Avian Influenza

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INTRODUCTION

The severe form of avian influenza (AI), historically known as “fowl plague”, was first described by the Italian scientist Perroncito in the late 19th century. AI can cause devastating losses in poultry, with flock mortalities of up to 100%. Coupled with the economic impact of trade restrictions and embargoes placed on infected areas, highly pathogenic notifiable avian influenza (HPNAI) is one of the most feared zoonotic diseases today, because of its potential to be involved in the next, supposedly imminent, human influenza pandemic.

AI is caused by viruses that are members of the family Orthomyxoviridae and placed in the genus Influenzavirus A. Serotypes are determined by the combination of two major antigens coating the virus surface, viz. the hemagglutinin (H) glycoprotein, and the neuraminidase (N) glycoprotein. 16 different H and 9 different N types have been isolated thus far, but H17, H18, N9 and N10 have been detected in bats. H and N glycoproteins can occur in any combination to form the serotype (also referred to as subtype), e.g. H5N1, H1N1 etc. However, only two of the “H” subtypes, viz. H5 and H7 cause the scale of outbreaks that require the presence of the virus to be notifiable to the World Organization for Animal Health (OIE). As the term HPNAI and the historical term ‘fowl plague’ refer to infection with virulent strains of influenza A virus, it is necessary to assess the virulence of an isolate for domestic poultry. Although all virulent strains isolated to date have been either of the H5 or H7 subtype, most H5 or H7 isolates have been of low virulence. Due to the risk of a low virulent H5 or H7 becoming virulent by mutation in poultry hosts, all H5 and H7 viruses have also been classified as notifiable AI viruses (NAI).

EPIDEMIOLOGY

Type A are the only influenza viruses (AIVs) known to infect birds, and have been isolated from most wild water birds including ducks, geese, terns, shearwaters, gulls, as well as a wide range of domestic avian species such as turkeys, chickens, quail, pheasants, geese, ducks, and less frequently, from passerine birds such as starlings and budgerigars. The disease signs associated with influenza A infections vary considerably with the strain of virus and the species of the bird. Inapparent infections in waterfowl, together with the fact that all HA and NA subtypes of influenza A viruses have been recovered from waterfowl in most combinations of subtypes, and that mammalian influenza viruses are directly or indirectly derived from this reservoir, strongly suggest that waterfowl, shorebirds and gulls are the natural hosts and biological reservoirs of low pathogenic AIVs (LPAI). Any poultry in a region inhabited by or on the migratory stopovers of wild waterfowl are consequently at risk for avian influenza, if contact (directly or indirectly) occurs. Influenza viruses that have become established in humans show a restricted combination of HA and NA types, limited to H1, H2, H3, N1 and N2 types. Certain avian influenza viruses have been transmitted directly to and have caused epidemics in other mammals including H3N8 in horses, H7N7 in seals, and H1N1 in pigs.
In ducks, AIV replicates in the cells of the respiratory and intestinal tracts and infected birds usually show no signs of disease. The viruses, despite the low pH of the gizzard, and are shed in high concentration in the faeces up to 108 EID 50 (mean egg infectious doses per gram of faeces) into the environment, or alternatively, in mucosal secretions of the trachea directly between birds or into environmental water. High titres of AIVs have been isolated from unconcentrated water samples of different lakes in the breeding areas of ducks in northern high latitudes in summer, and furthermore, the viruses remained viable in the lake water after the ducks left for migration to the south. Survival of influenza viruses in water is dependent on the virus strain and the salinity, pH, and the temperature of the water. At 17°C, some strains remain infectious for more than 100 days, and at 4°C they remain infectious for a longer period. Thus, ducks coming back from the south are infected with viruses preserved in frozen lake water in spring when the ice melts. In the southern hemisphere and more tropical climates, the prevalence of AIV in the wild duck population is more difficult to predict, because breeding seasons are longer, sometimes occurring more than once a year, and migrations are more likely to be driven by rainfall patterns. Immunologically-naive juvenile waterfowl excrete the highest viral titres, although older birds that have had prior exposure to viruses (both homologous or heterologous serotypes) do become infected and excrete virus, albeit at greatly reduced levels.

