

Global Threat of Highly Pathogenic Avian Influenza, A Review

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Abstract: Avian influenza (AI) is one of the greatest concerns for public health that has emerged from the animal reservoir in recent times. It is caused by infection with viruses of the family *Orthomyxoviridae* placed in the genus influenza virus A. Influenza viruses are dynamic and are changing by antigenic drift and shift which results in the periodic emergence of novel strains. A human influenza pandemic happens when a new subtype emerges that has not previously circulated in humans and therefore the human immune system has no defense against it. Avian influenza (H5N1) is a strain with pandemic potential, since it might ultimately adapt into a strain that is contagious among humans and can cause a pandemic. Influenza pandemics causes millions of deaths, social disruption and profound economic losses worldwide. Most influenza experts agree that the specific characteristics of a future pandemic virus cannot be predicted and nobody knows how pathogenic a new virus would be. This paper reviews highly pathogenic avian influenza pandemic threat to reduce economic loss and safeguard the public and aware countries to prepare and adopt a control and prevention methods.

Key words: Highly Pathogenic Avian Influenza • Wild Birds • Pandemic Threat

INTRODUCTION

Over the past few years, increasing numbers of infectious diseases in humans, wildlife and domestic animals have emerged. Most recently, with the emergence of highly pathogenic avian influenza (HPAI), subtype H5N1, global attention increased as people were informed that the virus could potentially represent the source of the next human influenza pandemic [1].

Avian influenza viruses are highly contagious, extremely variable viruses that are widespread in birds, particularly wild water fowl and shore birds [2]. Because of high mortality rates, high rates of contagion and the possibility of cross-species infection to mammals including humans, high pathogenic avian influenza is a major concern both to consumers and producers of poultry. Highly pathogenic avian influenza A H5N1 viruses remain a significant health threat to humans given the continued rare occurrence of human cases with a high case fatality rate [3]. The implications of the avian influenza for international poultry markets are large and include the loss of consumer confidence, loss of competitiveness, loss of market shares, supply shortages and disruptions of trade flow [4].

Avian influenza A virus strains are classified as low pathogenic (LPAI) or highly pathogenic (HPAI) on the basis of specific molecular genetics and pathogenesis criteria that require specific testing [5]. Most avian influenza A viruses are LPAI viruses that are usually associated with mild disease in poultry. In contrast, HPAI viruses can cause severe illness and high mortality in poultry [6]. Avian influenza viruses are therefore key contributors to the emergence of human influenza pandemics [7].

Avian influenza viruses (AIV) by virtue of their infective potential pose a significant threat to human health. AIV subtypes, namely H5, H7 and H9, currently endemic in poultry in some regions of the world, have been shown capable of infecting humans [8, 9]. Therefore, AI infections represent risk factors either for direct infection of humans from the avian host or for the consequences of genetic reassortment between a mammalian and an avian influenza virus, which could become the basis for a generation of a new pandemic virus for humans [10].

Because of its behavior of variation in antigenicity, highly pathogenic avian influenza viruses might evolve and increase its ability to jump the species barrier and may

become easily transmissible between humans and may cause series pandemic threat on the world. Therefore early emergency preparedness, adopting strategies for early surveillance and prevention of HPAI is important for efficient prevention and control of the disease. Thus, the objective of this paper is to present an overview of HPAI pandemic threat and forward recommendations that would help to reduce economic loss and safeguard the public.

Review on Highly Pathogenic Avian Influenza

History of Highly Pathogenic Avian Influenza: Fowl plague was first reported in Italy in 1878 by Edoardo Perroncito who described a severe, rapidly spreading disease that produced high mortality in chickens [5]. However, for over 100 years, HPAI proved to be a poultry disease of rare occurrence that, in most cases, affected an irrelevant number of birds. Generally speaking, it was either self-limiting or controlled efficiently through the application of measures aimed eradicating the infection from the affected area. At approximately the turn of the millennium, however, a sharp increase in the number of outbreaks of AI in poultry occurred [11]. In 1955, it was discovered that the virus causing Fowl Plague was an influenza virus [12].

