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Review on highly pathogenic avian influenza, public health and economic importance

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Abstract

Avian influenza, also known as avian flu or bird flu, is an infectious disease of birds caused by type A strains of the influenza virus with a worldwide distribution. Avian influenza A virus is a zoonotic pathogen with a natural reservoir entirely in birds. In poultry, it is unusual in that it can cause a range of disease symptoms from a subclinical infection to being highly virulent with 100% mortality. In the natural environment, it is generally spread by ingestion or inhalation. Virus-laden feces and respiratory secretions present on fomites are effective means of transmitting the virus. Airborne dissemination is also an important means of transmission. Strains are classified into low and high pathogenic types depending on the severity of diseases which they cause. The viruses are now widely recognized as important threats to agricultural biosecurity and public health, and as the potential source for pandemic human influenza viruses. The economic consequence of HPAI outbreaks is severe due to the cost of culling and bird replacement, loss of customer confidence, local and international trade losses, the cost of biosecurity, and the cost for veterinary and infrastructure improvement. In Ethiopia, there is a pandemic threat because ofits wetland areas that are visited by migratory birds and illegal trade. A definitive diagnosis of AI is established by direct detection of AI viral proteins or genes in specimens such as tissues, swabs, cell cultures, or embryonated eggs and isolation and identification of AI virus or by a molecular detection. There is no effective treatment for avian influenza. However, good husbandry, proper nutrition, and broad spectrum antibiotics may reduce losses from secondary infections. Therefore, timely development of an effective influenza vaccine must and should be made a public health priority, and biosecurity measures can be established to prevent interaction of wild birds and domestic poultry.

Keywords: Avian influenza; Economic Consequence; HPAI; Zoonotic pathogen.

1. Introduction

Avian influenza (AI) is an important viral disease caused by type A influenza viruses belonging to the taxonomic viral family *Orthomyxoviridae*. Avian influenza viruses (AIV) cause mild to severe infection in a wide range of domestic and wild birds as well as other mammals including humans. AIV are mostly detected in water fowl that inhabit wetland and aquatic environments, for example *Anseriformes* and *Charadiiformes.* These wild bird species are considered to represent the virus natural reservoirs (Olsen *et al*., 2006). The 16 hemagglutinine (H1-H16) and 9 neuraminidase (N1-N9) viral subtypes and all subtype combinations have been found in those species (Munster *et al*., 2007; Dugan *et al*., 2008).

Avian influenza virus especially the subtypes H5N1 and H9N2 can spread rapidly to domestic poultry and cause large-scale outbreaks resulting severe damage to the poultry industry. AIV of subtype H5 and H7 are divided into 2 groups based on their ability to cause disease and are designated as low pathogenic avian influenza (LPAI) and highly pathogenic avian influenza (HPAI) virus (Alexander, 2000). Some AIV subtypes (e.g. H5, H7 and H9) have also been reported to cross the species barrier and cause disease or subclinical infections in humans and other mammals (Alexander, 2007a; WHO, 2014b).

When an avian influenza virus (usually of subtype H5 or H7) is transmitted from reservoir hosts to highly susceptible poultry species such as chickens and turkeys, generally it initially induces only mild disease, termed Low Pathogenic Avian Influenza (LPAI). However, in cases where the particular poultry species supports several sequential cycles of infection, these strains may undergo a series of mutation events resulting in adaptation to their new hosts, and the virus may switch into a highly pathogenic avian influenza, (HPAI)(OIE.,2009). HPAI in poultry is characterized by sudden onset, severe illness of short duration, and mortality approaching 100 % in susceptible species. Due to heavy commercial losses to the poultry industry, HPAI attracts considerable attention. Because of their potential to give rise to HPAI viruses, LPAI viruses of subtypes H5 and H7 are also notifiable disease agents at international level(OIE.,2009).

The global publicity surrounding the impacts of the H5N1 highly pathogenic avian influenza virus has fostered wide public recognition of the potentially serious economic and public health impacts of avian influenza outbreaks(Alexander,2006) and it is identified as a source for pandemic human influenza viruses that could have severe economic and public health impacts on countries worldwide(WHO,2005).

A definitive diagnosis of AI is established by direct detection of AI viral proteins or genes in specimens such as tissues, swabs, cell cultures, or embryonating eggs or by isolation and identification of AI virus(Swayne, 2008) or by a molecular detection. Presently, no practical, specific treatment exists for AI virus infections in commercial poultry (Easterday *et al.*,1997) and antiviral resistance is an increasingly important issue because human avian influenza vaccines are not yet widely available, and treatment of human infections is currently limited to supportive therapy and treatment with antivirals(Hayden *et al.*, 2005;Hayden, 2006).

Avian influenza virus is hard to control because of the frequent contact with chickens, ducks in the live poultry markets and the birds in our daily life. In addition, the migration of the wild birds from one area to another every year in the world made the viruses transmit more in the world(Wang, *etal*.,2007). Important factors often overlooked in avian influenza risk analyses are that vaccination, and concurrent infection by low-pathogenic avian influenza viruses, do not prevent poultry from becoming infected with the H5N1 highly pathogenic influenza virus but can prevent poultry infected from exhibiting disease symptoms or mortality(Webster *etal.*,2006). In Jimma university no document review about highly pathogenic avian influenza

Therefore, the objectives of this seminar paper are:-

- To make an overview on the occurrence, mode of transmission, control and prevention of avian influenza and
- To high light the public health (zoonotic) and economic importance of avian influenza.

2. Literature Review on avian influenza

2.1 History

Descriptions of epidemics and pandemics of respiratory disease with characteristics suggestive of influenza have been recorded for over four centuries. Animals may have played a crucial role in past influenza epidemics as well as in modern pandemics. Outbreaks of respiratory disease among horses were recorded concurrently with outbreaks in humans during the eighteenth and nineteenth centuries, and in recent years swine and birds are prominently involved in the generation of influenza pandemics(Global epidemiology, 2000).

Among the previous pandemic are highly pathogenic influenza A H1N1 (Spanish flu)virus that occur since 1918–1919 some controversy by historian about their origin some suggest that the virus from China and others suggest that it began circulating in March 1918 in mid western US military camps. Subsequently the pandemic expanded throughout the world and it is responsible for the mortality of 20-50 million people around globe. The next pandemic occur in February, 1957 in Chinese province of Guizhou (formerly known as Kweichow)by Asian influenza A H2N2 virus and then it expands to Singapore and Hong Kong (stauart-Harnis *et al.*, 1985). Thecausative agent was first isolated in Japan in May1957. This pandemic virus possessed completely different HA and NA antigens from the formerly circulating H1N1 viruses and rapidly spread worldwide by November 1957.Total influenza-associated excess mortality during this pandemic was estimated at 69,800 (Swayne *et al.*,2008).

