pacificus*) in Australia (36). Also in 1972, during a surveillance study of wild ducks in California, ostensibly for Newcastle disease, 41 AI viruses of several different subtypes were isolated over a two-month period (100). Considerable impetus was given to the surveillance of wild birds, especially ducks, by emerging evidence that the H3N2 1968 pandemic virus differed from the 1957 to 1968 H2N2 virus in the substitution of two genes, encoding PB1 and the important surface glycoprotein haemagglutinin (HA), with genes closely related to those in a virus isolated from ducks in the Ukraine in 1963 (43, 50, 90). This led to the suggestion that antigenic shift occurred as a result of the reassortment of genes in dual infections with viruses of human and avian origin. As a result, systematic surveillance studies were undertaken into the presence of influenza viruses in avian species. These revealed enormous pools of influenza A viruses in wild birds, especially migratory waterfowl. In a series of surveillance studies involving over 20,000 birds from 1973 to 1986, AI viruses were isolated from about 10%, with an isolation rate of approximately 15% from ducks and geese and 2% from other birds (4). One study by Hinshaw *et al.* (46) was particularly noteworthy. Over the three-year period 1976 to 1978, a total of 4,827 ducks were sampled as they congregated on lakes in Alberta, Canada, prior to migration. This sampling yielded 1,262 AI viruses (26%) and, in 1978, 60% of the 1,098 juvenile ducks sampled were excreting influenza viruses.

These surveillance studies revealed the presence of enormous pools of influenza viruses in wild birds and completely changed the concept of the epidemiology of influenza viruses, not only in birds but other animals as well. In addition, unlike mammals, in which the number of subtypes that have become established appears to be limited, all 16 H and 9 N subtypes recognised currently have been recorded in birds in most possible combinations.

# Avian influenza virus nomenclature

Although there had already been some problems with the nomenclature of fowl plague viruses, mentioned above, as long as there were relatively few influenza viruses known they could be referred to by names such as 'virus N', 'the British duck virus' or the 'Czechoslovakian duck virus' (35), with some reliability. However, with the large number of viruses being isolated from the late 1960s onwards, it was clear that some rules were necessary to establish a meaningful nomenclature and classification system for influenza viruses.

The WHO addressed this problem by setting up an expert committee to review the taxonomy and classification of influenza viruses. The first report following the committee meeting in 1971 (121) established three types of influenza, A, B and C, which now have genus status. These three types were based on the antigenic relatedness of the nucleoprotein and matrix proteins of the viruses. The influenza A viruses were further divided into subtypes, based on the antigenic relatedness of the haemagglutinin (H) and neuraminidase (N) surface glycoproteins.

In the initial report, the H and N subtypes were given a suffix to indicate the animal from which the virus had been isolated, e.g. Hsw1, Heq2, Hav4, since – at that time – it appeared that viruses from different hosts had distinct H and N antigens. The committee met again in 1979 and, while acknowledging some discrepancies in the system, since some H and N subtypes found in different hosts had been shown to be the same, recommended that the existing nomenclature should still be used (122). However, when the committee met once more, in 1980 (123), it was decided to dispense with the H and N suffixes, as clearly no antigenic demarcation between animal species existed. It was further decided to regroup several subtypes that had, at one time, been considered to be distinct, but were now shown to be closely related (Table I).

The way that strains and isolates should be named was also addressed by the committee and strict rules were put forward. The name should include:

*a)* type (A, B or C)

*b)* host of origin (this is omitted for humans, and if the virus was isolated from inanimate material, this material should be used instead of the host)

*c)* geographical location (usually country or state)

*d)* strain reference number

*e)* year of isolation

*f)* for type A viruses: the H and N subtypes.

**Table I**
**The past and present nomenclature of influenza A subtypes**

| Haemagglutinin (H) subtype | | Neuraminidase (N) subtype | |
|---|---|---|---|
| **Current** [a] | **Previous** [b] | **Current** [a] | **Previous** [b] |
| H1 | H0, H1, Hsw1 | N1 | N1 |
| H2 | H2 | N2 | N2 |
| H3 | H3, Heq2, Hav7 | N3 | Nav2, Nav3 |
| H4 | Hav4 | N4 | Nav4 |
| H5 | Hav5 | N5 | Nav5 |
| H6 | Hav6 | N6 | Nav1 |
| H7 | Heq1, Hav1 | N7 | Neq1 |
| H8 | Hav8 | N8 | Neq2 |
| H9 | Hav9 | N9 | Nav6 |
| H10 | Hav2 | | |
| H11 | Hav3 | | |
| H12 | Hav10 | | |
| H13 [c] | | | |
| H14 [c] | | | |
| H15 [c] | | | |
| H16 [c] | | | |

a) World Health Organization expert committee 1980 (123)
b) World Health Organization expert committee 1971 (121)
c) first identification after the current nomenclature was introduced
Hsw1: haemagglutinin swine 1
Heq2: haemagglutinin equine 2
Hav7: haemagglutinin avian 7

Adherence to these rules means that detailed information about an influenza virus is immediately available from the name, e.g.:

– A/lake water/Alberta/1/77 (H4N6)

– A/chicken/Pennsylvania/1370/83 (H5N2)

– A/turkey/England/50-92/91 (H5N1).

The system of nomenclature for influenza viruses laid down by this expert committee has remained unchanged since 1981.

# Defining the virulence of avian influenza viruses

Any disease as pathogenic and as easily spread as HPAI obviously requires control and preferably eradication, and will therefore be the subject of trade embargoes and legislative control measures. However, one of the first problems for control is that the disease must be well defined, and the definition universally accepted, or inevitably there will be misdiagnoses and unjustified restrictions of trade. At the beginning of the 20th Century, outbreaks of HPAI were widespread across certain areas of

Europe, especially in Germany and Austria, and it was made a notifiable disease in these countries as early as 1903 (48). Most countries that experienced outbreaks followed this example and introduced legislation on the notification and control of the disease. While the only AI viruses known were those of the H7 subtype, and all viruses of the H7 subtype were virulent, diagnosis was fairly straightforward, even within the limitations of the available technology.

The isolation of AI viruses that were virulent for poultry but had a different H subtype, H5, in England in 1959 (9), and from terns in South Africa in 1961 (21), confused the issue but was largely ignored. However, the H7 subtype AI viruses of low virulence isolated from turkeys in the USA in 1971 (18), and then from a parrot in Northern Ireland in 1973 (65), made much more of an impact. Most people in the field concurred with the view of Beard and Easterday (18), that the only sensible criterion for AI viruses that required government intervention was the virulence of the virus for poultry. In several studies, various *in vivo* laboratory techniques, which resulted in calculating indices following infection by various routes, were used to make valid assessments (8, 11, 12, 73, 118).