Avian influenza outbreaks occur sporadically throughout the world. This disease has been very disruptive to the poultry industry; millions of chickens, geese and turkeys have been destroyed to prevent further spread of the disease [13]. It has been calculated that the impact of AI on the poultry industry has increased 100-fold, with 23 million birds affected in the 40-year period between 1959 and 1998 and over 200 million from 1999 to 2004 [14]. In addition, since 1997, the implications for human health of AI infections of poultry have been identified, especially as a result of the spread of Asian lineage HPAI H5N1 virus. This has dramatically attracted the attention of the scientific community and AI infections have assumed a completely different profile in both the veterinary and medical scientific communities [15].

The H5N1 virus subtype -highly pathogenic AI virus first infected humans in 1997 during a poultry outbreak in Hong Kong SAR, China. Since its widespread re-emergence in 2003 and 2004, this avian virus has spread from Asia to Europe and Africa and has become entrenched in poultry in some countries, resulting in millions of poultry infections, several hundred human cases and many human deaths [16].

Etiologic Agent and its Evolution: Avian influenza results from infection by viruses belonging to the species influenza A virus, genus *influenzavirus A* and family *Orthomyxoviridae*. Influenza A viruses are classified into subtypes based on two surface proteins, the hemagglutinin (HA) and neuraminidase (NA)[17].

At present, the *Orthomyxoviridae* Family consists of five genera: Influenza virus A, Influenza virus B, Influenza virus C (These genera were originally regarded as ‘influenza types A, B and C’ and this terminology is still in use), *Thogoto virus* and *Isa virus*. Only viruses of the Influenza virus A genus are known to infect birds [15].

Type A influenza viruses have eight gene segments that encode ten different proteins [18]. Avian influenza viruses are sensitive to heat and strongly resistant to low temperature. They can be inactivated either by heating for 30 minutes at 65° or boiling for two minutes. The virus can survive in feces for 1 week at low temperatures and also can survive in 4? water for 1 month [19]. The incubation period of avian influenza A (H5N1) may be longer than for other known human influenzas. In 1997, most cases occurred within two to four days after exposure [20]. The recent report indicated by Chotpitayasunondh *et al.* [21] reveals similar intervals but with ranges of up to eight days.

Avian influenza viruses are classified as either HPAI or LPAI viruses, based on the genetic features of the virus and the severity of disease in experimentally infected chickens. Although there are exceptions (Viruses that fit the genetic description of HPAI viruses but cause mild illness), HPAI viruses usually cause severe disease in poultry, while LPAI infections are generally much milder [22]. More recently, some HPAI viruses (H5N1) have been found to cause no illness in some poultry, such as ducks. LPAI viruses have the potential to evolve into HPAI viruses and this has been documented in some poultry outbreaks [6].

Influenza Type A Viruses and Subtypes: Influenza A viruses are classified into 17 HA and 9 NA subtypes, based on the two viral surface proteins—hemagglutinin (HA) and neuraminidase (NA) [23]. The HA/NA proteins play a key role during cellular infection. Different HA/NA combinations allow AIV subtype discrimination [24]. As illustration “H7N2 virus” designates an influenza A virus subtype that has an HA 7 protein and an NA 2 protein. Similarly an “H5N1” virus has an HA 5 protein and an NA 1 protein [25]. Subtypes of influenza A viruses are classified into strains. Strains of influenza viruses are

described by their type, host, place of first isolation, strain number, year of isolation and antigenic subtype. For example, one H5N1 virus isolated from chickens in Hong Kong in 1997 is A/chicken/Hong Kong/y385/97 (H5N1). For human strains, the host is typically omitted [22]. While many different subtypes of avian influenza A viruses have infected humans, the subtypes known to more commonly cause human disease include H5N1, H9N2?H7N7?H7N2?and H7N3[19].

CDC (6,) and Balish *et al.* [26] reported that all known subtypes of influenza A viruses can infect birds, except subtype H17N10 which has only been found in bats. They also reported that only the two influenza A virus subtypes (H1N1, & H3N2) are currently circulating within a population.

The reports of CDC [25] revealed, that there are three prominent subtypes of avian influenza A viruses (Influenza A H5, Influenza A H7 and Influenza A H9) which are known to infect both birds and people. To date, only subtypes containing H5 or H7 have been highly pathogenic; subtypes that contained other hemagglutinins have been found only in the LPAI form[22].