AIV is transmitted to susceptible poultry (e.g. domestic ducks, fowls, guinea fowl turkeys, ostriches, quails) most commonly though close contact with wild species by the faecal-oral route or by sharing of infected. When H5 or H7 subtypes are introduced to poultry, LPNAI viruses convert to HPNAI through mutation events. Virulence of AIVs is a polygenic trait that usually results from insertion or substitution of multiple basic amino acids at the cleavage site of the HA protein (these multi-basic amino acids are not normally present in LPAI viruses). This mutation allows the HA protein to be cleaved by a broad range of proteases, allowing the viruses to multiply in a broader range of tissues and spread systemically. Other novel mechanisms for conversion of LPAI viruses to HPAI viruses have been described in outbreaks of HPAI in Chile (2002) and Canada (2004). These arose through recombination between the HA gene and that of another gene coding for an internal protein, leading to insertion of additional amino (non-basic) acids at the HA cleavage site. Modification of the cleavage site appears to be an essential condition, but is not the only factor that determines virulence.

Even though the molecular events surrounding mutation from an LPAI virus to an HPNAI virus are known, the factors that lead to this mutation are not clear for many outbreaks of H5 and H7 avian influenza viruses, including the first of the Asian lineage H5N1 HPNAI viruses. An HPAI virus has been generated experimentally by repeat passage of a LPNAI virus through chickens by air sac and intracerebral inoculation but the exact triggers for this change under natural conditions are unknown. In some earlier outbreaks of HPNAI, it was evident that the change from a LPNAI virus to an HPAI virus followed introduction of LPNAI virus to large flocks of commercial poultry. This change apparently occurred within a matter of days in some outbreaks (as was the case during the 2004 Canadian outbreak). In the case of Mexico, where mutation of a LPAI H5N2 virus to an HPAI virus occurred in 1994. This HPAI virus strain was subsequently eliminated, but H5N2 LPAI viruses continue to circulate but have not converted to highly pathogenic strains.
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In previous outbreaks, illegal trade or movements of infected live birds or their unprocessed products, and unintended mechanical transmission of virus through human movements (travellers, refugees, etc.) have been the main factors in the spread of HPNAI, and outbreaks seemed to remain localised. However, outbreaks of an unprecedented scale began to erupt late in 2003. From mid-December 2003 through to early February 2004, outbreaks in poultry caused by the Asian lineage HPNAI H5N1 virus were reported in the Republic of Korea, Vietnam, Japan, Thailand, Cambodia, Lao People’s Democratic Republic, Indonesia, and China. All efforts aimed at the containment of the disease have failed so far. Despite the culling and the pre-emptive destruction of some 150 million birds, H5N1 is now considered endemic in many parts of Indonesia and Vietnam and in some parts of Cambodia, China, Thailand, and other South-East Asian countries.

The original H5N1 virus, encountered for the first time in 1997, was of a reassortant parentage, including at least an H5N1 virus from domestic geese (A/goose/Guangdong/1/96\(^1\), donating the HA) and a H6N1 virus, probably from teals (A/teal/Hong Kong/W312/97, donating the NA) and the segments for the internal proteins). It underwent many more cycles of reassortment with other unknown avian influenza viruses. AIVs rely on two mechanisms of change: drift though accumulating point mutations in genes ("antigenic drift", HA had the highest of these rates) and "antigenic shift", exchange of gene segments (influenza A genomes consist of 8 RNA segments). Since its re-emergence in 2003, Asian HPNAI H5N1 strains have demonstrated both of these mechanisms to evolve and spread. Currently, two lineages of HPNAI H5N1 exist, and the latter is sub-divided into 3 clades.

In April 2005, yet another level of the epidemic was reached, when, for the first time, the H5N1 strain spread to wild bird populations on a larger scale. At Lake Qinghai in North Western China, several thousands of bar-headed geese, a migratory species, succumbed to the infection. Several species of gulls as well as cormorants were also affected at this location. When, in the summer and early autumn of 2005, H5N1 outbreaks were reported for the first time from geographically adjacent Mongolia, Kazakhstan, and southern Siberia, migratory birds were suspected of spreading the virus. Further outbreaks along and between overlapping migratory flyways from inner Asia towards the Middle East and Africa affected Turkey, Romania, Croatia, and the Crimean peninsula in late 2005. In all instances (except those in Mongolia and Croatia) both poultry and wild aquatic birds were found to be affected. Often the index cases in poultry appeared to be in close proximity to lakes and marshes inhabited by wild aquatic birds. While this seems to suggest spread of the virus by migratory aquatic birds, it should be noted that Asian lineage HPNAI H5N1 virus has only been detected in moribund or dead wild aquatic birds thus far. Domestic avian species do not have a long-term carrier status for HPNAI H5N1, and while the virus can persist in the environment for substantial periods of time (several weeks under the right conditions), it does not replicate outside the body of susceptible animals. To date, no permanent reservoir other than