Viruses causing the influenza A H3N2 pandemic were first isolated in Hong Kongin July 1968. These viruses had a different HA but shared the N2 NA with previously circulating H2N2 viruses. Widespread disease with increased excess mortality was observed in the United States during the winter of 1968–1969. Total influenza-associated excess mortality for this pandemic was estimated at 33,800 in the United States (Noble, 1982). Before the 1990s, HPAI caused high mortality in poultry, but infections were sporadic and contained. Human infections were first reported in 1997 in Hong Kong(WHO, 2012). Since 2003, more than 700 human cases of Asian HPAI H5N1 have been reported to the WHO, primarily from 15 countries in Asia, Africa, the Pacific, Europe, and the Middle East, though over 60 countries have been affected(Alexander and Brown, 2009;WHO, 2012).

2.2 Etiology

Influenza viruses belong to the family Orthomyxoviridae and genus *influenza* virus. They are classified into three main types (A, B, C). Influenza type A viruses infect multiple species. Influenza type B and C both infect humans, but type C is also known to infect swine. Several human influenza strains are type B while all avian strains are type A. They are considered the most virulent group, although not all strains cause clinical disease. Type A Influenza viruses are classified into subtypes based on two surface proteins, the hemagglutinin(HA) and neuraminidase (NA). At least 16 hemagglutinins (H1 to H16), and 9 neuraminidases (N1 to N9) havebeen found in viruses from birds, while two additional HA and NA types have been identified, to date, only inbats (Swayne, 2008).

The viralHA, and to a lesser extent the NA, are major targets for the immune response. There is ordinarily little or no cross-protection between different HA or NA types. Two important proteins present on the surface of the virus type A Hemagglutinin (HA), sticks the virus to cell receptors. Neuraminidase (NA), frees the virus to infect other cells. These proteins serve as the basis for the classification of influenza viruses(Bidjeh*et al.*, 2017).

Type A influenza virus is defined as highly pathogenic AI (HPAI) or Lowly pathogenic AI (LPAI) byits ability to cause severe disease in intravenously inoculated young chickens in the laboratory, or by its possession of certain genetic features associated with HPAI viruses. To date, the fully virulent HPAI viruses found in nature have always contained H5 or H7, although there are rare examples of other viruses that could technically be considered HPAI (OIE, 2014) (Gonzalez and Perez, 2012).The viruses are roughly spherical (120 nm)with glycoprotein spikes on the surface and genome consisting of also eight RNA fragments that encode 10 proteins. The Haemagglutinin(HA), Neuraminidase (NA) and Matrix (M2) proteins are embedded in the envelope lipid bilayer derived from the host cell (Noda *etal.*,2001).The M1 protein underlying the envelope is the major determinant of virion morphology(Takedu *et al.*, 2003). The Nucleoprotein (NP) associates with each RNA segment to form the Ribonucleoprotein (RNP) complex, which also contains small amounts of the three polymerase subunits. The non structura lproteins NS1 and NS2 are found only in infected cells (Bidjeh *et al.*, 2017).

2.2.1 Antigenic Drift and Shift

Evolution of Influenza A viruses are known for their rapid evolution in aberrant hosts as well as humans although the genetic evolution are uncommon in the natural reservoir hosts (Webster and Laver, 1975; Oxford *et al.,* 2003). AIV once introduced into the land based domestic poultry or mammalian species can evolve rapidly (Ludwig *et al.,*1995). Genomic diversity is acquired through two fundamental mechanisms an intrinsically high rate of mutations and the ability of the virus to reassort their gene segments. Changes in viral genomic sequence mainly by mutations or amino acid substitutions over time, is referred to as antigenic drift. In contrast, reassortment can yield major genetic changes, referred to as antigenic shift (Lewis, 2006). The segmentation of the influenza A genomes facilitates reassortment among strains when two or more strains infect the same cell (Webster *et al.,*2006). The changes in the amino acid sequence over time are more likely in the HA and NA genes (Nobusawa *et al.,* 1991). Geneticdrift of the influenza HA protein in poultry occurs at rates similar to those observed in human H3influenza viruses that exhibited approximately 7.9 nucleotide and 3.4 amino acid substitutions per year in the HA1 gene (Bean *et al*., 1992; Suarez, 2000). The mutation rate of the HA1 of H5 and H7 AI viruses from live bird markets in the U.S. showed 7.8 and 4.9 substitutions per 1000 nucleotide sites per year, respectively (Suarez and Senne, 2000; Spackman *et al.,* 2003).

Table 1: Episode of antigenic shift in the last century.

Year	Influenza A	Comment
1918	H1N1	Spanishflu
1957	H2N2	Asian flu
1968	H3N2	Hong-kongflu
1977	H1N1	Beijing flu

Source: (Bidjeh *et al.,* 2017)

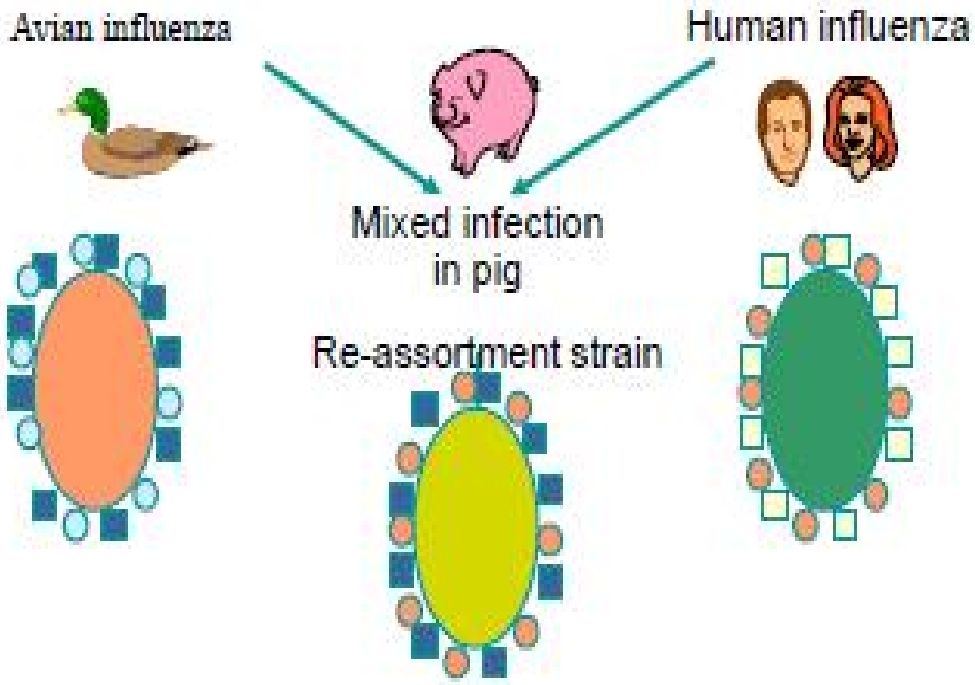


Figure 1: Genetic re-assortment influenza A virus antigenic shift
Source: (Bidjeh *et al.,*2017)

2.3 Epidemiology

2.3.1Host Range

All domestic and wild avian species especially migratory birds of the family Anatidae and water birds are sensitive to avian influenza. The most sensitive domestic species are adults: Chickens, turkeys, faintly pheasants, peacocks, quails or guinea fowl. Domestic ducks appear to be resistant to AI viruses or less susceptible. Some of the viruses isolated from birds can infect horses, humans, rats, mice, mink, ferrets, pigs, cats, tigers and dogs. In aquatic birds, domestic ducks or wild ducks, infection may be with or without clinical signs (Swayne,2008).

