

AVIAN INFLUENZA: A REVIEW

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INTRODUCTION

Avian influenza (AI) has often occurred as a sporadic disease in different parts of the world. It attracted more public interest in 1997 and 2003 in Hong Kong, China when people died because of contact with infected poultry. Early in, 2004, AI was again reported in Thailand and other Southeastern Asian countries and its effects on humans and poultry were more severe and widespread as compared to those in 1997 and 2003 (WHO, 2005). AI has been reported in Zimbabwe in 1995 and South Africa in 1998 (Pfitzer *et al.*, 2000; OIE, 2004). Although AI has not been reported in Nigeria (Abegunde and Mbibu, 1987) it is nevertheless pertinent to present a brief review on the disease and highlight its economic and public health importance to stakeholders in the Nigerian poultry industry.

SYNONYMS, DEFINITION, HISTORY
AND DISTRIBUTION OF AI

The synonyms for AI include avian influenza A, bird flu, fowl pest, fowl plague and highly pathogenic avian influenza disease (HPAI) (Whiteman and Bickford, 1989; Easterday *et al.*, 1997; Larson, 1998; Alexander, 1999).

AI is a viral disease affecting the digestive, nervous and respiratory systems of almost all domestic and wild birds that is characterized by respiratory, digestive and/or nervous signs with high morbidity

and mortality and an incubation period of few hours to few days (Whiteman and Bickford, 1989; Easterday *et al.*, 1997; DEFRA, 2003).

The name, 'influenza' originated in Italy in the eighteenth century. Because the illness affected so many people over a large area, it was attributed to the 'universal influence, *influenza*, of the stars' (Meredith, 2004).

Perroncito initially reported AI in 1878 in Italy (Bankowski and Samadieh, 1980; Easterday *et al.*, 1997; DEFRA, 2003). Other reports of AI outbreaks include Oregon (1971), Australia (1975 and 1988), England (1979), the United States of America (USA) (1983-84), Ireland (1983-84), Mexico (1994) and Pakistan (1994) (Esterday *et al.*, 1997). Turkeys in North America were initially infected with AI virus in 1963 and serious outbreak in chickens in the USA occurred in 1929, 1975, 1979 and 1983-84 (Hanson, 2005).

The incubation period of AI ranges from few hours, 2-4 days to 1-2 weeks depending on the virus dose, route of infection and specie of bird infected (Easterday *et al.*, 1997).

AI is worldwide in distribution and has been reported in North and South Africa, Australia, North and South America (USA, Canada, Mexico, Chile), Middle and East Asia (Pakistan, Hong Kong) and Europe

(Italy, Germany, UK, Netherlands, Belgium) (Easterday *et al.*, 1997; Alexander, 1999; DEFRA, 2003).

AETIOLOGY

Influenza type A virus, a member of the family *Orthomyxoviridae* causes AI. It is an enveloped, spherical or filamentous (80-100 nm in diameter or cross section) single stranded segmented (8) negative-sense RNA virus. It codes for 10 proteins (haemagglutinin (H), neuraminidase (N), protein matrix (M), ribonucleoprotein (RNP), etc) with an M and a RNP, which give the virus its antigenic type specificity. AI type A virus (found in humans, birds, pigs and horses), B or C (found in humans) have two surface (envelope) glycoproteins-H and N give the virus its antigenic subtype specificity. There are 15 H (H1 to 15) and 9 N (N1 to 9) subtypes (Alexander, 1999; Swayne *et al.*, 1998; Swayne, 2003). There are therefore 135 possible AI virus subtypes. There is no cross protection between subtypes. Subtypes H1, H5 and H7, N1, N2, N3, N7 and N8 are the most pathogenic AI viruses. Others are mildly pathogenic or avirulent although they could later mutate without warning and become virulent without a change in their H and N subtype antigen (Alexander, 1999; Eckroade *et al.*, 2002; Suarez, 2003; Hansen, 2005). The time it takes for avirulent or mildly pathogenic AI virus to become virulent varies. For example the low virulent H5N2 virus in the USA became virulent within six months while the low virulent H2N1 virus in Italy caused severe outbreak of AI within nine months (Easterday *et al.*, 1997; WHO, 2005). Due to their segmented nature and the presence of different surface proteins, AI viruses are susceptible to both random mutations within the genome segments (*antigenic drift*) as well as reassortment (*swapping*) of gene