\(^1\) Standard notation for influenza strains: A (denotes Influenza A)/ host species/ region/ sample reference/ year of isolation, usually followed by the subtype in parentheses.
live animals has been identified. The role of domestic species as a reservoir of disease is clear, particularly in flocks of domestic ducks. However, the question whether wild birds are a long-term reservoir of infection is still unresolved. HPNAI H5N1 has disappeared or been eradicated from some countries yet persists and/or has been re-introduced in others: 16 countries reported H5N1 avian influenza in domestic poultry/ wildlife in 2010: Bangladesh, Bhutan, Bulgaria, Cambodia, People’s Republic of China, Hong Kong (P.R. China), India, Israel, Japan, Republic of Korea, Laos, Myanmar, Nepal, Romania, Russia and Vietnam. Up-to-date information and maps of current distribution are available on the OIE website.

It is theoretically possible that AIV could be spread via air over a few tens of metres but this has never been found to be important in the epidemiology of the disease. Live bird markets (LBMs) have been an important source of infection especially when poultry are present. There is little information on the role of hunting wild birds, cock fighting, poultry fanciers and exotic birds in the transmission of the disease. A recent epidemiological investigation in Turkey has indicated that hunters may act as an important route of virus introduction between wild birds and domestic poultry, but there is no indication of how widespread this finding might be. Fighting cocks, poultry fanciers and exotic birds have been implicated in epidemics of Newcastle disease in the past thus their potential role in HPAI should not be overlooked.

The epidemiological links between wild birds and domestic poultry in outbreaks of HPNAI is well-illustrated by recurring events in South Africa’s ostrich-farming industry. In 2004, HPNAI H5N2 broke out in the Eastern Cape Province, and an apparent progenitor LPAI H5N2 virus was identified in an Egyptian goose from Western Cape Province. Other genes of the ostrich outbreak strain were also phylogenetically linked to South African wild duck virus isolates. In 2006 it was the turn of the Western Cape Province to be affected by an HPNAI H5N2 outbreak, but it was caused by a second introduction from the wild bird reservoir, as indicated by molecular analyses. In 2011, HPNAI H5N2 emerged in the Western Cape Province ostriches again, linked as before to the wild bird population by genetic sequences of the viral genes. Conditions on ostrich farms are ideal to facilitate transmission of the virus. Abundant water (rivers, farm dams, canals, water troughs in camps) and feed (feed troughs and irrigated pastures) attract vast numbers of wild birds such as ibises, pigeons, doves and Egyptian geese to the arid ostrich-producing areas. Once introduced, it is presumed that the virus spreads between ostriches via the drinking water (tracheal spread), and between farms through the movement of infected ostriches (e.g. at auctions, or rearing birds to stock farms), vaccination crews and their equipment and other mechanical means.

PATHOGENESIS

Avian influenza pathogenesis is essentially a multi-genic trait: genetic differences between different viral proteins and different combinations of variants affect how these proteins interact with each other and cellular components. An entire field of study is dedicated to mapping and characterizing point mutations through reverse-genetics technology and infection studies, and indeed important molecular virulence
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determinants have been mapped to the NA, NS, PA, PB1, PB2 and NP proteins. The first step towards infection, however, is viral entry into the host cell, and this function is fulfilled by the HA protein. HA facilitates the recognition and binding of the virus cellular receptors and subsequent entry, and thus is the major virulence determinant of AIV.

The HA protein must first bind to sialic acid-containing cell receptors to initiate receptor-mediated endocytosis. Then, to release the viral components into the host cell, the viral envelope and endosomal membrane can only be fused by an “activated” HA protein: the inactive precursor HA0 is recognized and enzymatically cleaved into active HA1 and HA2 proteins by host proteases. For LPAIV, HA0 is cleaved by trypsin-like proteases, which are restricted to epithelial cells, resulting in infection and lesions in epithelial cell-containing organs, primarily respiratory and digestive tracts. However, with HPAIV, HA0 is cleaved by ubiquitous furin-like proteases resulting in infections and lesions in many cell types in numerous visceral organs, the nervous system and cardiovascular system.