Turkeys and Chickens are the most frequently involved in disease outbreaks. A particular strain may produce severe disease in turkeys, but not in chickens or any other avian species. Many species of wild birds, particularly waterfowl and sea birds, are also susceptible, but infections in these birds are generally subclinical. AI Viruses were isolated from domestic and wild avian species such as guinea fowl, domestic geese, quail, pheasant, parrots, gulls, shorebirds, seabirds, etc. Pigs, ferrets, cats, mink, monkeys and humans can be affected also by AI viruses (WHO, 2015).

In Italy from 1999 to 2000 in intensively reared chickens and turkeys the migratory waterfowl particularly ducks have yielded more viruses than any other group, while domestic turkeys and chickens have experienced the most substantial diseases problems due to influenza (Capua and Alexander, 2000). Highly pathogenic AI isolates have been obtained primarily from chickens and turkeys. It is reasonable to assume that all avian species are susceptible to infection (Crawford, 2005).

2.3.2 Geographic Distribution

Avian influenza has been known as a disease of birds since the late 1800`s and the virus has continued evolving and adapting throughout the world to the present day. LPAI viruses are cosmopolitan in wild birds. Different viral lineages circulate in North America and Eurasia, although assortment occurs between these lineages at some locations. LPAI viruses are usually absent from commercial poultry in developed countries, but they may be present in other domesticated birds. The H9N2 viruses circulating in poultry are currently limited to Eurasia. The zoonotic H7N9 LPAI viruses causing outbreaks in mainland China have not been reported from other regions, except as imported cases in traveler (OIE, 2014). In 1997, a HPAI emerged in Southeast Asia and spread throughout numerous Asian, Middle, Eastern, African and European countries (OIE, 2017).

According to OIE (2007), since 2003 HPAI affected 62 countries in the world out of them 12 countries in Africa. In 2015, countries likeLibya, Nigeria, Cameroon, Niger and Burkina Faso have reported to OIE cases of HPAI A(H5N1) and in 2017 Cameroon, Uganda and Egypt have reported to OIE cases of HPAI A(H5N8). Tunisia has reported case of HPAI A(H5) South Africa reported case of LPAI A(H7N2) (OIE, 2017).From the sub-Saharan countries, Ethiopia and Kenya have not yet experienced any outbreaks, but the virus has been circulating in neighboring countries, e.g. Sudan and it could enter these countries through various pathways, including illegal bird trade. However, Ghana and Nigeria have both experienced several outbreaks and are on the same bird flyways(Ito *etal*.,2000).

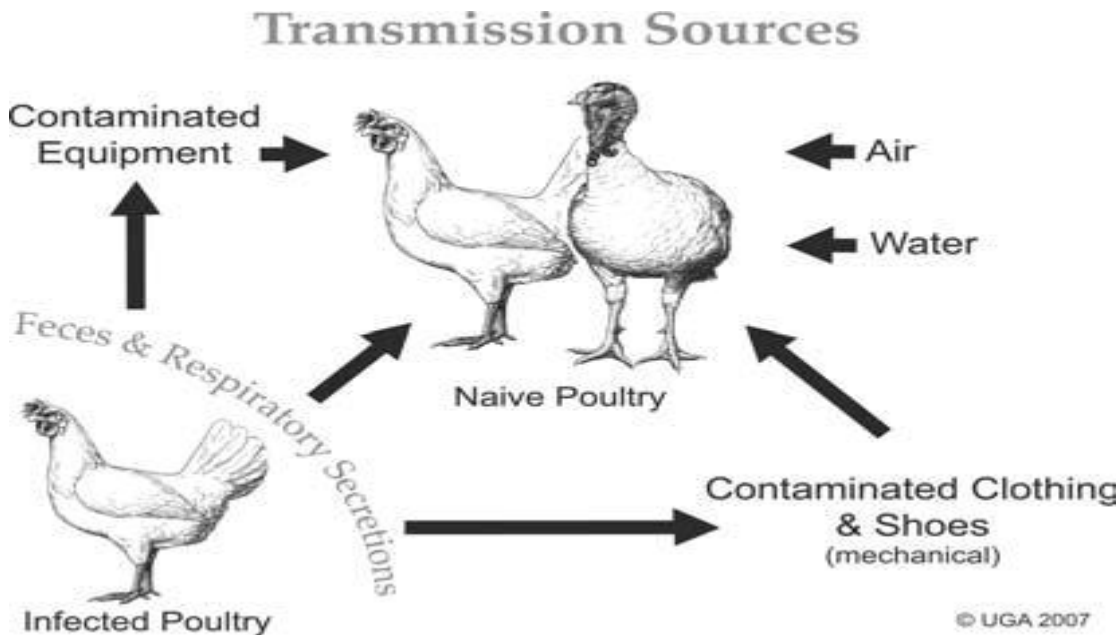
2.3.3 Transmission

Aquatic wild birds are the natural reservoir of influenza A viruses and are thought to be the principal source of viral spread to other species (Crawfordetal *et al.,* 2005). The virus replication is primarily limited to the epithelial cells of the intestinal tract (Webster *et al*., 2007;Hinshaw *et al.*, 1985), and infected birds remain asymptomatic but shed the virus into the environment via feces, and less frequently saliva and nasal secretions (Philipa *et al*., 2005). Sources of infection may also include other animals like swine (Brown *et al*., 2007). In birds, avian influenza viruses are shed in the feces and respiratory secretions(Swayne, 2008). Fecal-oral transmission is the predominant means of spread in aquatic wild bird reservoirs. All susceptible

species can eventually act as reservoirs and thus maintain nonpathogenic strains which following mutation or recombination (mixed infection), can become pathogenic to domestic poultry. The main species are domestic palmipeds. Wild avifauna is not a reservoir of the HPAI virus(Crawford *etal.*, 2005). Wild Pets and exotic birds, dogs, cats, mice consuming the corpses of birds; Ticks, flies, earthworms can be contaminated by AI viruses.

