Avian Influenza

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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-naïve 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.
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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 HPAI, it was evident that the change from a LPNAI virus to an HPNAI 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.

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

\(^1\) Standard notation for influenza strains: A (denotes Influenza A)/ host species/ region/ sample reference/ year of isolation, usually followed by the subtype in parentheses.
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 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/ wildife 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.