The actual HA0 cleavage site has been identified and characterized, and provides a useful molecular marker that designates the pathotype. The HA0 sequence of HPAIV usually contains insertions of multiple basic amino acids [(arginine (R), lysine (K) or glutamine (E)] so that a typical HPNAI H5 sequence might read PQREKRRKKRGLF (whereas the original H5 LPNAI trypsin-cleavable sequence at HA0 was PQRETQRGLF, for example). A list of HPNAI H5 and H7 HA0 sequences identified to date is published by the OIE.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

**Clinical signs and pathology**

In industrialised poultry holdings, a sharp rise followed by a progressive decline in water and food consumption can signal the presence of a systemic disease in a flock. In laying flocks, a drop in egg production is apparent. Individual birds affected by HPNAI often reveal little more than severe apathy and immobility. Oedema, visible at featherless parts of the head, cyanosis of the comb, wattles and legs, greenish diarrhoea and laboured breathing may be inconsistently present. In layers, soft-shelled eggs are seen initially, but any laying activities cease rapidly with progression of the disease. In less vulnerable species such as ducks, geese, and ratites, nervous signs including tremor, unusual postures (torticollis), and problems with co-ordination (ataxia) have been observed. During an outbreak of HPNAI in Saxonia, Germany, in 1979, geese compulsively swimming in narrow circles on a pond were among the first conspicuous signs leading to a preliminary suspicion of HPNAI.

The illness in fowls and turkeys caused by HPNAI is characterised by a sudden onset of severe signs and a mortality that can approach 100% within 48 hours. Spread within an affected flock depends on the form of rearing: in flocks which are litter-reared and where direct contact and mixing of birds is possible, spread...
of the infection is faster than in caged holdings but would still require several days for complete contagion. Often, only a section of a house is affected. Many birds die without premonitory signs with the result that poisoning may be suspected in the early stage of an outbreak. It is worth noting that a particular HPNAI virus strain may provoke severe disease in one avian species but not in another: in live poultry markets in Hong Kong prior to a complete depopulation in 1997, 20 % of the fowls but only 2.5 % of ducks and geese harboured H5N1 HPAIV while all other galliforme, passerine and psittacine species tested virus-negative and only the fowls actually showed clinical disease. Ostriches infected with HPNAI do not usually display severe clinical signs, and when inoculated into chickens, ostrich HPNAI viruses do not cause severe disease at first, but rapidly become pathogenic upon passage.

LPAI has an incubation period in poultry usually of a few days (and rarely up to 21 days), depending upon the characteristics of the viral strain, the dose of inoculum, the species, and age of the bird. The clinical presentation of avian influenza in birds is variable and signs are fairly non-specific, therefore a diagnosis solely based on the clinical presentation is impossible. The signs following infection with low pathogenic AIV may be as discrete as ruffled feathers, transient reductions in egg production or weight loss combined with mild respiratory signs. Some LP strains such as certain Asian H9N2 lineages, that have adapted to efficient replication in poultry, may cause more prominent signs and also significant mortality.

The following diseases must be considered in the differential diagnosis of HPNAI because of their ability to cause a sudden onset of disease accompanied by high mortality or cyanosis in wattles and combs:

- velogenic Newcastle disease
- infectious laryngotracheitis (fowls)
- duck plague
- acute poisonings
- acute fowl cholera (Pasteurellosis) and other septicaemic diseases
- bacterial cellulitis of the comb and wattles

Less severe forms of HPNAI can be clinically even more confusing. Rapid laboratory diagnosis therefore, is pivotal to all further measures.