Contamination of poultry is mainly through direct contact with respiratory secretions and feces of sick birds (air suction loaded viral particles, excretion or droppings of dust). The contaminated feces can remain infectious for several months' indirect contact by exposure to contaminated materials food, water, equipment, clothing, etc. The consumption of food contaminated by excretions (droppings, streams) is possible, but not proven. Spread from one place to another is through infected animals, working materials, humans (staff and visitors), domestic and wild animals that have been in contact with contaminated poultry (Munster *et al.*, 2007). Confined spaces favor the transmission of the virus, and close contacts, prolonged and repeated with infected live birds' farms, markets, and surfaces and or objects contaminated by manure, dried manure dust from infected animals (Bidjeh *et al.*, 2017).

Ecological data indicate that various migratory waterfowl, sea birds, and shore birds are the reservoir for all avian influenza viruses. In addition, epidemiological and molecular genetic evidence supports the hypothesis that these aquatic birds are generally responsible for introducing the LPAI viruses into poultry. Once introduced into poultry, the viruses adapt to poultry and are spread from flock to flock or village to village by human endeavor such as the movement of infected birds. Most of outbreaks start with direct or indirect contact of domestic poultry with water birds. Direct contact between infected and susceptible birds, indirect contact including aerosol droplets or exposure to virus contaminated fomites, equipment, shoes clothing, egg flats, feed trucks, and service crews. No evidence of vertical transmission, however, virus can be present within or on the surface of eggs when the hen is infected (FAO, 2010).



Source:(Nuradji *et al.*,2015)

Figure 2: Five means or modes by which avian influenza viruses are introduced into Poultry.

2.3.4 Risk Factor

The emergence of Avian Influenza depends upon Production systems (mixed farming) globalization and international trade of poultry and poultry products (legal and illegal), sociocultural and economic practices, including marketing in bird markets living, environment. The highly pathogenic virus can survive for a long time in the environment, especially at low temperatures, in bird droppings it can survive for at least 35 days at low temperature (4 °C). Wild birds may carry avian influenza viruses in their respiratory or intestinal systems usually without clinical signs of the disease (Gohrbandt *et al.,* 2011).

It has been discovered that the development of large-scale commercial farming will enhance the potential for epidemic transmission and evolution of influenza viruses. High stocking densities in large commercial farms will facilitate rapid and efficient transmission of highly virulent viruses such as H5N1 that might otherwise kill their hosts before being transmitted (Glezen, 1982; Glezen, 1996). Free-ranged flocks have been identified to be more likely exposed to wild birds carrying the LPAI strains rather than commercial poultry flocks, thus providing these free-range birds with constant challenge and immunity maintenance (Frost, 1919). It has been established that there are other media through which these viruses can be maintained, sustained, and perpetuated in nature, especially in Africa (Beare, 1991, Cox J. and Kawako Y.1998). Perpetuation of HPAI H5N1 are either reflected as a result of antigenic drift (which tends to cause only small changes in the biological behavior of the virus) or antigenic shift (the exchange of hemagglutinin antigens or neuraminidase antigens) between different influenza A virus subtypes co infecting a particular host thereby resulting in genetic reassortment; these subtypes have conveniently adapted to both humans and swine, and currently circulate in nature (Walker, 1919; stuart*et al*., 1985). Human populations at risk of contamination by the avian influenza virus are those in regular contact with the sick poultry include breeders and their families, sellers of live poultry, sinners, exposed to droppings in stained water environment, veterinarians and livestock technicians, personnel collecting live poultry before slaughter and carcasses (renderers), cleaning and disinfection teams Poultry farms, technical staff of diagnostic and research laboratories (Bidjeh *et al.,* 2017).

2.4 Pathogenesis

Avian influenza viruses are classified as either low pathogenic avian influenza viruses or highly pathogenic avian influenza viruses and defined as HPAI or LPAI by its ability to cause severe disease in intravenously inoculated young chickens in the laboratory, or by its possession of certain genetic features that have been associated with high virulence in HPAI viruses (i.e., the sequence at the HA cleavage site) (OIE,2005;Gohrbandt *etal*.,2011). HPAI viruses usually cause severe disease in chicken and turkey flocks, while LPAI infections are generally much milder in all avian species (Swayne and Saurez, 2011).

Pathogenicity as a general viral property in influenza A viruses is a polygenic trait and depends largely on an optimal gene constellation affecting host and tissue tropism, replication efficacy and immune evasion mechanisms amongst others. In addition, host and species specific factors contribute to the outcome of infection, which, after interspecies transmission, is therefore unpredictable. LPAI viruses can be introduced by various pathways into poultry flocks. Following a variable and indecisive period of circulation (presumably by adaptation) in susceptible poultry populations, these viruses can saltatorily mutate into the highly pathogenic form(Vahlenkamp *et al.*,2010).

First, in poultry, the process of pathogenesis begins by inhalation or ingestion of infectious LP or HPAI virions. Because trypsin-like enzymes in respiratory and intestinal epithelial cells allow cleavage of the surface hemagglutinin, multiple replication cycles occur in respiratory and/or intestinal tracts with release of infectious virions. Second, with HPAI viruses, after initial replication in respiratory epithelium, the virions invade the submucosa, entering capillaries (Gohrbandt *et al.,* 2011). The virus replicates

within endothelial cells and spreads via the vascular or lymphatic systems to infect and replicate in a variety of cell types in visceral organs, brain, and skin. Alternatively, the virus may become systemic before having extensive replication in vascular endothelial cells. The virus is present in the plasma, red and white blood cell fractions. Macrophages appear to play a role in systemic virus spread. The presence of a hemagglutinin proteolytic cleavage site that can be cut by ubiquitous furin like cellular enzymes is responsible for this pantropic replication. Clinical signs and death are due to multiple organ failure(Swayne,2008).

Third, for the LPAI viruses, replication usually is limited to the respiratory or intestinal tracts. Illness or death is most often from respiratory damage, especially if accompanied by secondary bacterial infections. Sporadically in some species, the LPAI viruses spread systemically, replicating and causing damage in kidney tubules, pancreatic acinar epithelium, oviduct and other organs with epithelial cells having trypsin-like enzymes. Pathogenesis of the infection process is less well understood in non-gallinaceous birds (WHO,2015).

2.5 Clinical Manifestation and Pathological Lesion

The incubation period for an individual bird is usually 1-7 days, and up to 14 days in a flock depending upon the isolate, the dose of virus, the route of exposure, the species exposed and the age of bird. However, OIE recognizes a 21- day incubation period, which takes into account the transmission dynamics of the virus within a population. For LPAI and HPAI, the infectious period of time that virus is shed from infected birds- may be a more appropriate concept for control of the disease (Capua and Mutnell, 2001).