The importance of having an acceptable definition should not be underestimated. For example, the definition of 'fowl plague' for government intervention in the USA was: 'an avian influenza having the haemagglutinin antigen avian 1 and causing high death loss or lethality in the appropriate susceptible poultry species' (15). However, this was no better than the simple definition: 'a virus antigenically related to other fowl plague viruses', which was in use in some other countries. It meant, for example, that the outbreaks caused by A/chicken/Scotland/59 (H5N1) and, closer to home, A/turkey/Ontario/7732/66 (H5N9) (57) were not considered 'fowl plague' in the USA, despite their high virulence for poultry.

One of the objectives of the First International Symposium on Avian Influenza, held at Beltsville, USA, in 1981, was to: 'develop criteria for highly pathogenic isolates causing outbreaks that may need government intervention'. Although the merits of having a definition based on an *in vivo* test that took into account both disease and death were considered, it was decided to recommend the simpler method of assessing deaths alone. It was also recommended that the term 'fowl plague' be discarded for 'highly pathogenic avian influenza' and:

'... that influenza virus highly pathogenic for avian species be considered any influenza virus that results in not less than 75% mortality within 8 days in at least 8 healthy susceptible chickens, 4-8 weeks old, inoculated by the intramuscular, intravenous, or caudal airsac route with bacteria free infectious allantoic or cell culture fluids' (16).

In 1983, this definition was adopted by the International Office of Epizootics (OIE), later to become the World Organisation for Animal Health, the organisation responsible for monitoring animal disease throughout the world, especially in relation to trade, in its role as adviser to the World Trade Organization (3, 56).

The discovery that some influenza viruses were extremely virulent for chickens, while others caused little or no disease, led to investigations of virus virulence in a number of laboratories. At about the same time as the veterinary world was reaching general agreement on how to assess and define HPAI, the research on influenza virus virulence, conducted over a number of years, was reaching fruition, due largely to the work of Rott and co-workers in Germany. The work from this group has been reviewed by Rott (85, 86). They found that, in influenza viruses, the haemagglutinin protein consists of a trimer of identical glycosylated polypeptides of molecular weight 75,000 to 80,000 (HA0), or as a disulphide-bonded complex of two smaller glycopolypeptides of about 50,000 and 30,000 molecular weight, which are produced as a result of post-translational proteolytic cleavage of the precursor HA0 (52). Without this cleavage, the haemagglutinin is unable to function and the virus particles are not infectious. The virus does not have its own protease capable of achieving this cleavage, but relies on host enzymes.

Rott and co-workers demonstrated that, whereas all viruses grown in embryonated eggs have cleaved haemagglutinin, in cell cultures only HPAI viruses were produced with cleaved haemagglutinin, unless trypsin was added to the culture medium (53). They further demonstrated that a similar mechanism occurs in infections of chickens, in that the HA0 of LPAI viruses are cleaved in the respiratory and intestinal tracts (where there are trypsin and trypsin-like enzymes) but not in other tissues and organs, whereas HPAI viruses spread and replicate systemically, causing severe disease and death. Examination of the haemagglutinin at the molecular level revealed that, although all influenza A viruses have fundamentally the same structure, in the HPAI viruses examined, there was a series of basic amino acids adjacent to the cleavage site of the HA0 protein which was absent in LPAI viruses (22, 23).

This important early work by Rott and his group has served as an invaluable basis from which the current understanding of AI virus virulence has been built over the intervening years. The HA0 precursor proteins of AI viruses of low virulence for poultry have a single arginine at the cleavage site and another basic amino acid (arginine or lysine) at position –3 or –4. These viruses are limited to cleavage by extracellular 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.

In contrast, HPAI viruses possess multiple basic amino acids at their HA0 cleavage sites, either as a result of apparent insertion or apparent substitution (92, 113, 120), and appear to be cleavable by an ubiquitous protease or proteases, probably one or more proprotein-processing subtilisin-related endoproteases, of which furin is the leading candidate (105). Vey *et al.* (113) suggested that the probable minimum requirement is RXK/RR*GLF, which would be in keeping with the proposed class of proteases, but several very virulent viruses do not entirely comply with this minimum. A/turkey/England/50-92/91 (H5N1), with a motif of PQRKRKTR*GLF (47), and A/chicken/Pennsylvania/1370/83 (H5N2), with the motif PQKKKR*GLF, do not meet this minimum, nor do the Chile 2002 (107) or the Canada 2004 (75) H7N3 HPAI viruses, as discussed below. All the current evidence indicates that HPAI viruses arise by mutation after LPAI viruses of the H5 or H7 subtype have been introduced into poultry. Several mechanisms may be responsible for this mutation. For most HPAI viruses, there appears to have been spontaneous duplication of purine triplets, which results in the insertion of basic amino acids at the HA0 cleavage site, and this seems to occur due to a transcription error by the polymerase complex (76). However, as pointed out by Perdue *et al.* (76), this is clearly not the only mechanism by which HPAI viruses arise, as some appear to result from nucleotide substitution rather than insertion, while others have insertions without repeating nucleotides. The Chile 2002 (107) and the Canada 2004 (75) H7N3 HPAI viruses have emerged as the result of an entirely different mechanism and show distinct and unusual cleavage site amino acid sequences. They appear to have arisen as a result of recombination with other genes (the nucleoprotein gene and matrix gene, respectively), resulting in an insertion at the cleavage site of 11 amino acids for the Chile virus and seven amino acids for the Canadian virus.