segments (*antigenic shift*) between different AI viruses in 'mixing vessels' such as pigs and humans following concurrent infection in the hosts (Beard, 1998; Shane, 2002; Suarez, 2003; Meredith, 2004; WHO, 2005). Therefore thousands of avian influenza type A viruses have been isolated from domestic and wild birds (Alexander, 1995; Easterday *et al.*, 1997; Alexander, 1999).

TRANSMISSION

The AI virus is present in secretions from the eyes, mouth and nostrils and faeces from infected birds. About one gram of contaminated faeces from infected chickens can contain enough of a HPAI virus to infect 1,000,000 birds (Chalmers, 2005). Transmission may be direct by inhalation of aerosol and contaminated dust or indirectly via ingestion of contaminated water (especially surface water), food or infected carcasses. Broken contaminated eggs may infect chicks in the incubator (DEFRA, 2003). The faecal-oral route is the main route of spread. The virus is more frequently isolated from waterfowls, domestic ducks, turkeys and chickens in descending order (Swayne *et al.*, 1998). Domestic and wild ducks, migratory, sea and pet birds may harbour more than one virus subtype for long periods without becoming clinically sick. Live-bird market, contaminated poultry houses and equipment, clothing, shoes, vehicles and eggs are good sources of the AI virus (Mubiru, 1998). The virus can survive for four to 30 days in contaminated water depending on its temperature and remain viable for up to 44 days in faeces and for more than three months in poultry manure and litter (Alexander, 1999; DEFRA, 2003; Hanson, 2005). The AI virus has been recovered from poultry houses more than 100 days after the flock has been marketed (Hanson, 2005). Pigs

and humans may transmit AI to poultry (Shane, 2002).

HOSTS

Birds of all ages and almost all avian species are susceptible to AI. Humans, pigs and horses can be infected with AI virus. Chickens and turkeys are the most adversely affected birds by AI (Hanson, 2005). Chickens (in live-bird markets), turkeys and ducks are potential sources of AI. Domestic and wild ducks (particularly mallard ducks) have asymptomatic infection and may excrete AI virus for long periods, they are carriers and harbour more than one AI virus subtype and rarely produce precipitating antibodies. They are thus the natural reservoirs of AI viruses. Ratites (ostriches and rhea), quail, muscovy ducks, geese, guinea fowls, chukars, game (partridges and pheasants), pet, sea and shorebirds are susceptible to AI to varying degree (Hansen, 2005). Antibodies and the AI virus could not be detected in pigeons either naturally or when they were experimentally inoculated with a HPAI virus (Shane, 2002; Chalmers, 2005). For now therefore pigeons are considered as resistant to AI. AI is seasonal in high-risk areas due to migratory activity of waterfowl, the only specie of bird in which the AI virus was found to be present year round (Hansen, 2005). AI prevalence is highest in birds on range. Interspecies (e.g. between chickens, turkeys, pigs and humans with H1N1 subtype; chickens, emus, geese and waterfowls with H5N1 subtype; and ducks, pigs and humans) infection with AI virus do occur (Alexander, 1995; Swayne *et al.*, 1998; Shane, 2002).

CLINICAL SIGNS

At present AI is recognized in two forms, HPAI and low pathogenic AI (LPAI). The

signs of AI in domestic birds vary depending on the age, health status, specie and sex of bird, the dose and strain of the virus and route of virus entry (Hanson, 2005). The signs may appear as respiratory, enteric or reproductive abnormalities (Hansen, 2005).