Evolution of HPAI: Influenza viruses are dynamic and are continuously evolving [6]. Studies on the ecology of influenza viruses have led to the hypothesis that all mammalian influenza viruses are derived from avian influenza reservoirs support for this theory comes from phylogenetic analyses of nucleic acid sequences of influenza A viruses from a variety of hosts, geographic regions and virus subtypes [27].

Rapid viral evolution by accumulation of mutations has resulted in at least 32 clades, as defined by the World Health Organization (WHO), World Animal Health Organization (OIE) and Food and Agriculture Organization (FAO) on H5N1 Evolution Working Group, descending from the ancestral A/goose/Guangdong/96-like H5 HA gene, imparting distinct antigenic characteristics to some members of specific clades or potentially novel phenotypic properties [26, 28-30]. Virus evolution by genetic reassortment results in the emergence of new genotypes which may possess additional novel characteristics [31, 32]. Several lines of evidence indicate that the currently circulating influenza A (H5N1) viruses have in fact evolved to more virulent forms since 1997, with a higher mortality among human cases, different antigenic properties, a different internal gene constellation and an expanded host range [33].

In most years, one or two of the three virus strains in the influenza vaccine are updated to keep up with the changes in the circulating influenza viruses. For this reason, people who want to be immunized against influenza need to be vaccinated every year [24].

The antigenicity of influenza viruses changes gradually by point mutation (Antigenic drift) or drastically by genetic reassortment (Antigenic shift) [2]. Antigenic shift is caused by either direct transmission of non-human influenza viruses to humans or the reassortment of genes from two different influenza viruses that have infected a single cell [7]. Reassortment between two different strains results in the periodic emergence of novel strains. Reassortment between subtypes can result in the emergence of a new subtype[27].

Antigenic drift produces new virus strains that may not be recognized by antibodies to earlier influenza strains. It is true that: a person infected with a particular influenza virus strain develops antibody against that strain. As newer virus strains appear, the antibodies against the older strains might not recognize the "newer" virus and infection with a new strain can occur [2]. This is one of the main reasons why people can become infected with influenza viruses more than one time and why global surveillance is critical in order to monitor the evolution of human influenza virus strains for selection of which strains should be included in the annual production of influenza vaccine [6].

Host Range: Avian influenza viruses have been shown to infect birds and mammals. both the ecological and phylogenetic studies suggested that wild waterfowl are the principal reservoirs for influenza A viruses, which occasionally are transmitted to other host animals and leading to influenza outbreaks in both animals and human populations [7, 25].

Transmission: Infected birds can shed influenza virus in their saliva, nasal secretions and feces [34]. Human influenza is transmitted by inhalation of infectious droplets and droplet nuclei, by direct contact and perhaps, by indirect (Fomite) contact, with self-inoculation onto the upper respiratory tract or conjunctival mucosa [35]. The relative efficiency of the different routes of transmission has not been defined. For human influenza A (H5N1) infections, evidence is consistent with bird-to-human, possibly environment-to-human and limited, non-sustained human-to-human transmission to date [36].

In 1997, it was believed that the exposure to live poultry within a week before the onset of illness was associated with disease in humans, whereas there was no significant risk related to eating or preparing poultry products or exposure to persons with influenza A (H5N1) disease [37]. Recently, most patients have had a history of direct contact with poultry, although not those who were involved in mass culling of poultry. Plucking and preparing of diseased birds; handling fighting cocks; playing with poultry, particularly asymptomatic infected ducks; and consumption of duck's blood or possibly undercooked poultry have all been implicated [36].

Continuing cases of bird-to-human transmission provide opportunities for the virus to adapt, either through reassortment or adaptive mutation, so that sustainable transmission among humans can occur. This increases the risk that an avian influenza may cause a human pandemic [38].

Human-to-human transmission of influenza A (H5N1) has been suggested in several household clusters [39] and in one case of apparent child-to-mother transmission [40] Intimate contact without the use of precautions was implicated and so far no case of human-to-human transmission by small-particle aerosols has been identified.

All human infections with animal influenza viruses are of concern, not only because of the cases of disease and deaths in individual people, but also because if these viruses become able to spread from human to human they could spark a pandemic. All of the past pandemic influenza viruses have contained gene components originating in animals [41].