**Laboratory confirmation**

The classical method of AIV diagnosis is virus isolation in embryonated fowl eggs. Tracheal or cloacal swabs, faeces from live birds or homogenized organs of dead birds are used. The sample or pooled samples are treated with antibiotics and the clarified supernatants are then inoculated into the allantoic sac of nine to eleven-day-old embryonated specific pathogen-free (SPF) eggs, or specific antibody-
negative (SAN) eggs. At least five eggs are inoculated per sample, and incubated for four to seven days at 35-37°C. Allantoic fluid is harvested from eggs containing dead or dying embryos, and then tested for hemagglutinating (HA) activity. Detection of HA activity (HA test) indicates a high probability of the presence of influenza A virus or of an avian paramyxovirus (e.g. Newcastle disease virus). The presence of influenza A virus can be confirmed in various other serological tests, including the agar gel immunodiffusion (AGID) test that demonstrates the presence of antibodies against the nucleoprotein (NP) or matrix (M) antigens, HI tests, and various commercially available ELISAs. Alternatively, the presence of influenza virus, and subtyping, can be confirmed with the use of reverse transcription polymerase chain reaction (RT-PCR) or real time reverse transcription PCR (rRT-PCR). rRT-PCR is able to detect the presence of AIV nucleic acids even if the viruses are no longer viable, and is therefore considered to be a more sensitive method than virus isolation. The matrix gene (M) is a common AIV group-specific target for rRT-PCR assays, and once presence of Al RNA is confirmed, subsequent rRT-PCR assays targeting the H5 and H7 genes are applied. Sensitive type-specific (H5/H7) conventional RT-PCR assays are used to amplify a short gene segment that spans the hemagglutinin cleavage site (HA0), and DNA sequence analysis is applied to determine the peptide cleavage signal sequence at HA0. Non-specific RNA amplification coupled with next generation sequencing technologies are increasingly being applied to determine full genomic sequences of AIVs. These techniques are providing new insights into adaptation of AIVs in the host, and have the added advantage of potentially retrieving partial or full genomic sequences directly from samples (swabs, tissues) i.e. in the absence of virus isolation, where very low levels or viruses are present, or viruses have lost its infectivity. Nowadays, a genomic sequence is sufficient to reconstruct an infective virus using reverse genetics technology.

The intra-venous pathogenicity index (IVPI) test is used as a method of clinically assessing the virulence of AIVs. Cultivated virus is injected intravenously into each of ten six-week-old SPF chickens, and the birds are examined at 24-hour intervals for ten days. At each observation, each bird is scored (0) if normal, (1) if sick, (2) if severely sick, and (3) if dead (dead individuals are scored as (3) at each of the remaining daily observations after death). The IVPI is the mean score per bird per observation over the ten-day period. An index of 3.0 means that all birds died within 24 hours, and an index of 0.00 means that no birds showed any clinical sign during the ten-day observation period. The OIE and European Union (EU) have adopted the following definition to confirm disease for the purposes of disease control: 'HPNAI is defined as an infection of poultry caused by an influenza A virus that has an IVPI in 6-week-old chickens >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'.

CONTROL / PREVENTION

The majority of HPNAI outbreaks are due to local secondary spread between domestic poultry after initial introduction. This is particularly true in endemically-infected countries. Most secondary spread is largely
human-mediated. People create spread directly by moving live birds (domestic and captive species), indirectly through contaminated materials (fomites), and in some cases through hunting and other sporting activities (e.g. cock-fighting). In some countries, live-bird markets (LBMs) have been one of the important elements in maintaining and spreading the virus, and have been the source of infection in humans. Any disease that is spread primarily through human activities lends itself to biosecurity control measures along the production and marketing chain. Biosecurity is thus a very important tool for the control and eradication of H5N1 HPAI, and the focus is on changing the behaviours of people in such a way that the risk of disease transmission is decreased.

Infectious disease prevention and control, although not easy to undertake, can be simply described as having three major goals, each of which has one or more methods to achieve it:

- Surveillance for early detection
- Rapid and humane targeted culling and disposal
- Biosecurity and vaccination to limit or stop the spread of infection

Disease control is most effective and efficient when all three goals are achieved together, and they are equally important acting additively to decrease infection pressure. However, while the methods to achieve these goals all decrease infection pressure, there are differences among them. Surveillance and killing of infected animals as quickly and humanely as possible are both vital tools but can only respond to infection that has already occurred. They act to limit spread by decreasing the amount of virus released from any one site, but cannot prevent it completely because some virus will have been released before culling commences, and often before the disease is detected.

Pre-emptive culling (the culling of animals before they are found to be infected) can be used to attempt to make this a more proactive measure. However, the use of widespread pre-emptive culling based on defined areas around an outbreak (1km, 3km or in some instances even 10km) has been shown to be very difficult to implement effectively in developing countries and can best be achieved by using limited and targeted risk-assessed pre-emptive culling. Widespread pre-emptive culling may also be counterproductive because it can cause birds to be moved and can result in the loss of cooperation by bird keepers; there is evidence from the field that draconian control measures have led to resentment and resistance to further control measures. As important, if not more so, is the creation of impediments to spread. Single introductions of HPAI are always possible but, if kept small, outbreaks are more easily dealt with; a key step therefore is to limit, slow down and stop spread. An essential part of this is to create an environment in which there are relatively few vulnerable locations and the two main methods available for this are vaccination and biosecurity. Vaccination is a proactive measure in that it protects animals from disease. Vaccination of domestic poultry against H5N1 HPAI has been useful in some countries in preventing human infection and controlling the epizootic through limiting spread in domestic poultry, but no country that has employed it extensively has yet been able to eliminate the virus. While vaccination is certainly a useful and important tool in the control of the disease, it is never likely to be sufficient on its
own to eradicate HPAI, in particular in scavenging poultry and ducks. Besides, vaccination of whole populations of domestic poultry requires political commitment and investment and this is difficult to maintain in the longer term.