The LPAI viruses cause drop in egg production and mild respiratory disease with low mortality. However, if there is secondary bacterial or viral infection there may be severe respiratory disease with high mortality (Paul and Schrier, 2001; Swayne, 2003). The most notable sign of illness is silence with lack of normal sounds (Halvorson *et al.*, 1980). HPAI viruses such as H5N2 and H7N7 subtypes cause a disease that spreads rapidly among flocks and sudden onset of high morbidity (100%) and mortality (50-100%), cessation to moderate or severe drop in egg production and the laying of eggs with abnormal shell and pigmentation. Other signs include greenish diarrhoea, anorexia, depression and ruffled feathers, coughing, sneezing, rales, dyspnoea (due to oedema of glottis), sinusitis (particularly in quails, ducks and turkeys) and mucoid ocular and nasal (blood-tinged) discharges. Cyanosis and oedema of the eyes, head, comb and wattles; discolouration of the shanks and feet; nervous disorders, excitation, convulsion, circling and ataxia, in birds that survive the acute phase of the disease have been reported (Whiteman and Brickford, 1989; Easterday *et al.*, 1997; Aiello, 1998; Swayne *et al.*, 1998; Alexander, 1999; DEFRA, 2003).

GROSS LESIONS

The organs involved and the lesions at postmortem vary with location and severity depending on the specie of bird and the pathogenicity of the infecting AI virus.

LPAI cause catarrhal, fibrinous, serofibrinous, mucopurulent or caseous inflammation of the sinuses. Air sacs are thickened with fibrinous or caseous exudate. In the peritoneum there is catarrhal or fibrinous peritonitis and egg yolk peritonitis. In the intestine and caeca catarrhal or fibrinous enteritis is seen. Abnormalities in the oviduct include presence of exudates and oviduct involution. There is regression of ovarian follicles. In the heart, occasional fibrinous pericarditis may be seen.

With some HPAI viruses, death is sudden and there are no lesions seen. Some viruses cause oedema of the head with swollen sinuses, cyanotic, congested and haemorrhagic wattles and comb, congestion and haemorrhage on the legs, severe congestion and oedema of the lungs and enlargement and congestion of the kidneys with urates and presences of necrotic foci in the wattles, skin, liver, spleen, kidneys and lungs. Others cause severe swelling of the comb and wattles with periorbital oedema. Vesicles to severe swelling and cyanosis, ecchymosis and frank necrosis of the comb are seen. Sometimes there are swellings of the shanks and feet with ecchymotic discolouration. Petechial haemorrhages of serosal and mucosal surfaces especially of the heart and the junction between the ventriculus and the proventriculus, small intestine, mouth muscles and abdominal fat are seen. The pancreas may have light yellow and dark red areas along its length and the spleen with mottled appearance (Bankowski and Samadieh, 1980; Aiello, 1989; Whiteman and Brickford, 1989; Easterday *et al.*, 1997; Swayne *et al.*, 1998; Alexander 1999; DEFRA, 2003).

MICROSCOPIC LESIONS

Microscopic lesions depend on the infecting AI virus, the specie and type of bird. In LPAI caseous exudates are seen in the nares and paranasal sinuses. There is loss of cilia, swelling and vacuolation and necrosis of epithelial cells in the sinuses associated with oedema, heterophil and mononuclear cell infiltration. In the trachea, there is necrosis of the epithelium, heterophil infiltration, hyperplasia and mononuclear cell infiltration. In the lungs the bronchi, atria and air capillaries are filled with serofibrinous exudates mixed with macrophages, heterophils and epithelial cells and with some lobules completely necrotic, there is prominent cuboidalization of atrial epithelium, presence of fibrin thrombi in small arterioles and diffuse severe congestion of pulmonary vasculature. In the spleen, there is severe congestion, fibrin deposition and lymphocytes depletion. The blood vessels of the kidneys are severe congestion