Global Pandemic Threat: A pandemic is the biggest possible epidemic: a disease that spreads around the globe. A human influenza pandemic happens when a new subtype emerges that has not previously circulated in humans and therefore the human immune system has no defense against it nor is a vaccination ready at the point in time the pandemic breaks out [41]. H5N1 is a strain with pandemic potential, since it might ultimately adapt into a strain that is contagious among humans and can cause a pandemic. Three pandemics occurred in the previous century: "Spanish influenza" in 1918, "Asian influenza" in 1957 and "Hong Kong influenza" in 1968. The 1918 pandemic killed an estimated 40–50 million people worldwide. It was exceptional and is considered one of the deadliest disease events in human history [42].

The last two pandemics were caused by hybrid viruses, or reassortants, that harbored a combination of avian and human viral genes [7].

Previously, outbreaks of highly pathogenic avian influenza in poultry and wild birds were rare but Since December 2003, more than 50 countries in Africa, Asia, Europe and the Middle East have reported outbreaks of H5N1 avian influenza in poultry and/or wild birds. More than ten countries have also reported human H5N1 influenza cases. Before the outbreaks in Hong Kong (1997) and in the Netherlands (2003), human infection with avian influenza viruses were rarely reported and usually resulted in mild disease [41].

Africa recorded its first outbreak of Highly Pathogenic Avian Influenza (HPAI) when Nigeria officially reported an outbreak of the disease on February 8, 2006 [43]. It is widely believed that legal and illegal trade in infected poultry and poultry products might have precipitated the outbreaks, although the possibility remains that the outbreaks may have resulted from interaction between infected wild birds and domestic poultry. Since the Nigerian outbreaks of HPAI, Egypt, Niger, Cameroon, Burkina Faso, Sudan, Côte d'Ivoire and Djibouti have reported outbreaks of the disease in poultry and human cases have been confirmed in Egypt and Djibouti [44].

Human Cases of HPAI in Different Parts of the World:

From 2003 through 3 October 2016, 856 laboratory-confirmed human cases of avian influenza A (H5N1) virus infection have been officially reported to WHO from 16 countries table (1)[41].

Consequences of an Influenza Pandemic: During the 20th century, influenza pandemics caused millions of deaths, social disruption and profound economic losses worldwide [43]. HPAI (H5N1) has caused the largest number of detected cases of severe disease and death in humans. However, it is possible that those cases in the most severely ill people are more likely to be diagnosed and reported, while milder cases are less likely to be detected and reported [45]. Of the human cases associated with the ongoing HPAI (H5N1) outbreaks in poultry and wild birds in Asia and parts of Europe, the Near East and Africa, about 60% of those people reported infected with the virus have died [34].

Table 1: Cumulative number of confirmed human cases for avian influenza A (H5N1) reported to WHO, 2003-2016

Country	2003-2009*		2010-2014**		2015		2016		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	8	5
Bangladesh	1	0	6	1	1	0	0	0	8	1
Cambodia	0	7	47	30	0	0	0	0	56	37
Canada	0	0	1	1	0	0	0	0	1	1
China	38	25	9	5	6	1	0	0	53	31
Djibouti	1	0	0	0	0	0	0	0	1	0
Egypt	60	27	120	50	136	30	10	3	356	110
Indonesia	162	134	35	31	2	2	0	0	199	167
Iraq	3	2	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	1	0
Nigeria	1	1	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	12	4
Viet Nam	112	57	15	7	0	0	0	0	127	64
Total	468	282	233	125	145	42	10	3	856	452

* 2003-2009 total figures. Breakdowns by year available on subsequent tables.
 ** 2010-2014 total figures. Breakdowns by year available on subsequent tables.
 Total number of cases includes number of deaths
 WHO reports only laboratory cases
 All dates refer to onset of illness
 Source: WHO/GIP, data in HQ as of 3 October 2016



Economic Impact and Public Health Concern: In addition to their human toll, epidemics can have enormous social and economic consequences in a closely interconnected and interdependent world. Direct economic effects of illness resulting from influenza include increased health care expenditures by patients and funders (Governments, insurers) and increased work loads for health care workers. Indirect effects include a smaller labour supply due to deaths and increased absenteeism from work by sick workers and by workers wishing to reduce the risk of contracting illness in the workplace, [46]. Reduced domestic and international travel and reduced public gatherings at sporting and other events also has great economic impact [47]. Non-voluntary risk-modifying behavior may be imposed on workers with children by school closures intended to mitigate the spread of the virus [48]. A pandemic will reduce business investment due to increased uncertainty and risk, leading to excess capacity. Similarly, consumer confidence will decline due to uncertainty and fear, leading to reduced spending as people elect to be homebound to reduce the probability of infection. Reduced consumer confidence may particularly affect services involving face-to-face contact (Like tourism, transportation and retail spending [46].