Although only a preliminary understanding of these details was available in the early 1980s, the HPAI outbreak of then unprecedented size in 1983 to 1984 in the USA was to greatly accelerate studies in this area and bring about further changes in the definition of HPAI. This outbreak essentially began in April 1983 in Lancaster County, Pennsylvania, when infection of chickens with an AI virus of H5N2 subtype, which was of low virulence in *in vivo* tests, was first detected. As the virus did not meet the criteria for HPAI defined at the Beltsville meeting, no statutory control measures were invoked. Between April and September 1983, the virus spread to numerous flocks, generally causing respiratory disease and egg production losses, but with only low mortality (41). However, in October 1983, a virus of the H5N2 subtype emerged that was highly virulent in *in vivo* tests (41). Although control measures, including stamping out, were immediately invoked, the earlier and continued presence of the virus of low virulence complicated diagnosis and control, not least because birds infected earlier with the virus of low virulence had some protection against disease, but not infection, when challenged with the HPAI virus. The outbreak in Pennsylvania and surrounding states resulted in the loss of over 17 million birds. Amino acid sequencing of the haemagglutinin of viruses isolated during the outbreaks produced surprising results. The viruses classified as virulent by the *in vivo* tests had a cleavage site motif with the expected multiple basic amino acids, PQKKKR*GLF, but, surprisingly, the isolates of low virulence had an identical cleavage site motif (51). What appears to have happened with this virus is that the haemagglutinin of the isolates of low virulence had a carbohydrate chain whose three-dimensional position placed it close to the cleavage site, preventing most host proteases (but not trypsin-like proteases) from gaining access. However, as the result of a point mutation, the glycosylation site was lost and the potential virulence of the virus was released (115). That such a small genetic change could bring about such a significant phenotypic change caused considerable consternation and prompted calls for a change in the definition of viruses for which there could be government intervention.

In the USA, a sub-committee of the United States Animal Health Association was established to consider the problem and published its report in 1988 (112). The sub-committee recommended retaining the *in vivo* test of virulence, although limiting inoculation of virus to intravenous administration. However, in addition, H5 or H7 viruses that did not meet the *in vivo* criterion for HPAI should be subjected to amino acid sequencing at the HA0 cleavage site and treated as HPAI viruses if additional basic amino acids were present. At that time, there were some drawbacks to this recommendation, in that the minimum requirement of basic amino acids was not known and very few laboratories were capable of determining the cleavage site sequence. Nevertheless, the OIE Biological Standards Commission adopted a very similar definition, including amino acid sequencing.

In the European Community, an 'Expert Group on Contagious Diseases of Poultry' was established in 1984 to give advice on the control of AI and Newcastle disease. Its recommendations on AI culminated in Council Directive 92/40/EEC of 19th May 1992, introducing Community measures for the control of avian influenza (33). In this Directive the following definition was used:

'For the purpose of the diagnostic procedures for the confirmation and differential diagnosis of avian influenza the following definition shall apply. "Avian influenza" means an infection of poultry caused by any influenza A virus which has an intravenous pathogenicity index in six-week-old chickens greater than 1.2 or any infection with influenza A viruses of H5 or H7 subtype for which nucleotide sequencing has demonstrated the presence of

multiple basic amino acids at the cleavage site of the haemagglutinin.'

Note: the intravenous pathogenicity index (IVPI) is the mean score per bird per daily observation over 10 days of 10 six-week-old chickens, inoculated intravenously with the virus under test when birds are scored as follows:

– Score 0 = normal
– Score 1 = sick
– Score 2 = very sick or paralysed
– Score 3 = dead.

An IVPI of 0 means that no signs were seen in the 10-day observation period. An IVPI of 3 means that all birds died within 24 hours.

Although it had been decided to use the IVPI test, the definition was essentially similar to that of the OIE. In later revisions, the OIE amended the definition to give the choice of using an IVPI test or mortality of inoculated chickens.

Although these definitions should have brought harmony, as they were universally adopted, they were not entirely successful. During the 1990s, the evidence that HPAI viruses emerged as a result of the mutation of LPAI viruses of H5 or H7 subtypes became overwhelming and this led to problems in controlling LPAI H5 and H7 outbreaks and international trade disputes when such outbreaks occurred. In reviewing the situation at the Fifth International Symposium on Avian Influenza in 2002, Alexander (6) pointed out that some countries were already imposing a stamping-out policy for H5 and H7 LPAI, while, in others, companies had practised voluntary depopulation. The ultimate demonstration of what could occur without statutory control of H5 and H7 subtype LPAI viruses took place in Italy in 1999 and 2000. Between April and December 1999, LPAI virus of the H7N1 subtype spread to 199 farms before mutating to HPAI virus (26). The situation was very similar to that seen in Pennsylvania in 1983, with the same difficulties in bringing the spread of HPAI under control, which was only achieved after 413 farms had been affected with the loss of nearly 14 million birds. The European Union (EU) Commission asked the EU Scientific Committee on Animal Health and Animal Welfare to reconsider the definition of avian influenza requiring statutory control and, in a report adopted in 2000 (91), the Committee recommended that the control measures should be extended to include infections with all viruses of the H5 and H7 subtypes.

As a result of recommendations made by OIE *ad hoc* expert groups, which met in 2002 and 2004, the definition of notifiable AI was revised to include infections with LPAI H5 and H7 subtype viruses and this was adopted by the International Committee in May 2005. In the current *Terrestrial Animal Health Code* (124), notifiable AI is defined as follows:

'For the purposes of international trade, avian influenza in its notifiable form (NAI) is defined as an infection of poultry caused by any influenza A virus of the H5 or H7 subtypes or by any AI virus with an intravenous pathogenicity index (IVPI) greater than 1.2 (or as an alternative at least 75% mortality) as described below. NAI viruses can be divided into highly pathogenic notifiable avian influenza (HPNAI) and low pathogenicity notifiable avian influenza (LPNAI):

a) HPNAI viruses have an IVPI in 6-week-old chickens greater than 1.2 or, as an alternative, cause at least 75% mortality in 4-to 8-week-old chickens infected intravenously. H5 and H7 viruses which do not have an IVPI of greater than 1.2 or cause less than 75% mortality in an intravenous lethality test should be sequenced to determine whether multiple basic amino acids are present at the cleavage site of the haemagglutinin molecule (HA0); if the amino acid motif is similar to that observed for other HPNAI isolates, the isolate being tested should be considered as HPNAI;

b) LPNAI are all influenza A viruses of H5 and H7 subtype that are not HPNAI viruses.'

The term 'low pathogenicity avian influenza' (LPAI) is then used to define all infections caused by AI viruses that are not NAI viruses. It is worth noting that LPNAI and LPAI infections can only be confirmed by *in vivo* tests.