HPAI cause widespread lesions. In the comb the following lesions are seen; oedema of dermis and vesicles in epidermis, microvesicles in the epithelium, larger vesicles or focal necrosis underneath the epithelium, surrounded or invaded by heterophils, lymphocytes and accompanied by a marked lymphocytic perivascularitis in the dermis. There is oedema, hyperemia, haemorrhages and foci of perivascular cuffing in the wattles. In affected heart, there is severe myocarditis and myocardial necrosis, oedema, hyperemia, haemorrhages and foci of lymphoid cuffing. Focal areas of necrotic muscles and necrotizing myositis in external, ocular and skeletal muscles characterized by focal necrosis of fibers and infiltration of mononuclear cells are observed. In the pancreas the lesions varying from multifocal, to wide spread oedema, hyperemia, haemorrhages and necrosis and vacuolation of acinar cells and necrosis of

exocrine cells and loss of normal structure. Scattered heterophil infiltration is present and eosinophilic intranuclear inclusion bodies can be seen in the islets of Langerhans. In the brain there is wide-spread perivascular cuffing with mononuclear cells, focal gliosis, focal degeneration and necrosis of neurons, neuronophagia, oedema and necrosis of nervous tissue and vascular proliferation and some haemorrhages in the brain and vascular endothelial swelling, along with some infiltration of mononuclear cells in the meninges. Some AI virus isolates induce severe lymphoid necrosis in the spleen, thymus, bursa, intestine and lungs with fibrinoid degeneration of sheathed arteries in the spleen. Haemorrhage associated with necrosis in collection of lymphoid cells is present in the proventriculus, oedema, hyperemia, haemorrhages and necrotic foci in the intestine, oedema, hyperemia, haemorrhages and foci of perivascular lymphoid cuffing in the spleen, lungs, liver and kidneys and parenchymal degeneration and necrosis in the spleen, liver and kidneys are observed (Riddell, 1987; Ficken *et al.*, 1989; Easterday *et al.*, 1997).

DIFFERENTIAL DIAGNOSES

Differential diagnoses for AI include acute fowl cholera, avian adenoviruses causing respiratory disease or drop in egg production (e.g. EDS76) and viscerotropic velogenic Newcastle disease, as well as infectious laryngotracheitis, infectious bronchitis, mycoplasmosis, infectious coryza, chlamydiosis and pulmonary aspergillosis (Whiteman and Brickford, 1989; Easterday *et al.*, 1997; Aiello, 1998; Alexander, 1999; DEPRA, 2003).

DIAGNOSIS

Tentative diagnosis is based on clinical signs and gross lesions. Definitive diagnosis requires (a) virus isolation and/or identification from cloacal swabs in embryonated chicken eggs, (b) detection of viral (proteins) antigenic type using agar gel diffusion (AGID), solid phase enzyme linked immunosorbant assay (ELISA) or indirect fluorescent antibody tests or viral nucleic acid using reverse transcriptase polymerase chain reaction and (c) serology (which is useful in surveillance for AI) using AGID. AGID is the preferred serological test and it is used for detecting type antigens, A, B or C, with antigens from Office International des Epizooties reference laboratory, National Veterinary Services Laboratories, Ames Iowa USA or antigen in ground chorioallantoic membrane or yolk sac. Indirect ELISA or HIT using control sera and antigens representing H1 to H15 subtypes and allantoic fluid as antigen and virus neutralization test to detect the neutralizing character. Sera of at least 20 birds per flock are tested and paired sera taken. Positive sera should be sub typed using HI & NI tests (Swayne, 1998; Shane, 2002). However, the virulence of an AI virus cannot be determined by the antigenic subtype but by animal inoculation tests (Hansen, 2005).

TREATMENT

Amantadine hydrochloride reduces mortality due to AI in some avian species. However, its use is not economical in commercial birds because of cost and shortage in supply (Aiello, 1998). Resistance to amantadine and/or rimantadine frequently develops (Aiello, 1998; Mungall *et al.*, 2003; CDC, 2005; WHO, 2005). Zanamivir (Relenze) and oseltamivir (Tamiflu) have been shown to inhibit both human (influenza A&B) and AI (influenza B) viral neuraminidases and

has been approved in several countries for the treatment and prophylaxis of influenza infections (Mungall *et al.*, 2003; MDTH, 2005). For example, the influenza A (H5N1) viruses identified in human patients in Asia in 2004 and 2005 have been resistant to amantadine and rimantadine (CDC, 2005). Treatment with broad-spectrum antibiotics, proper nutrition and increasing house temperatures may also control secondary bacterial infection, relieve respiratory distress and reduce mortality (Whiteman and Brickford, 1989; Aiello, 1998).