The symptoms following infection with low pathogenic AIV may be as discrete as ruffled feathers, transient reductions in egg production or weight loss combined with a slight respiratory disease (Nakatani *et al.,* 2005). In its highly pathogenic form, the illness in chickens and turkeys is characterized by a sudden onset of severe symptoms and a mortality that can approach 100% within 48 hours(Rohm *etal.*,1995). Often, only a section ofa stable is affected. Many birds die without premonitory signs so that sometimes poisoning is suspected in the beginning(Kwon *etal.*,2005).Oedema, visible at feather-free parts of the head, cyanosis ofcomb, wattles and legs, greenish diarrhoea and laboured breathing may also be inconsistently present. In layers, soft -shelled eggs are seeninitially, but any laying activities cease rapidly with progression of the disease (Capula *et al.,* 2001). Nervous symptoms including tremor, unusual postures (torticollis), and problems with co-ordination (ataxia) also dominate the picture in less vulnerable species such as ducks, geese, and ratites(Gordan, 1977). Microbiological features found in infected poultry are infarction of tissue and inflammation of inner organs which are generally found in brain, heart, lungs, pancreas, primary and secondary lymphoidorgans (Gohrbandt *et al.*, 2011).

2.6 Diagnosis

2.6.1 Clinical Diagnosis

Clinically the disease is in distinguishable because lesions and symptoms are to variable and confuse with other diseases and AI virus cannot be diagnosed by clinical signs and symptoms alone. Therefore, confirmation should be undertaken by specialized laboratories, serology and virology are necessary (Chen, 2010).

2.6.2 Laboratory Diagnosis

Avian influenza viruses can be detected in oropharyngeal, tracheal and/or cloacal swabs from live birds, with differing recovery rates from each site depending on the virus, speciesof bird and other factors. Very small swabs can be valuable in small birds, but feces can be substituted if cloacal samples are not practical (Lamb and Krug,2001). Immature feathers may also be a useful sample (Nuradji *et al*., 2015). Samples from internal organs are also tested in dead birds suspected of having HPAI(OIE,2005).

Virus isolation: virus isolation by inoculating the sample into hatching chicken eggs for detecting a property of red blood cells precipitation can be performed in all species, and can be useful for virus characterization (Spackman *et al.*,2013) This technique is the "gold standard" but laborious and time insensitive, used primarily for diagnosis of first clinical case and to obtain virus isolated for further laboratory analysis(Swayne *et al*., 2003). Laboratory diagnosis of AI viruses can also be performed by serological test such as hemagglutinin inhibition test, Agar Gel Immune Diffusion (AGID), antigen-detection ELISAs orother immunoassays, or by a molecular test such as RT-PCR. The viruses can be identified as influenza A viruses with hemagglutination inhibition test, in which the Hemagglutinin (HA) protein of avian influenza has the property to agglutinate erythrocytes from a number of species including horses. A specific antibody to the antigenic sites on the avian influenza HA molecule prevents or inhibits the hemagglutination reaction. Therefore, hemagglutination inhibition test can be used to type the patient antibodies to avian influenza virus when standard avian influenza antigen is available as reference material (Spckman *et al.*,2013).

Use of the AGID test to demonstrate nucleocapsid or matrix antigens is also a satisfactory way to indicate the presence of influenza A virus in amnioallantoic and chorioallantoic fluid, but various experimental and commercial rapid, solid-phase antigen-capture ELISAs (AC-ELISAs) are an effective alternative(Chua *etal.*,2007). They use a monoclonal antibody against the nucleoprotein they should be able to detect any influenza A virus. The main advantage of these tests is that they can demonstrate the presence of influenza A within 15 minutes. The disadvantages are that they may lack sensitivity, they may not have been validated for different species of birds, subtype identification is not achieved and the kits are expensive(Saurez*etal*.,2007).

Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)is another powerful technique for the identification of influenza virus genomes and allow for sensitive and specific detection of viralnucleic acid(Fenner*etal*.,1987).

RT-PCR techniques on clinical specimens can, with the correctly defined primers, result in rapid detection and subtype identification (at least of H5 and H7), including a DNA product thatcan be used for nucleotide sequencing (Das *et al*.,2006). However, the preferred molecular detection tests for influenza A virus is the real-time RTPCR, a modification to the RT-PCR that reduces the time for both identification of virus subtype and sequencing(Espanol,2007). A disadvantage of RT PCR methods is its proneness for contamination and the consequent risk of false positive results(Fenner*etal.*,1987).

2.6.3 Differential Diagnosis

Diseases must be considered in the differential diagnosis of HPAI because of their ability to cause a sudden onset of disease accompanied by high mortality or haemostasis in wattles and combs are velogenic Newcastle disease, infectious laryngotracheitis (chickens), duck plague, acute poisonings, acute fowl cholera (Pasteurellosis) and other septicaemic diseases, bacterial cellulitis of the comb and wattles (Capua and Mutinell,2001). For LPAI viruses, other causes of respiratory disease and drops in egg production must be investigated such as lentogenic Newcastle disease virus, avian pneumovirus and other paramyxoviruses, infectious laryngotracheitis, infectiousbronchitis, chlamydia, mycoplasma, and various bacteria(Easterday *et al.*,1997).

2.7 Impact of the Disease

2.7.1 Public Health Impact

Outbreaks of HPAI viruses in wild and domestic birds are rare, but once infection occurs it can be serious from veterinary, medical, and public health perspectives(Liu *etal.*,2014). The two most commonly reported avian influenza viruses from human clinical cases have been the Asian lineage H5N1 HPAI viruses, and recently, H7N9 LPAI viruses in China(Meng*etal.*,2015;Chen and Zhang,2015). There are currently no reported human infections caused by Asian lineage H5N8 viruses, although four infections withH5N6

viruses have been detected in China since 2014 (Pan *et al*.,2016; Zhang *et al*.,2014).

Illnesses caused by other subtypes have also been reported sporadically, with documented clinical cases caused by H9N2(Eurasian lineage), H6N1 and multiple H7 and H10 avian influenza viruses (Abdelwhab *et al*., 2014; Cong *et al*., 2007). Whether these infections are truly less common than subtypes such as H5N1 is unclear: viruses that tend to cause milder illnesses (e.g., H9N2 viruses) are less likely to be identified than those causing severe disease. Serological surveys in some highly exposed populations suggest the possibility of low level exposure to HA types found in birds, including H4, H5, H6, H7, H9, H10, H11 andH12(Smith *et al*., 2009). Adaptation to humans is possible, though rare, and some previous human pandemics were caused by partially or wholly avian viruses (Vana *et al*., 2009; Swayn,2000).

In general, influenza viruses exhibit host species adaptation with transmission occurring most frequently and with ease between individuals of the same species; occasionally interspecies transmission to closely related species occurs (Kilbourne, 2006). On rare occasions, AI viruses have exhibited interspecies transmissibility to humans(Easterday *et al*., 1997). Although rare, AI viruses or their genes have been transferred to humans: transfer of complete AI viruses with individual sporadic infections, and appearance of individual AI viral gene segments in pandemic human influenza viruses i.e., reassortment of gene segments(Swayne *et al*., 1997).