# Highly pathogenic avian influenza outbreaks

## 1877 to 1958

Two detailed reviews covering the early outbreaks of HPAI in Europe and Asia (48) and the Americas (108) have appeared recently, so it is intended simply to summarise the outbreaks here. Despite the difficulties in diagnosis mentioned above, there is little doubt that, at the time Perroncito wrote his landmark paper (79), Italy was experiencing outbreaks of HPAI. Kaleta and Rülke (48) considered that the literature indicates that this epizootic lasted until 1880 and the disease then reappeared in Italy in a larger series of outbreaks from 1895 to 1906. The disease spread to other European countries, such as Germany, Austria, France, Belgium, Denmark, the Netherlands, the Czech Republic and Poland, and possibly further afield to Sudan and Egypt (48). Kaleta and Rülke further considered that there was a third epizootic from

1919 to 1931, involving several European countries. Other authors have implied that the disease was endemic in Italy and some other European countries throughout 1877 to 1935, but that it underwent waves of activity (62, 80, 109). In addition to the countries mentioned above, Todd and Rice (109) stated that there had been outbreaks in Switzerland, China, Japan, Argentina and Brazil, though some doubt has been raised over the authenticity of the two outbreaks in South America (108). In England, HPAI was first diagnosed in 1922 (82) and then again in 1929 (2), although the origins were not clear in either case.

Well-recorded outbreaks occurred in the USA between 1924 and 1925 and again in 1929, which have been reviewed in detail by Swayne (108). The initial outbreak was observed first in New York City in August 1924 and, by May 1925, had spread to the rest of New York State, New Jersey, Pennsylvania, Connecticut, Indiana, Michigan, Illinois, West Virginia and Missouri (106). Mohler (68) states that the only known introduction of the virus into the USA was the tubes of virus imported in 1923 by an investigator working at an eastern research institute and this research worker was subsequently vilified as responsible for the outbreaks. Whether this was true or not is not known. As Swayne (108) points out, since the virus has not survived, modern genetic techniques that would have settled the question cannot be used and it is not even known unequivocally that the virus responsible was of the H7 subtype. The 1929 outbreak was restricted to New Jersey, causing disease in a few flocks in the same locality, and was promptly eradicated (20).

Between 1930 and 1959, very few outbreaks of HPAI were reported. Petek (80) refers to the isolation of a 'fowl plague' virus in Italy in 1935, while Wells (116), writing in 1963, considered the virulent disease to be still enzootic in Egypt and 'not uncommon in other parts of Africa, Asia and Eastern Europe'. However, without substantiating references, it is not clear on what evidence this was based. In view of what had happened before, and what was to occur in future years, it does seem surprising that, for over 20 years, there were no substantiated outbreaks of HPAI recorded anywhere in the world.

## 1959 to 1995

Detailed reviews of the outbreaks that occurred between 1959 and 1995 have been published recently (9, 99, 108), and thus will only be summarised in this review. During this 37-year period, the emergence of HPAI viruses was recorded on 15 occasions. Fourteen of these were initially detected in poultry (Table II) and one in wild terns in South Africa in 1961 (21). It is possible that the two outbreaks in 1979, in Germany and England, may have represented a single emergence of H7N7 HPAI virus that was spread by wild birds (9). Of the outbreaks in poultry, the one that had the least impact – occurring on a small chicken farm on the east coast of Scotland in 1959 – is probably the most historically significant, since the virus responsible, A/chicken/Scotland/59 (H5N1), was the first HPAI virus to be isolated that was not of H7 subtype (78). Within two years, another H5 virus virulent for poultry, A/tern/South Africa/61 (H5N3), was isolated as the result of an investigation into the deaths of thousands of common terns (*S. hirundo*) along the southern coast of South Africa in 1961 (21). This virus was the first reported isolation of an AI virus from wild birds, and for many years represented the only time there had been significant deaths caused by AI virus infection in the wild. There had been no contemporaneous outbreaks of HPAI in poultry in South Africa and, since mutations from LPAI to HPAI are thought to occur in poultry, the origins of the virulent H5N3 virus remain an anomaly.

As can be seen from the outbreak summaries in Table II, HPAI viruses emerged sporadically during this period as a relatively rare event. Eleven of the 14 outbreaks were restricted to three farms or fewer. Eight outbreaks resulted in the loss of relatively low numbers of birds, but the single chicken farm infected in Germany in 1979 (600,000 birds) and another in Australia in 1985 (240,000 birds) contained a large number of birds, reflecting the increase in the size of poultry farms during the accelerated industrialisation of poultry rearing during the 1970s and 1980s.

The outbreak in Ireland in 1983, caused by an HPAI H5N8 virus, although restricted to four farms, was also of historic interest. As described by Murphy (69), confirmed infections were first seen on two turkey farms and then on a third farm among turkeys, although the 28,000 apparently healthy broiler chickens on this farm were also slaughtered. Subsequent surveillance of poultry farms in the area revealed that ducks on a large breeding and rearing farm situated between the first two turkey farms were also infected and these too were slaughtered. This farm had 270,000 ducks, representing about 97% of all the commercial ducks in the Republic of Ireland. This was the first occurrence of HPAI in such a large commercial duck enterprise and demonstrated the potential problems that may arise due to the lack of clinical signs in commercial ducks infected with some HPAI viruses. Such problems were to become especially significant with the advent of HPAI of the H5N1 subtype in Southeast Asia more than a decade later.

Three outbreaks during this period involved many more farms and birds. The first has been mentioned above, as it was the catalyst for changes in HPAI definitions. It began as an infection of chickens with an LPAI virus in Pennsylvania in April 1983 and, over the following six months, spread until an H5N2 HPAI virus emerged by mutation in October 1983 (41). The presence of the LPAI

**Table II**
**Reported highly pathogenic avian influenza isolates obtained from primary outbreaks in poultry, 1959 to 1995**

| Highly pathogenic avian influenza virus | Subtype | Number of infected farms | Approximate numbers of poultry involved in epizootic | Reference |
|---|---|---|---|---|
| A/chicken/Scotland/59 | H5N1 | 1 small farm | Not known | 9 |
| A/turkey/England/63 | H7N3 | 3 small farms | 29,000 | 116 |
| A/turkey/Ontario/7732/66 | H5N9 | 1 farm | 8,000 | 57 |
| A/chicken/Victoria/76 | H7N7 | 1 chicken farm, duck farm with LPAI H7N7 also slaughtered out | 58,000 | 114 |
| A/chicken/Germany/79 | H7N7 | 1 chicken farm, 1 goose farm | 600,000 chickens 80 geese | 9 |
| A/turkey/England/199/79 | H7N7 | 3 small farms | 9,000 | 10 |
| A/chicken/Pennsylvania/1370/83 | H5N2 | 356 farms HPAI plus 90 farms with LPAI or H5 antibodies | > 17,000,000 | 41 |
| A/turkey/Ireland/1378/83 | H5N8 | 3 farms (turkeys/chickens), one duck farm (270,000 ducks) | 307,000 | 69 |
| A/chicken/Victoria/85 | H7N7 | 1 farm | 240,000 | 17 |
| A/turkey/England/50-92/91 | H5N1 | 1 house on 1 farm | 8,000 | 10 |
| A/chicken/Victoria/1/92 | H7N3 | 1 chicken farm, duck farm with H7 antibodies | 18,000 | 117 |
| A/chicken/Queensland/667-6/94 | H7N3 | 1 farm | 22,000 | 117 |
| A/chicken/Mexico/8623-607/94 | H5N2 | Many farms LPAI H5N2 still enzootic | Not known | 108, 114 |
| A/chicken/Pakistan/447/94 | H7N3 | Many farms | > 6,000,000 | 70 |