Protection against HPAI in poultry largely depends on HA-specific antibodies. Therefore, the vaccine virus should belong to the same H subtype as the field virus. An ideal match of vaccine and field virus, as demanded for vaccine use in humans, is not mandatory in poultry. Whole virus AI vaccines are almost always inactivated because of the reassortment risk associated with live vaccines. Vaccines are prepared from infective allantoic fluid inactivated by betapropiolactone or formalin and emulsified with mineral oil. The inactivated vaccines produced have either been autogenous, i.e. prepared from isolates specifically involved in an epizootic (autogenous vaccines are homologous vaccines), or have been heterologous. Heterologous vaccines use the same HA type as the field virus but contain a heterologous NA (e.g. H5N9 vaccine vs. H5N2 field outbreak strain). This type of vaccine has the advantage over the homologous vaccine of being distinguished from the field infection, because antibodies produced against the NA can be used as a marker, and this approach is commonly known as the DIVA (Differentiating Infected from Vaccinated Animals) strategy. The internal proteins NS1 and M2 have also been used as markers in a DIVA strategy, as both are abundantly expressed during viral replication in infected cells, eliciting specific antibodies that can be detected, whereas this is not the case with an inactivated, non-replicating vaccine. Under field conditions, protection afforded by inactivated vaccines could be undermined by improper vaccination technique, improper storage and handling of vaccines and infections that suppress the immune system of the bird.

MARKETING AND TRADE / SOCIO-ECONOMICS

Outbreaks of HPNAI can be catastrophic for single farmers and for the poultry industry of an affected region as a whole, but economic losses are usually only partly due to direct deaths of poultry from HPAI infection: measures put up to prevent further spread of the disease levy a heavy toll. Additionally, nutritional consequences can be equally devastating in developing countries where poultry is an important source of animal protein. Once outbreaks have become widespread, control is difficult to achieve and may take several years.

Due to its potentially devastating economic impact, HPNAI is subject world-wide to vigilant supervision and strict legislation. Measures to be taken against HPAI depend on the epidemiological situation of the region affected. In the European Union (EU) (and South Africa) where HPAIV is not endemic, prophylactic vaccination against avian influenza is generally forbidden. Thus, outbreaks of HPAI in poultry are expected to be conspicuous due to the clinically devastating course of the disease (in ostriches however, mortalities are generally only observed in younger age groups). Consequently, when facing such an outbreak, aggressive control measures, e.g. stamping out affected and contact holdings, are put in place, aiming at the immediate eradication of HPAI viruses and containing the outbreak at the index site. It has
also been necessary in some outbreaks (e.g. Italy) to not only destroy birds on infected or contact holdings, but also flocks with a risk of infection within a radius of one kilometre from the infected farm. The creation of buffer zones of one to several kilometres around infected farms completely devoid of any poultry was also behind the successful eradication of HPAIV in the Netherlands in 2003 and in Canada in 2004. So, not only the disease itself, but also the pre-emptive culling of animals led to losses of many millions of birds. In 1997, the Hong Kong authorities culled the entire poultry population (1.4 million birds) within three days. The application of such measures, aimed at the immediate eradication of HPAIV at the cost of culling also non-infected animals, may be feasible on commercial farms and in urban settings. However, this will affect the poultry industry significantly and also prompt ethical concerns from the public against the culling of millions of healthy and uninfected birds in the buffer zones.

HPNAI outbreaks have severe implications for international poultry trade. While industry profitability, employment, household livelihoods, and, potentially, food security are being adversely affected by AI outbreaks in many countries around the globe, the market impact has broadened to include the major poultry trading countries. Impacts include poultry meat supply buildups, poultry consumption declines, potentially sharp drops in global poultry trade, and declining international poultry prices and industry profitability, as well as disruptions in normal trade flows. Extending beyond the poultry sector, the market impact has implications for feed and other input industries.