2.7.1.1 Human pandemic

Over the past 150 years at least four pandemic sof avian influenza occurred at irregular intervals, including three inthe 20th century. These have caused high attack rates in all susceptible age groups with high morbidity and mortality. Earliest pandemic occurred in 1918-19 and is widely known as "Spanish flu.” It was caused by (H1N1) and lead to the highest number of known flu deaths; more than 500,000 people died in the United States alone and 20 to 50 million may have died worldwide. Second was "Asian flu" which occurred in 1957-58. Its causative agent was (H2N2). It resulted in about 70,000 deaths in the United States. Third pandemic commonly called as "Hong Kong flu" was caused by (H3N2) in 1968-69. There were approximately 34,000 deaths in the United States. This virus was first detected in Hong Kong in early 1968(Dunham *et al*., 2009).

Since the outbreaks of H5N1 HPAI in poultry and humans in Hong Kong in 1997 and H7N7HPAI in the Netherlands in 2003,there have been concerns that AI viruses could persist in some poultry populations and emerge as a pandemic virus for humans through multiple mutations or reassortment (Llu *et al*., 2014). The 2009 pandemicH1N1 was the result of a reintroduction of H1N1, which over time had mutated and reassorted influenza A genes from various avian, human, and swine influenza viruses(Llu *et al*., 2009; Sinha *et al*., 2009;Zhu *et al*., 2016). Human infection with avian influenza A (H7N9) was also first reported in China in March2013, and since then hundreds of human cases have been confirmed. Today, AI viruses of concern as potential pandemic strains are someH5, H7, and H9 subtypes that have crossed the human species barrier multiple times to produce sporadic infections(Durrheim andFerson,2006).

The current spread of avian influenza H5N1 in domestic poultry flocks and wild birds across the world, as well as the demonstrated ability of this virus to cross the species barrier and infect humans, hasl ed to a high level of concern that a pandemic may develop. For a pandemic to arise, three pre-requisites have been identified such as anew virus subtype to which the population has little or no immunity must emerge, the new virus must be able to replicate in humans and cause serious illness, and the new virus must be efficiently transmitted from one human to another(WHO,2005).

2.7.1.2 Transmission to human

The close proximity of birds to humans increases the risk of transmission to humans via aerosol or large air borne droplets, fecal contamination with dispersion via fomites, and direct contact with infected birds. Direct contact with

Infected poultry, or surfaces and objects contaminated by their faeces, is presently considered the main route of human infections. As infected birds shed large quantities of virus in their faces, opportunities for exposure to infected droppings or to environments contaminated by the virus are abundant under such conditions. Also, sick birds maybe slaughtered for consumption in the developing world, leading to increased risk of exposure(Das A. *et al.,* 2006). This is because of many households in developing countries depends on poultry for income and food, many families sell or slaughter them or even consume them when signs of illness appear in a flock(WHO,2007).

In general, people at greatest risk for AI virus exposure and infection include farm workers, live bird market workers, butchers and home processors of poultry, hunters that slaughter, eviscerater, and defeather infected wild birds, and those preparing to cookcontaminated meat getting viruses on their hands and transferring them by touching mucus membranes(Gao*et al*., 2009). However, properly cooked and properly handled poultry and poultry products can safely be consumed (WHO,2007).

H5N1 HPAI virus has expanded its host range, as it has infected dogs and other mammals through the consumption of uncooked infected poultry, wild birds, or their products(Lluetal, 2014; Gao *et al*., 2009). This has raised concern that dogs and other pets also have the potential to be intermediate carriers that can transfer the H5N1 influenza virus to humans. Although rare, evidence of direct human to human transmission of H5N1 associated with a poultry outbreak also occurred in Southeast Asia. Sustained human to human transmissibility of H5N1 HPAI would require genetic adaption of AIPB2 internal protein (WHO, 2014).

2.7.1.3 Clinical sign in human

Most zoonotic infections caused by Asian lineage H5N1 HPAI viruses seem to become apparent within approximately 5 days, although the incubation period for some cases may be as long as 8 and possibly 17 days(Uyeki,2009;Gao *et al*., 2013). Estimates of the mean incubation period for the zoonotic H7N9 viruses have varied from 3 days (in two analyses, which considered large numbers ofcases) to 5-6 days, with a range of 1-13 days(Virlogeux *et al*., 2015;Chan,2002).

Clinical symptoms of avian influenza infections in humans range from asymptomatic infection or mild conjunctivitis to fatal systemic disease and multiorgan failure including severe or fatal respiratory, gastrointestinal, or neurological syndromes (Fenner *et al*., 1987; Abdel w. *etal*.,2008). Initial symptoms include headache, fever, fatigue, myalgia, odynophagia, cough andrhinorrhea, abdominal pain, vomiting, diarrhea, hepatic dysfunction, Reye's syndrome, pancytopenia, renal failure, pulmonaryhemorrhage, acute respiratory distress syndrome and septic shock have been reported with varying frequency (Tran *etal*.,2004; Lasley,1986).

For instance, some cases of H5N1 infection are characterized by rapid clinical progression, with signs of involvement of the lower respiratory tract, to hospital admission, after which the disease rapidly evolved to the stage in which mechanical ventilation becomes necessary. Patients with severe H5N1 infection develop primary viral pneumonia, early-onset lymphopenia and renal failure within one to two weeks aft er the onset of symptoms. Elevated transaminase levels have also been detected prior to respiratory deterioration in the majority of patients presenting the severe forms (Tran *etal*.,2004).

2.7.2 Economic Impact

Economic losses from AI have varied depending on the strain of virus, species of bird infected, number of farms involved, control methods used, and the speed of implementation of control or eradication strategies. Most outbreaks and economic losses have occurred from epidemics of HP or LPAI in commercially raised poultry, predominately chickens and turkeys. Direct losses in HPAI outbreaks have included depopulation and disposal costs, high morbidity and mortality

losses, cleaning and disinfection, quarantine and surveillance costs, and indemnities paid for the birds. However, indirect costs such as uncompensated losses to the poultry industry including temporary or permanent loss in poultry exports, income lost by farmers and communities during the production down time, increased consumer costs from reduced supply of poultry products, and losses from decreases in consumer purchases can easily escalate losses by 5-10 folds(EC,2005).

The economic costs for eradication of HPAI have varied greatly, but eradication costs have been very high and appear to be proportional to the number of birds that died and were culled(EC,2005).. Furthermore, economic losses due to death and culling of domestic poultry, market closures and trade restrictions, have been considerable. The direct and indirect impact of an influenza pandemic would likewise been ormous, affecting the economy as a whole, and in particular health systems, health-care services, political machinery, trade, tourism, biodiversity and essential services such as public transport, education, police and general administration(Lee *et al*., 2005).