PREVENTION, CONTROL AND ERADICATION

Prevention

The prevention of entry of the AI virus is the first line of defence (Hansen, 2005). Prevention of AI includes avoidance of flock additions and exclusion of wild, water and migratory birds from poultry, locating farms away from migratory bird routes, encouraging good husbandry practices (prevention of stress, confinement, reducing movement of people and equipment in and out of the farm and institution of flock bio-security measures through keeping birds of different species and age separately, wearing of appropriate clothing and boot cover, showering when going in and out of farm, disinfection of equipment, clothing and vehicles) and educating farmers about the disease (Alexander, 1995; Easterday *et al.*, 1997; Alexander, 1999).

Control

Control is used for LPAI and includes the use of inactivated oil emulsion polyvalent vaccines, containing the subtypes isolated and identified in affected areas. Vaccines have been found to be useful in the USA. The major protective antigen on the AI virus particle is the H and to a lesser extent

N i.e. it will only provide partial protection. Vaccines do not completely prevent infection but will protect birds from clinical signs and mortality and decrease the environmental AI virus load by reducing virus replication and shedding in vaccinated birds (Alexander, 1995; Aiello, 1998; DEFRA, 2003; Swayne, 2003). Reduction in AI virus shedding significantly reduces the chance that an infected farm will infect another farm and people (Anonymous, 2005a). A higher dose of the virus is necessary to infect vaccinated birds (Swayne *et al.*, 2001; Anonymous 2005b). Vaccination at the face of an outbreak also stops virus shedding and transmission (Anonymous, 2005b).

Eradication

Eradication is used for HPAI and includes active and passive serological testing of serum and yolk for antibodies to AI virus, quarantine of flock found to be affected through clinical signs, serology or virology; the slaughtering, burying or burning of infected poultry and faeces on the site (stamping out policy) and restocking of farm three weeks after cleaning and disinfecting the houses. Dead or destroyed birds should not be fed to other animals nor their carcasses be sold. The AI virus is sensitive to heat, desiccation, extreme pH, formalin (2%) and sodium hypochlorite (Hanson, 2005). Poultry slaughtered are compensated for using prevailing market price. It also includes banning the importation of poultry and poultry products from affected areas and mandatory reporting of outbreaks of acute respiratory diseases to local, state and federal veterinary authorities (DEFRA, 2003; Swayne, 2003; Anonymous, 2005a).

ECONOMIC AND PUBLIC HEALTH SIGNIFICANCE OF AI

Under normal conditions, human strains of AI have belonged to the H1, H2 and H3 subtypes and poultry strains have been of the H5 and H7 subtypes (Hanson, 2005). Until 1997 AI viruses have not been known to be transmitted directly from birds to humans. That year, of the 18 people that became sick with severe respiratory disease after contact with poultry that were sick or died of HPAI caused by H5N1 subtype of AI, six died in Hong Kong, China (Larson, 1998; WHO, 2005). All the 1.5 million chickens in Hong Kong were killed in order to get rid of the source of infection (Mubiru, 1998). Human deaths were again reported from AI virus subtype H5N1 in Hong Kong in 2003 (Swayne, 2003). Between December 2003 and March 2004 an epidemic of AI in Southeast Asia involving South Korea, Cambodia, China, Indonesia, Japan, Laos, Thailand and Vietnam resulted in the infection of 34 and the death of 23 people, millions of birds and the emergency slaughter of about 100 million birds (WHO, 2005). Some health workers that took care of the sick also became severely ill (WHO, 2005). Between March and May 2003 an outbreak of HPAI caused by H7N7 virus in the Netherlands resulted in the death of a veterinarian after exhibiting respiratory symptoms and mild illness of conjunctivitis (pink eye) in 89 other humans working directly with poultry (WHO, 2005; Anonymous, 2005c; MDTH, 2005). Pigs were also infected in that outbreak (Meredith, 2004). AI has also caused the death of wild cats that were fed with slaughtered AI infected birds. Recently a family of three died of AI in Indonesia also without apparently having contact with infected poultry (BBC, 2005a). On the 1st of August 2005 an outbreak of AI was reported in ducks and