LPAI: low pathogenicity avian influenza
HPAI: highly pathogenic avian influenza

virus caused endless problems in the control and eradication of the HPAI virus, and it spread throughout Pennsylvania into Virginia, where there were 65 outbreaks, and Maryland and New Jersey, which each experienced a single outbreak. The control measures were extended to slaughtering flocks infected with LPAI H5N2 virus and those that tested seropositive for H5 antibodies. The last flock to be slaughtered was in Pennsylvania in September 1984. In all, a total of more than 17 million birds had died or been culled by this time. This devastating outbreak should have taught two lessons to the poultry industry and those engaged in disease control. The first was that if H5 (or H7) LPAI viruses are allowed to spread, they will eventually mutate into HPAI viruses. The second was that the trend towards establishing areas in which large numbers of birds are reared in close proximity, the so-called 'densely populated poultry areas' (DPPA), means that the birds reared in such areas are considerably more vulnerable to rapidly spreading disease.

In May 1994, chickens infected with LPAI H5N2 virus were identified in central Mexico, although the virus may have been circulating undiagnosed for some months (108). The virus continued to spread and, by the end of 1994, LPAI infections had been reported in 11 states. Clinical evidence suggested that the virus had become more virulent in late 1994, and in January 1995 it was confirmed that HPAI virus had emerged (77, 114). As in Pennsylvania ten years earlier, difficulties in diagnosis arose, due to the presence of the LPAI virus and partial protection of birds infected with this virus before the HPAI virus. The Mexican authorities implemented a stamping-out policy for HPAI virus, but also employed the use of H5 vaccination. The last HPAI virus was isolated in June 1995, but LPAI H5N2 continued to circulate and Swayne considered it still present in 2008 (108). Long-term circulation of a virus in a vaccinated population may raise further problems as a result of both genetic and antigenic changes in the virus and this has proven to be the case in Mexico (58).

The third of these significant HPAI epizootics occurred in Pakistan. An outbreak of HPAI caused by a virus of H7N3 subtype affected northern Pakistan in 1995, causing the death of 3.2 million birds, primarily broiler breeders and broilers. A vaccination campaign with a homologous vaccine was implemented. Together with upgraded biosecurity measures, this appeared to bring the outbreak under control (70). However, the situation became very complicated in 1998, due to the emergence of H9N2 infections, which became endemic, and the re-emergence of an H7N3 subtype virus, this time LPAI virus, in 2000 (71, 72). These infections caused considerable problems and vaccination was introduced, using a bivalent H7/H9 oil-based inactivated vaccine. Highly pathogenic AI virus

of H7N3 subtype was again isolated in November 2003 from diseased chickens in the Karachi area of Pakistan, a DPPA (71). This virus had been preceded by numerous outbreaks of LPAI H7N3 virus in the area. The HPAI virus spread throughout commercial layer flocks, covering an area of 80 km$^2$, with mortality usually around 70% to 80% of the infected flock. Diagnosis was often complicated by the presence of LPAI viruses of H7N3 or H9N2 subtypes or both on HPAI-infected farms.

Although the 14 HPAI epizootics during this period showed a wide geographical distribution, some areas of the world seemed to be far more disproportionately represented than others. The relatively small geographical area comprising the British Isles (the United Kingdom [UK] and Ireland) accounted for five of the 14, in 1959, 1963, 1979, 1983 and 1991, while four occurred on the east coast of Australia, in 1976, 1985, 1992 and 1994 (Table II). In marked contrast, there were only two outbreaks in North America, in 1963 and 1983; one in Central America, in 1994; one in the rest of Europe, in 1979; and one in the whole of Asia in 1994, while none was recorded in the rest of the world.

## 1996 to the present

In the 37-year period from 1959 to 1995, HPAI viruses emerged 14 times, i.e. at a rate of 1 outbreak every 2.64 years. In the 13-year period from 1996 to 2008, HPAI viruses emerged at least 11 times (Table III), equivalent to 1 outbreak every 1.18 years. This greater frequency alone would be cause for concern but, when the much greater number of birds involved and the spread of the HPAI H5N1 virus throughout Asia and into Europe and Africa are taken into account, it is particularly alarming.

## Outbreaks of H5N1

Even ignoring the human health aspects (7), the epizootic of HPAI that began in 1996, due to an H5N1 subtype virus, has dwarfed all other HPAI epizootics.

Although the progenitor virus for the subsequent outbreaks of HPAI of the H5N1 subtype appears to be the virus that was obtained from an infection of commercial geese in Guandong Province, China, in 1996 (31, 126), and it seems likely that the virus began circulating from that time in southern China, primarily in domestic ducks (97), the first indication of what was to become the most devastating HPAI epizootic yet occurred in Hong Kong. Outbreaks of HPAI caused by an H5N1 virus occurred in Hong Kong on three chicken farms between March and May 1997 and then re-emerged in November (95). Surveillance of Hong Kong poultry markets in December 1997 (95) indicated that H5N1 infections were widespread, especially in chickens but also in ducks and geese. Control was established by slaughtering all poultry in Hong Kong between 29 December 1997 and 2 January 1998. The HPAI H5N1 virus returned yet again in Hong Kong in 2001 and 2002 (98). The 2002 outbreaks resulted in the infection of 22 farms between January and March 2002 and the slaughter of 950,000 birds (98). There was little published information on the situation of HPAI H5N1 in mainland China during 1997 to 2002. However, in 2001, an HPAI virus isolate of subtype H5N1 was isolated in South Korea from duck meat imported from China (110).