Four key factors that are identified as contributing to the potential social and economic impact of HPAI includes the zoonotic nature of the disease and the potential for large-scale human deaths, the severe impact of outbreaks on local, and especially vulnerable, populations due to considerable livelihood and production losses, the prolonged financial drain for control costs as the disease becomes endemic, the simultaneous outbreaks across countries and regions as the disease spread rapidly across the continents. If widespread outbreaks persisted without rapid and adequate control measures global production and trade could be severely disrupted. The impact of a single animal outbreak of HPAI on national GDP would depend on the speed with which the disease was controlled, the size and structure of the poultry sector and its relative contribution to GDP. Estimates of global HPAI losses since the start of the outbreaks at the end of 2003 run into billions of dollars(Oner *et al.*, 2006).

The 2003 and 2004 outbreaks in Asia took Veterinary Services by surprise. As a result the avian influenza virus was not easily controlled; spread widely often re-emerged and resulted in the death or destruction of millions of birds. Direct losses were highest in Vietnam (44 million birds, amounting to approximately 17.5% of the poultry population) and Thailand (29 million birds, 14.5% of the poultry population), with long lasting effects on their respective poultry industries due to lost market share (Oner *et al*., 2006).

In regions of the world where there have been HPAI outbreaks, changes in the consumption pattern have been evident, with temporary decreases in poultry consumption. For example, the domestic impact in Turkey in 2006, where 2.5 million birds were culled due to an outbreak of H5N1 HPAI, had a cost of $ 226 million. In the capital city, Ankara, there was a 54% decrease in sales of poultry products, with a 32% decrease in poultry meat prices, and prices of eggs and other poultry products also decreased(Yalcin, 2005;Dunning *et al*., 2014).

At least 62 countries reported outbreaks of H5N1 HPAI in either domesticated or wild birds between 1996 and 2010(OIE,2009). So HPAIvirus has caused devastating economic losses to poultry growers and rural households in Asia, Europe, and Africa (Swayne,2008; Marzoratti *et al.*, 2012). In developing countries, most poultry production occurs in small backyard flocks in rural and periurban areas, so outbreaks economically impacted these small farmers more than commercial industries. Between 1996and 2003, there were 1,645 H5N1 HPAI outbreaks worldwide that resulted in 43 million birds dead or destroyed, and between 2004 and2007 more than 250 million birds died or were destroyed (Oner *et al.*,2006).

2.8 Treatment, Prevention and Control

2.8.1 Treatment

There is no effective treatment for avian influenza in poultry. However, good husbandry, proper

nutrition, and broad spectrum ntibiotics may reduce losses from secondary infections. In human, treatment for avian influenza may vary, depending on the severity f the case. In addition to symptomatic treatment, it can include various drugs, including antibiotics to treat or prevent secondary bacterial pneumonia, and antivirals (Hayden & Hay, 1992). Two groups of antiviral drugs such as the adamantanes (amantadine and rimantadine), and neuraminidase inhibitors (zanamivir, oseltamivir, peramivir andlaninamivir) are effective against some influenza A viruses, but some of these drugs (peramivir and laninamivir) are not licensed in all countries (Bossart *et al*.,1993).

The first antiviral drugs described against influenza were the adamantanes, amantadine and rimantadine. These compounds areM2 ion channel blockers that inhibit influenza A replication at the uncoating step (Hayden and Palese, 2002). However, the efficacy of such antiviral drugs is limited by the rapid emergence and transmission of drug-resistance variants(Von *etal*.,1993). Neuraminidase (NA)inhibitors, such as zanamivir and oseltamivir, were synthesized after the crystal structures of influenza NA complexes with sialic acid and the sialic acid derivative 2-deoxy-2,3-dehydro-N-acetyl-neuraminic acid were determined(Colman *etal*.,1993). These inhibitors block the active site of the NA enzyme, inhibiting virus release from infected cells and spread within the respiratory tract(OIE,2014). In general, these drugs can potentially offer protection against any influenza virus that might emerge in humans, as the NA enzymatic active site seems to be highly conserved among all influenza viruses(USGS, 2005).

2.8.2 Prevention and Control

2.8.2.1 Disease reporting

A quick response is vital for containing avian influenza outbreaks, and in some cases, for minimizing the risk of zoonotic transmission. In addition to national notification requirements, HPAI viruses and LPAI viruses that contain H5 or H7must be reported to the OIE by member nations(Guan *et al.*, 2009). Veterinarians who encounter or suspect a reportable disease should follow their country-specific guidelines for informing the proper authorities (state or federal veterinary authorities in the U.S. for diseases in animals). Unusual mortality among wild birds should also be reported (e.g., tostate, tribal or federal natural resource agencies in the U.S (Beard, 1998).

The control of AI in poultry, from village to commercial sectors, requires farm-to-table risk management. Some of the basic needs include implementation of good agricultural practices such as training of workers in good management and biosecurity practices, in particular poultry cullers, establishing a biosecure environment to isolate poultry from potential AI virus carriers, supplying a source of potable water, providing a feed supply that is secure and free of contaminants, disinfection and decontamination of the premises and equipment prior to the introduction of a new flock or after culling of poultry flocks, establishing routine composting of litter and carcasses for all flocks, and safe disposal of carcasses from known infected farms(Espanol, 2015). During outbreaks, HPAI viruses are normally eradicated by depopulation of infected flocks, combined with other measures suchas movement controls, quarantines and perhaps vaccination(HPAI, 2007).

Protective measures for zoonotic avian influenza viruses include controlling the source of the virus (e.g., eradicating HPAI viruses, closing infected poultry markets); avoiding contact with sick animals, animals known to be infected, and their environments; employing good sanitation and hygiene (e.g., hand washing); and using Personal Protective Equipment (PPE) where appropriate(Uyeki, 2009;Shermilan*et al.*, 2012). While the recommended PPE can vary with the situation and risk of illness, itmay include respiratory and eye protection such as respirators andgoggles, as well as protective clothing including gloves (Beard, 1998; Sherrilyn *et al*., 2012). The monitoring of travelers that arrive in a country, with quarantine approaches, the closure of agglomerating places, such as

publictrans portation and schools, could also be necessary actions(Normile,2005).

2.8.2.2 Vaccination

vaccination of poultry against avian influenza with inactivated vaccines and live recombinant vaccines (fowl pox H5)has the capacity to increase resistance to infection, to protect poultry from clinical disease and to reduce shedding of virus if vaccinated poultry become infected (Saad *et al*., 2007). So, well-managed vaccination of poultry can reduce the mortality and morbidity rate and the risk to humans by reducing the quantity of circulating virus (Van *et al.*, 2005). In addition to this, annual influenza vaccination is also the best public health intervention to prevent human influenza and available in two trivalent formulations inactivated and live-attenuated that contains an A (H1N1), an A (H3N2), and a B virus strain. A semiannual strain selection process is coordinated by the WHO to determine the composition of the northern and southern hemisphere vaccines (Wright and Webster, 2001).