International organizations, such as the OIE, the United Nations Food and Agriculture Organization (FAO), and the World Health Organization (WHO), provide assistance to countries for AI disease prevention, management, and eradication. Countries around the world are at various stages of developing infrastructure and regulations to respond to animal disease outbreaks of all kinds. Poultry product import bans have followed almost immediately after any announcement of AI outbreaks, whether low- or high-pathogenic outbreaks. Both international and individual country agencies have supported and adopted the position that trade bans should be based on science and established rules. In May 2005, the OIE adopted a new chapter on AI that was ratified by its members. The new OIE AI chapter first introduced the “notifiable” concept that applies to H5 and H7 strains discussed in this course, and furthermore, the chapter contains language that allows trade to occur from certain zones (geographical areas) or from “compartments” (a group of farms, an enterprise, or another managed unit) within a country even though AI may be present in a completely separate zone or compartment in that country.

2 Although the OIE holds no real enforcement authority, all major poultry-producing nations are OIE members. By virtue of membership, these countries are signatory to an agreement to abide by OIE protocols on trade restrictions based on animal diseases, unless additional restrictive measures can be justified by risk assessment.
### IMPORTANT OUTBREAKS

<table>
<thead>
<tr>
<th>Date</th>
<th>Country</th>
<th>Subtype</th>
<th>Impact: Birds Affected With High Mortality Or Culled; Human Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1959</td>
<td>Scotland</td>
<td>H5N1</td>
<td></td>
</tr>
<tr>
<td>1961</td>
<td>South Africa</td>
<td>H5N3</td>
<td>1 300 common terns</td>
</tr>
<tr>
<td>1963</td>
<td>England</td>
<td>H7N3</td>
<td>29 000 breeder turkeys</td>
</tr>
<tr>
<td>1966</td>
<td>Ontario, Canada</td>
<td>H5N9</td>
<td>8 100 breeder turkeys</td>
</tr>
<tr>
<td>1976</td>
<td>Victoria, Australia</td>
<td>H7N7</td>
<td>25 000 laying chickens, 17 000 broilers, 16 000 ducks</td>
</tr>
<tr>
<td>1979</td>
<td>Germany</td>
<td>H7N7</td>
<td>Chickens, geese</td>
</tr>
<tr>
<td>1979</td>
<td>England</td>
<td>H7N7</td>
<td>3 commercial turkey farms</td>
</tr>
<tr>
<td>1983-1985</td>
<td>Pennsylvania, USA</td>
<td>H5N2</td>
<td>17 million birds: mainly chickens and turkeys, total cost $641 million</td>
</tr>
<tr>
<td>1983</td>
<td>Ireland</td>
<td>H5N8</td>
<td>800 turkeys died on original farm, 8 640 turkeys, 28 000 chickens and 270 000 ducks culled in the region</td>
</tr>
<tr>
<td>1985</td>
<td>Victoria, Australia</td>
<td>H7N7</td>
<td>24 000 broiler breeders, 27000 layers, 69 000 broilers, 118 500 other chickens</td>
</tr>
<tr>
<td>1991</td>
<td>England</td>
<td>H5N1</td>
<td>8 000 turkeys</td>
</tr>
<tr>
<td>1992</td>
<td>Victoria, Australia</td>
<td>H7N3</td>
<td>12 700 broiler breeders, 5 700 ducks</td>
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<tr>
<td>1994</td>
<td>Queensland, Australia</td>
<td>H7N3</td>
<td>22 000 layers</td>
</tr>
<tr>
<td>1994-1995</td>
<td>Mexico</td>
<td>H5N2</td>
<td>Chickens</td>
</tr>
<tr>
<td>1995</td>
<td>Pakistan</td>
<td>H7N3</td>
<td>3.2 million broilers and broiler breeder chickens</td>
</tr>
<tr>
<td>Date</td>
<td>Country</td>
<td>Subtype</td>
<td>Impact: Birds Affected With High Mortality Or Culled; Human Cases</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------</td>
<td>---------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>1997</td>
<td>New South Wales, Australia</td>
<td>H7N4</td>
<td>128 000 broiler breeders, 33 000 broilers, 261 emus</td>
</tr>
<tr>
<td>1997</td>
<td>Italy</td>
<td>H5N2</td>
<td>~7000 birds consisting mainly of chickens, turkeys and ducks</td>
</tr>
<tr>
<td>1997-1998</td>
<td>Hong Kong</td>
<td>H5N1</td>
<td>Entire poultry population of Hong Kong culled, ~1.4 million birds</td>
</tr>
<tr>
<td>1999-2000</td>
<td>Italy</td>
<td>H7N1</td>
<td>413 cases, 14 million birds killed (mainly chickens and turkeys), total cost to industry $630 million</td>
</tr>
<tr>
<td>2001-2002</td>
<td>Hong Kong</td>
<td>H5N1</td>
<td>~2.5 million birds killed</td>
</tr>
<tr>
<td>2002</td>
<td>Chile</td>
<td>H7N3</td>
<td></td>
</tr>
<tr>
<td>Feb 2003</td>
<td>Hong Kong</td>
<td>H5N1</td>
<td>One of three human cases fatal</td>
</tr>
<tr>
<td>Apr 2003</td>
<td>Netherlands, Belgium, Germany</td>
<td>H7N7</td>
<td>250 farms affected, 30 million birds culled. One of 89 human cases fatal</td>
</tr>
<tr>
<td>Dec 03-Jan 04</td>
<td>Vietnam, Thailand, Korea, 8 other Asian countries</td>
<td>H5N1</td>
<td>24 of 34 human cases fatal, 100 million birds culled</td>
</tr>
<tr>
<td>Feb 2004</td>
<td>Texas USA</td>
<td>H5N2</td>
<td>1 600 birds</td>
</tr>
<tr>
<td>2004</td>
<td>Canada</td>
<td>H7N3</td>
<td>48 500 birds culled</td>
</tr>
<tr>
<td>2004</td>
<td>South Africa</td>
<td>H5N2</td>
<td>16 000 ostriches culled</td>
</tr>
<tr>
<td>2006</td>
<td>South Africa</td>
<td>H5N2</td>
<td>7 300 ostriches culled</td>
</tr>
<tr>
<td>2009</td>
<td>Spain</td>
<td>H7N7</td>
<td>3 000 deaths, 27000 birds culled</td>
</tr>
<tr>
<td>Date</td>
<td>Country</td>
<td>Subtype</td>
<td>Impact: Birds Affected With High Mortality Or Culled; Human Cases</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>---------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>2011</td>
<td>South Africa</td>
<td>H5N2</td>
<td>41 000 ostriches culled</td>
</tr>
<tr>
<td>2013-2014</td>
<td>China</td>
<td>H7N9</td>
<td>47/139 human fatalities in laboratory-confirmed cases</td>
</tr>
</tbody>
</table>