The situation changed suddenly from December 2003 to February 2004, when eight countries in East and Southeast Asia reported outbreaks of HPAI due to H5N1 virus (125). Although there seemed to be some success in controlling the outbreaks in some countries, HPAI re-emerged in a second wave from July 2004 onwards. The virus affected all poultry sectors in most of the affected countries, but its presence in free-range commercial ducks, village poultry, live bird markets and fighting cocks seemed especially significant in the spread of the virus (66, 97, 102).

The presence of HPAI H5N1 in poultry, especially free-range domestic ducks, meant that wild birds coming into contact with these birds could become infected. Apart from the die-off of terns in South Africa mentioned above, HPAI infections of wild birds had usually been restricted to birds found dead on or close to premises with HPAI-infected poultry. However, concerns had been expressed that, since some species, i.e. ducks, showed little or no disease when infected with HPAI viruses, there was a potential for them to act as a vector of HPAI viruses. The first reports of Asian HPAI H5N1 virus in wild birds were the outbreaks at two waterfowl parks in Hong Kong in 2002 (42), but infections in wild migratory birds detected in China and Mongolia in 2005 were considered much more significant. In particular, it was suggested that the presence of virus in bar-headed geese (*Anser indicus*) at Lake Qinghai in western China could become the means by which the H5N1 virus could spread west and south (32, 61), even though the virus caused disease and death in these birds.

There has been considerable debate as to whether wild birds or the movement of poultry were responsible for the spread of the HPAI H5N1 virus westward. In view of the isolations from wild birds, both then and subsequently, they seem likely candidates. However, those who oppose that view point to the lack of direct migration routes, the failure to isolate virus from healthy wild birds, except on one or two occasions (45), and the similarity between the route of spread of the H5N1 virus across Asia and the route of the railway systems, including the trans-Siberian railway.

Whatever the mechanism, an HPAI H5N1 virus, closely related genetically to isolates obtained at Lake Qinghai,

**Table III**
**Reported highly pathogenic avian influenza isolates obtained from primary outbreaks in poultry, 1995 to 2008**

| Highly pathogenic avian influenza virus | Subtype | Number of infected farms | Approximate numbers of poultry involved in epizootic [a] | Reference |
|---|---|---|---|---|
| A/goose/Guandong/96<br>A/chicken/Hong Kong/97<br>A/chicken/Eurasia & Africa/2003- | H5N1 | Very many | Not known<br>100s of millions? | 96 |
| A/chicken/NSW/97 | H7N4 | 3 | 310,000 | 99 |
| A/chicken/Italy/330/97 | H5N2 | 8 | 6,503 | 9, 27 |
| A/turkey/Italy/99 | H7N1 | 413 | 13,732,912 | 9, 26 |
| A/chicken/Chile/2002 | H7N3 | 2 | 634,000 | 108 |
| A/chicken/Netherlands/2003 | H7N7 | 255 [b] | > 28,000,000 | 9 |
| A/chicken/Texas/2004 | H5N2 | 1 | 6,608 | 59, 108 |
| A/chicken/Canada-BC/2004 | H7N3 | 53 | > 17,000,000 | 24, 108 |
| A/ostrich/S. Africa/2004 | H5N2 | 37 | > 30,000 | 9 |
| A/chicken/N. Korea/2005 | H7N7 | 3 | 219,000 | 9 |
| A/turkey/England/2008 | H7N7 | 1 | 6,528 | |

a) including birds culled pre-emptively on unaffected farms
b) the virus also spread to Belgium (8 farms, 2,300,000 birds) and Germany (1 farm, 419,000 birds)
NSW: New South Wales, Australia
B.C.: British Columbia
S. Africa: South Africa
N. Korea: North Korea

reached poultry in Russia in the summer of 2005. Whether the virus spread from there to other Western Asian and some Eastern European countries, or whether it was introduced independently into those countries, is not clear. Nor is it known whether the spread was associated with movements of poultry or wild birds (probably both were involved). Nonetheless, from 2005 until the beginning of 2006, closely related H5N1 viruses appeared in a number of countries in the region. Reports of HPAI H5N1 virus infections continued during the first three months of 2006. By early April 2006, 31 countries from Asia, Europe and Africa had reported HPAI caused by H5N1 virus to the OIE, since the end of 2003 (125).

Isolates from dead swans were obtained in Croatia in October 2005 (125). These infected swans were a forewarning of the apparent importance of these birds in the spread of HPAI H5N1. Between January and April 2006, wild mute swans (*Cygnus olor*) or other wild birds were shown to be infected in Azerbaijan, Iran, Kazakhstan, Georgia and 20 European countries. What appears to have occurred is that mute swans or other birds, over-wintering on the Black Sea, became infected at a time when adverse weather conditions made the Black Sea inhospitable and so the birds dispersed to other areas. However, this does not explain the appearance of apparently the same H5N1 strain (Lake Qinghai clade 2.2) in swans and wild birds on the Baltic Coast at the same time (103). By mid-2006, Asian H5N1 virus infections in birds had been reported in 26 European countries. Of these, 25 countries reported infections in wild birds and 11 reported infections of poultry (81).

The first outbreak of HPAI H5N1 virus in poultry in Africa occurred in January 2006 in Nigeria (125). The virus was subsequently reported in both commercial and backyard poultry in most areas of Nigeria, possibly as a result of multiple introductions (39). In West Africa, infections of poultry with HPAI H5N1 virus have been reported in Niger, Burkina Faso, Cameroon, Côte d'Ivoire, Ghana and Togo. Infections of poultry have also been reported in Egypt, Sudan and Djibouti (125).

Infections of HPAI H5N1 have continued to occur. In the first ten months of 2008, outbreaks in poultry were reported in at least 24 countries in Europe, the Middle East, Asia and Africa, while infections of wild birds were reported in China, Hong Kong and the UK (125). Perhaps most concerning is the number of countries in which Sims and Brown, writing in 2007, assessed the control methods being employed as unlikely to be successful (96).

The other point of interest in the emergence of the HPAI H5N1 virus is that, unlike all other HPAI viruses up to that time, the primary detection was not in chickens or turkeys, but in geese. Obviously, it is possible that the HPAI virus

had arisen in an unknown chicken flock and spread to geese directly or through commercial ducks. The isolation of an H5N1 virus of low virulence for chickens from the same goose flock (60) provides some evidence that the mutation may have taken place in the geese, but this is balanced by the low virulence virus already having a cleavage site with multiple basic amino acids (63).