In the field of influenza vaccination, neither commercially available nor experimentally tested vaccines have been shown so far to fulfill all of the requirements(One*etal.*,2006). The first aim, which is the protection from clinical disease induced by HPAIV, is achieved by most vaccines. The effectiveness of reduction of virus excretion is important for the main goal of control measures, that is, the eradication of virulent field virus(Alemu *et al.*,2008). Therefore, the best strategy to combat a pandemic flu is a rapid and effective vaccine production(Bush, 2006).

2.9 Status of the Disease in Ethiopia

Ethiopia has a new and imminent threat. Bird flu originating from Asia that is sweeping across Europe and into the Middle East is expected to arrive in Africa in December with the arrival of millions of migratory birds. The World Health Organization (WHO) warns that countries along the Rift Valley in eastern Africa - Kenya, Tanzania and Ethiopia, are at greatest risk and more vulnerable due to their lack of preparedness. Ethiopia along with other African countries is now bracing themselves for the worst. Like Asia, the risk to Africa is high. Almost every person owns and lives in close proximity with their poultry. This way of life increases the risk to the pandemic. With the majority of Ethiopia's population living in the same house as their poultry there is a much stronger possibility of the bird's dropping mixing with food items. The dead bodies and droppings of infected birds and poultry are identified as the major sources of infection of this influenza pandemic(UN FAO/OIE, 2005).

Ethiopia also lacks the infrastructure to police occurrences of the virus and manage disease outbreaks. In addition, Ethiopia has one of the poorest systems of health service delivery in Sub Saharan Africa. The potential health service coverage is 64 percent; however, most of the health institutions suffer from a serious shortage of health personnel, high turnover of staff and inadequate diagnostic facilities. There is no adequate early warning system in place and communication is highly unreliable (UN FAO/OIE, 2005)

While Ethiopia has not yet experienced an outbreak of Highly Pathogenic Avian Influenza (HPAI), there was an avian flu scare in 2006. This scare caused a significant demand shock that led to a sharp decline in poultry prices(Berhane and Tefera,2005). In the same year, a three-year preparedness plan for avian flu, worth US $ 124 million, was approved by the Ethiopian government and international agencies. The avian flu shock was particularly severe in urban areas, where poultry demand decreased by 25-30 percent. As a result of the reduction in urban demand and the subsequent oversupply, poultry prices dropped 50-60 percent, though this plunge was short-lived(FAO, 2008).

According to global status of *Influenza* in 2010, 12 cases of swine *Influenza* in Ethiopia were reported (Gideon, 2016). In March 2016, a total of 13 patients complaining of *Influenza*-like Illness (ILI) or Severe Acute Respiratory Infections (SARI) were reported with throat swab samples from predesigned *Influenza* sentinel sites. Among them four were tested positive for *Influenza* a H1N1 2009 pandemic and three were positive for

seasonal *influenza* A (H3N2). Starting from October 2015, the positivity rate of Pandemic *Influenza* H1N1 is increasing. In Ethiopia, currently there are confirmed cases with no death associated with the condition. The virus has been detected on February 4, in different hospitals. However, sources in the Ministry of Health say the subtype of the *influenza* detected in Addis Ababa is less dangerous than others and Ethiopia has testing and treating capabilities. Test samples are sent to the Center for Disease Control (CDC) of United States for further investigation as a matter precaution(Abiyot, 2016).

Ethiopia is at high risk of the flu pandemic for many reasons. Many birds that possibly carry the virus migrate from affected areas of Europe and Asia to East Africa and reach lakes and wetland found in the rift valley of Ethiopia (Hayden and Palese,2002). That potentially increases the risk of spread into the chicken population. As almost every household in rural areas in Ethiopia practices backyard poultry and humans commonly live with their poultry in the same house or in an attachment where there is no barrier the potential for coming in contact with infected poultry droppings and corpses, which are major sources of infection, is very high. Besides, the uncontrolled animal movements exercised under the prevailing management system arethe potential danger of risk of AI in Ethiopia (Markwell and Shortridge, 1982).

Legal and illegal trade routes: legal trade of days old chicks is carried out by large commercial farms that import day old chicks from Egypt, Germany, Holland, Kenya, Saudi Arabia and the United Kingdom. Illegal cross-border trade results in movement of live poultry from Djibouti and Sudan into Ethiopia. Demand for poultry via this route is high (Markwell and Shortridge, 1982). For this reason, the risk of illegal poultry traders introducing HPAI from an infected zone into Ethiopia should be considered. Generally, because of the importance of the poultry sector (56 million of poultry), the low level of biosecurity and the relatively high number of migratory water birds wintering in the Rift Valley Lakes, Ethiopia is considered at risk of introduction and spreading for highly pathogenic avian influenza (HPAI)(Henning *et al*., 2013).

3. Conclusion and Recommendation

Avian influenza is important veterinary and human health disease around the world. From 2003 to 2009, 62 countries have experienced of HPAI out of them 12 in Africa. There is evidence that H5 viruses of LPAI may mutate and become HPAI. The avian flu H5N1 remains a serious threat. The virus, which is originally only contaminating the birds mutates very quickly. Since 1997 known and the first human casein Hong-Kong that he can cross the barrier of species. If the disease is not transmitted from man to man, it is fatal in 60% of cases. Type A and B viruses are responsible for annual influenza epidemics, but only type A viruses are responsible for influenza pandemics. Type C virus appears to be linked to sporadic cases and most often gives a moderate expression of influenza. Viruses A and C infect several species, whereas virus B is almost specific to the human species. Wild birds may carry avian influenza viruses in their respiratory or intestinal systems without clinical signs of the disease.

The greatest concern typically has been for highly pathogenic AI because of its severe clinical disease and its effects on trade. However, LPAI also remains a concern because of its ability to cause disease and production losses, it is found more widely than HPAI, and for LPAI H5s and H7s the potential to mutate to HPAI remains ever present. As a result, its outbreaks have caused severe economic losses and agricultural trade restrictions. Ethiopia is at risk to the outbreak of AI because the country has a lot of wetland areas that are frequently visited by migratory birds from Asia and Europe and because of its illegal cross-border trade.AI viruses are difficult to control because of the wildlife reservoir, the adaptability of the virus, and the lack of good control tools(WHO, 2007).

Based on the above concluding remarks the following future directions are forwarded:

- Early detection of AI outbreaks and warning system should be designed and implemented.
- Timely treatment and annual vaccination should be available.
- There should be a public awareness about the health and economic importance of the disease through social and public media.
- There should be strong and close collaboration between medical and veterinary professionals to reduce the impact of the disease.
- Biosecurity measures should be established to prevent interaction of wild birds and domestic poultry, thereby reducing the risk of AI virus introduction into domestic poultry.
- Further research is also needed to develop the most effective vaccines and drugs.
- In Ethiopia, national policies should be set on the criteria of importation of poultry and poultry product.

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