geese in Siberia, Russia. Serotype H5N1 was isolated. About 2000 birds have to be destroyed by burning (BBC, 2005b). Also on the 6th and 8th of October 2005, AI outbreak have been reported in Romania and Turkey respectively. This shows clearly that HPAI in humans and poultry is gradually spreading and may soon become a global problem.

The reduction in growth rate, egg production and high mortality and high cost of treatment, control and eradication due to AI results in loss of income and livelihoods. Production loss due to AI subsequently results in high cost of poultry and poultry by-products because of the resultant scarcity of poultry products. Countries and regions affected by AI stand the risk of losing the right to export poultry and poultry by-products to free countries. Thus AI has been described as an international problem that requires international efforts and cooperation to solve (Swayne, 2003). It has to be considered as such also because the human influenza pandemic of 1918 killed about 21 million people worldwide when the means of world transportation was not as easy, cheap and fast as it is today and there is the possibility that the AI virus could one day be easily transmitted from human to human (Larson, 1998; WHO, 2005). To day traveling is faster and therefore the AI virus can be disseminated easily and faster around the world. An indication of the possibility of human to human transmission was shown in the Netherlands where about 60% of the people that had no contact with H7N7 AI virus infected poultry but were in close contact to an infected poultry worker had antibodies to the virus (Anonymous, 2005c).

SITUATION OF AI IN AFRICA

AI has been reported to have killed common terns (sea birds) in South Africa in 1961. The birds that died did not have gross lesions but a few had microscopic evidence of meningoencephalitis (Hansen, 2005). Non-pathogenic AI viruses, subtypes H7N1, H5N9, H9N2 and H6N8, were isolated from poultry in South Africa in 1991, 1992, 1994, 1995 and 1998 (OIE, 2004). In 2000 another non-pathogenic subtype H10N9 was isolated from wild aquatic birds in South Africa (Pfitzer *et al.*, 2000). On August the 6th 2004, HPAI outbreaks caused by subtype H5N2 were reported in the Middleton area in Eastern Cape Province of South Africa. The H5N2 subtype had earlier been found in 1995 to have caused outbreaks in Zimbabwe (OIE, 2004). No human cases were found in these two countries and past experiences in Taiwan, Mexico, Italy and the USA with HPAI subtype H5N2 viruses indicated that there was a low threat to public health (OIE, 2004).

SITUATION OF AI IN NIGERIA

AI has not been reported in Nigeria to date (Abegunde and Mbibu, 1987). However, it has been observed by the Federal Department of Livestock and Pest Control Services (FDL & PCS) (Anonymous, 2004) that there is lack of: conclusive scientific knowledge of the status of AI in Nigeria; strict control of livestock and poultry movement in Nigeria due to inadequate veterinary quarantine facilities and enforcement of legislative provision; organized marketing system for poultry and poultry products and emergency preparedness plan for AI. Also observed was the fact that the poultry industry in Nigeria is highly dependant on importation of hatchable eggs, day-old and grand parent stocks and there is inadequate

capacity for the definitive diagnosis of AI (Anonymous, 2004).

In the light of the observations above it was recommended that: there should be an immediate investigation and active surveillance of all acute respiratory disease syndrome and AI; strict monitoring and control of movement of all poultry and poultry products coming through land, air and sea ports; enforcement of the legal provision with regards to registration of poultry premises, farms and hatcheries in Nigeria; immediate preparation of a national emergency preparedness plan for AI; importation of hatchable eggs and day-old parent and grand parent chicks from certified disease-free countries and with duly issued import permit and provision of substantial financial support to establish and strengthen the capacity for AI diagnosis and research (Anonymous, 2004).

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