## Other highly pathogenic avian influenza outbreaks from 1995 to 2008

Even without the H5N1 HPAI outbreaks, the period from 1995 to 2008 would be considered significant in the history of AI, because of the vast numbers of birds that died or were culled in three of the other ten epizootics that occurred during this time.

In 1997, another HPAI epizootic took place in Australia, in Tamworth, New South Wales, caused by a virus of H7N4 subtype (93). It was the fifth outbreak to be recorded in that country. Only three farms were affected, but it is worth noting that the total of 310,000 birds that died or were slaughtered is only 20,000 fewer than the total of birds affected in the previous four outbreaks in Australia.

In October 1997, the first HPAI outbreak in Italy in over 60 years was recorded. Between October 1997 and mid-January 1998, HPAI H5N2 virus affected a total of eight backyard or small-trader flocks (27), involving 6,503 birds. Within two years, this outbreak was completely overshadowed by an epizootic due to an HPAI H7N1 virus which, at the time, was second only to the 1983 to 1984 Pennsylvania outbreak in its impact and the number of birds that died or were slaughtered. As in the Pennsylvania outbreak, initial infections were caused by LPAI virus, which became widespread. The first isolation of an LPAI virus of H7N1 subtype was reported in March 1999 and, in the absence of a compulsory stamping-out policy, the virus had spread to another 199 farms by December 1999 (27). On 17 December 1999, HPAI was confirmed in a meat turkey flock showing high mortality, with the characterisation of an H7N1 isolate with an IVPI value of 3.0 and a deduced HA0 cleavage site amino acid sequence of PEIPKGSRVRR*GLF, compared to 0.00 and PEIPKGR*GLF for the LPAI virus (27). The presence of LPAI and the dense population of poultry in the area resulted in the HPAI virus spreading to 413 farms. Eventually, depopulation of intensive and semi-intensive chicken and turkey farms was imposed over an area of 5,500 km$^2$ (28). The last outbreak of HPAI due to this virus was recorded in April 2000, following the death or slaughter of over 13 million birds (Table III).

The outbreak in Chile in 2002 also laid claim to two historically important events:

– it was the first outbreak to have been reported in South America since the doubtful reports at the beginning of the 20th Century

– the H7N3 virus, which was shown to be HPAI in *in vivo* tests (84), had the HA0 cleavage site motif PEKPKTCSPLSRCRETR*GLF, which is extremely unusual and appears to have arisen by recombination between the HA gene and the nucleoprotein gene of the progenitor LPAI virus (107).

The initial outbreak occurred on a large farm of 617,800 broiler breeders that were stamped out, along with the destruction of 116,000 hatching eggs. The virus spread to a turkey breeder farm 4 km away, which had links to the broiler breeder farm.

In 2003, HPAI returned to the Netherlands for the first time since 1927, with devastating consequences. Outbreaks caused by HPAI virus of H7N7 subtype began in February 2003 in the extremely densely populated poultry area of the Gelderse Vallei, and spread rapidly. In all, there were 255 confirmed outbreaks but, as a result of the pre-emptive culling policy that was put in place to control the rapid spread, 1,255 commercial and 17,421 backyard flocks were culled, resulting in the deaths of 25.6 million birds (9, 104). In the middle of April the infection spread to Belgium, causing eight outbreaks and the deaths or culling of 2.3 million birds. A single outbreak also occurred in Germany, close to the border with the Netherlands, causing the deaths or culling of 419,000 birds (9).

An outbreak that occurred in Gonzales, Texas, on a small chicken farm with 6,608 birds, became the first outbreak to be confirmed as HPAI without the isolation of a virus that was virulent in *in vivo* tests (59). An investigation of respiratory signs and raised mortality resulted in the isolation of an H5N2 virus which, although of low virulence in laboratory-infected chickens, had the HA0 cleavage site motif of PQRKKR. Since this was identical to that of a known HPAI virus, A/chicken/Scotland/59, the virus was confirmed as HPAI, in line with the OIE definition discussed above (108). Viruses with multiple basic amino acids in the cleavage site motif, but showing low virulence for chickens, have been isolated on three other occasions, but in these cases virulent viruses have been isolated too (63).

Another devastating epizootic in a DPPA occurred in Canada in February 2004. An LPAI virus of H7N3 subtype, with a cleavage site motif of PENPKTR*GLF and an IVPI of 0, was isolated from birds on what appeared to be the index farm. However, on the second farm to be infected, both H7N3 LPAI virus and an HPAI virus (IVPI 2.96) were isolated (108). This HPAI virus had a cleavage site motif of PENPKQAYRKRMTR*GLF and appeared to have arisen as

a result of recombination with the matrix gene, resulting in an insertion at the cleavage site of seven amino acids (75). The virus appeared to be spreading through the dense poultry population of the Fraser Valley (British Columbia) and it was decided to pre-emptively slaughter all birds in the area to prevent further spread. In total, 42 commercial and 11 backyard flocks were infected, representing 1,204,564 birds, but an additional 16 million birds were culled pre-emptively (108). A further HPAI H7N3 outbreak was reported in Saskatchewan, Canada, in 2007 but limited to a single broiler breeder flock (108).

Outbreaks in South Africa in 2004, involving 37 ostrich farms infected by an HPAI virus of H5N2 subtype with the HA0 cleavage site PQREKRRKKR*GLF, may also have some significance as there was no evidence that the virus first emerged in poultry (74).

In addition, there were relatively small and quickly eradicated HPAI outbreaks in North Korea in 2005 (on three farms) and on a single farm in England in 2008, both due to viruses of H7N7 subtype (Table III).

# Conclusions

Although the evidence is mainly anecdotal, it seems likely from historical reports that HPAI caused by H7 subtype virus was widespread across the world in the late 19th and early 20th centuries. Why reports of the disease suddenly ceased in the 1930s is unclear, and it is difficult to explain why nearly 60 years should pass before HPAI showed comparable spread, this time due to an H5N1 virus. The increase in HPAI outbreaks in recent years is equally difficult to explain. Probably the improvements in diagnosis during that time have had a considerable impact, but over the past 50 years the nature of the poultry industry has also changed, moving away from small flocks, in which high mortality may have gone unreported, to much larger integrated flocks in which HPAI has much greater significance. This industrial development has also resulted in the creation of DPPAs, which contributed to the devastating impact of HPAI emergence, leading to the loss of millions of birds, in Pakistan (1994), Italy (1999 to 2000), the Netherlands (2003) and Canada (2004). This was despite the fact that historical HPAI outbreaks in Pennsylvania in 1983 to 1984 had demonstrated how costly HPAI could be in a DPPA. Since 1959, HPAI has emerged on 25 occasions and five of these have occurred in the UK, yet these five outbreaks resulted in the loss of only just over 52,000 birds. Even if the losses due to the two incursions of Asian H5N1 HPAI virus into poultry in the UK are included, the total is still less than 300,000. The reasons for the lack of spread in the UK are probably complex. Prominent among them is the fact that, while the poultry industry is highly developed and highly integrated, the areas where poultry are reared tend not to have the concentrations of poultry populations seen in the DPPAs in countries where there has been significant spread.