FAQs

1. Why do LPNAI viruses mutate in poultry?

   In waterfowl influenza viruses are stable and only certain enzymes present in the respiratory tract and gut of birds are able to “activate” virus infectivity. When AIVs are transmitted to terrestrial poultry, the cellular machinery that the virus “hijacks” to replicate itself is slightly different due to species-specific factors, and errors are introduced into the viral genome. These genetic errors allow a wider range of enzymes present in the bird to activate the virus, enabling it to spread systemically.

2. I suspect that my chickens are infected with HPNAI, what must I do?

   Notify your nearest State Veterinarian’s office immediately, and they will direct you in the procedure for submitting samples for laboratory diagnosis. In the meantime, try to isolate the sick birds, dispose of carcasses properly, and apply sanitary measures with a bleach solution or a disinfectant that is proven to kill viruses.

3. What are the clinical signs in poultry associated with HPNAI?

   Birds may die suddenly without any clinical signs, but common signs include lethargy, oedema (swelling) visible on the featherless parts of the head, cyanosis of the wattles, combs and legs, green diarrhoea and respiratory difficulties.

4. Can I eat meat infected with HPNAI?

   Cooking meat properly completely inactivates the H5N1 virus. In fact, cooking meat for 4 minutes at a temperature of 57°C is sufficient to completely inactivate the virus, making it safe to consume.

5. Did wild birds spread HPNAI H5N1?
Opinions are divided, but it is important to note that the virus was detected in mainly dead or severely sick wild migratory birds. Sick birds are unlikely to fly long distances. Theoretically, birds that had prior exposure to LPAI H5 strains would have developed specific antibodies that might have enabled a subclinical carrier status. However, thousands of wild birds have been surveyed, and no reservoirs of HPNAI H5N1 have been identified to date.

REFERENCES


11. OIE/FAO Network of expertise on animal influenzas (OFFLU) website: http://www.offlu.net