In the recent period from 1997 to 2008, HPAI emerged on ten occasions on the continents of Australia, Europe, Africa, North America and South America. Seven outbreaks were due to H7 viruses and three to H5 viruses. It is probable that no poultry flock should be excluded as being potentially the primary source of HPAI, unless strict biosecurity measures have been undertaken. Yet, in many countries, HPAI is considered to be an 'exotic' or 'foreign' disease, implying that spread will come primarily from poultry in other countries. While the situation with H5N1 has consolidated that viewpoint, it is important that the more conventional epidemiology of HPAI is not ignored. Along with good biosecurity, it is crucial that other measures are put in place to ensure early warning and rapid diagnosis of infections of poultry with *any* HPAI virus.

The disease now termed HPAI has been recognised for over 130 years and has been known to be caused by a virus for over 100 years. During that time, much has been learnt of the aetiology, diagnosis, epidemiology, prevention and control of the disease. Nevertheless, in recent years outbreaks have occurred more frequently than in the past and, when they have occurred, they have often resulted in the loss of far more birds. In addition, for more than ten years, an HPAI virus of the H5N1 subtype has been spreading from Southeast Asia across large areas of Asia and into Europe and Africa, becoming endemic in poultry in a number of countries. There is currently little hope that it will be eradicated easily (96).

# Histoire de l'influenza aviaire hautement pathogène

D.J. Alexander & I.H. Brown

**Résumé**
Il est généralement admis que l'histoire écrite de l'influenza aviaire remonte à 1878, année où l'existence d'une pathologie aviaire (d'abord désignée sous le nom de peste aviaire puis d'influenza aviaire hautement pathogène), distincte des autres maladies aviaires à forte mortalité, a été établie pour la première fois par les scientifiques. On sait aujourd'hui que l'émergence des virus de l'influenza aviaire hautement pathogène résulte d'un processus de mutation consécutif à l'introduction de souches faiblement pathogènes de sous-types H5 ou H7 dans les populations aviaires. Entre 1877 et 1958, plusieurs épizooties d'influenza aviaire hautement pathogène ont été décrites dans presque toutes les régions du monde. De 1959 à 1995, le virus de l'influenza aviaire hautement pathogène a causé 15 épisodes émergents, avec néanmoins des pertes minimes. En revanche, de 1996 à 2008, le virus est réapparu au moins 11 fois et quatre de ces épisodes ont affecté plusieurs millions d'oiseaux.
Les épisodes les plus récents sont dominés par la panzootie en cours d'influenza aviaire hautement pathogène due au virus H5N1 qui s'est propagée dans toute l'Asie jusqu'en Europe et en Afrique, avec plus de 60 pays affectés et des pertes atteignant plusieurs centaines de millions d'oiseaux. Tous les segments de la population aviaire sont touchés, mais les canards élevés en liberté, les volailles de basse-cour, les marchés de volailles et les coqs de combat semblent jouer un rôle prépondérant dans la propagation du virus. Le rôle de l'avifaune a également été évoqué à maintes reprises, mais les oiseaux sauvages semblent partager avec les volailles domestiques la responsabilité de la propagation du virus.
Indépendamment des foyers dus au virus H5N1, la période comprise entre 1995 et 2008 marque un jalon significatif dans l'histoire de l'influenza aviaire hautement pathogène : en effet, trois des dix épizooties d'influenza aviaire (hors celles à virus H5N1) survenues pendant cette période ont causé la mort ou rendu nécessaire l'abattage d'un nombre impressionnant de volailles.

**Mots-clés**
Définition – Foyer – Histoire – Influenza aviaire – Nomenclature – Virulence – Virus de l'influenza aviaire hautement pathogène.

# Historia de la influenza aviar altamente patógena

D.J. Alexander & I.H. Brown

**Resumen**
1878 es la fecha que con mayor frecuencia se atribuye al primer brote registrado de la enfermedad debido a que ese año los investigadores comenzaron a diferenciar una infección de las aves de corral (que inicialmente se denominó peste aviar y, más tarde, influenza aviar altamente patógena) de otras patologías

con una elevada tasa de mortalidad. Actualmente se ha demostrado que los virus de la enfermedad son producto de la mutación de los subtipos H5 o H7 del virus de la influenza aviar de baja patogenicidad en las aves de corral. Entre 1877 y 1958 se registraron varias epizootias provocadas por virus altamente patógenos en la mayoría de las regiones del mundo. Entre 1959 y 1995 se asistió a la aparición de 15 brotes de la infección, aunque las pérdidas fueron insignificantes. Pero entre 1996 y 2008 se produjeron, como mínimo, 11 focos, cuatro de los cuales afectaron a varios millones de aves.

Los brotes más recientes se vieron eclipsados por la panzootia del subtipo H5N1 del virus que se propagó por todo Asia, se extendió hasta Europa y África, afectó a más de 60 países y provocó la pérdida de cientos de millones de aves. Todos los sectores avícolas se han visto afectados, pero los patos criados al aire libre con fines comerciales, los criaderos familiares de aves de corral, los mercados de aves vivas y los gallos de riña parecerían haber constituido un vector de propagación del virus particularmente importante. Si bien se ha estudiado exhaustivamente el papel de las aves silvestres, es probable que las aves de corral también sean vectores de la difusión de la enfermedad.

Incluso si esos focos de H5N1 no hubieran tenido lugar, tres de los 10 brotes registrados entre 1995 y 2008 se recordarán como los más graves de la historia de la influenza aviar altamente patógena debido a las enormes cantidades de aves que murieron o debieron sacrificarse sistemáticamente.

**Palabras clave**

Definición – Foco – Historia – Influenza aviar – Nomenclatura – Virulencia – Virus de la influenza aviar altamente patógena.

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