Diagnosis, Outbreak Investigation and Surveillance: Surveillance programs are difficult, complicated and require a large, coordinated planning team(s). Successful programs require biologists/ornithologists veterinary services and chief veterinary officers trained in proper

monitoring and sample-collection techniques, year round monitoring at wildlife habitat where species of concern are known to aggregate [49]. In response to the spread of HPAI H5N1 viruses to Europe and Africa in 2005–2006, many countries developed surveillance plans to detect AI viruses; a large portion of these sampling efforts was targeted at migratory avian species [50].

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, species of bird and other factors [51].

The viruses can be isolated in embryonated eggs and they can be subtyped with specific antisera in hemagglutination and neuraminidase inhibition tests, by RT-PCR, or by sequence analysis of the viral HA and NA genes. RT-PCR assays can detect influenza viruses directly in clinical samples and real-time RT-PCR is the diagnostic method of choice in many laboratories. Viral antigens can be detected with ELISAs including rapid tests, but these tests are more reliable as flock tests than in individual birds [10, 52].

Serology can be valuable for surveillance and demonstrating freedom from infection, but it is not very useful in diagnosing HPAI infections in highly susceptible birds, as they usually die before developing antibodies. Agar gel immunodiffusion (AGID) tests and ELISAs to detect conserved influenza virus proteins can recognize all avian influenza subtypes, but hemagglutination inhibition (HI) tests are subtype specific

and may miss some infections. Cross-reactivity between influenza viruses can be an issue. Tests that can distinguish infected from vaccinated birds (DIVA tests) should be used in surveillance when vaccination is part of a control program [52].

Control and Prevention: It has been clear that countries with well-developed veterinary services, with strong early disease detection and response capacities, can effectively control and eliminate H5N1 HPAI. Countries that have had most difficulty in achieving effective control are those with weak veterinary capacities and that face major risk factors such as high poultry population densities with poor biosecurity, particularly related to large small holder production sectors and substantial duck populations [53].

OIE affirms the most effective strategy for dealing directly with avian influenza; early detection and early warning, rapid confirmation of suspects, rapid and transparent notification, rapid response (Including containment, management of poultry movement, zoning and compartmentalization, humane stamping out and vaccination where appropriate) [54].

Avoid Sources of Exposure: People who work with poultry or who respond to avian influenza outbreaks are advised to follow recommended biosecurity and infection control practices; these include use of appropriate personal protective equipment and careful attention to hand hygiene [55]. In addition, highly pathogenic avian influenza (HPAI) poultry outbreak responders should adhere to guidance from CDC and World Health Organization (WHO) and receive seasonal influenza vaccination annually and take prophylactic antiviral medication during response [56].

Restriction on Bird Movement: Restriction was imposed on the movement of live poultry in the country- inter-state, intra-state movement and transportation of poultry in passenger vehicles [54, 57].

Depopulation and Decontamination: Infected farms should be depopulated by trained personnel who buried the affected birds in dug-out pits. Bio security measures such as fallowing of farms for 3 months before restocking, movement control, foot dipping and perimeter fencing of farms should be put in place to control spread of infection from farm to farm[57,58].

Public Awareness and Communication: Public enlightenment and awareness programs on HPAI identification, diagnosis, prevention and controls involving all stakeholders should be carried out in form of trainings, workshops, seminars, television and radio in all states of the country [15]

Vaccination: Vaccination is the principal measure for preventing influenza and reducing its impact. However, current flu vaccines would not offer protection against a future pandemic strain. However, with the increasing likelihood that the next pandemic strain will originate from H5N1 and may not differ from it significantly, WHO is telling Member States that stockpiling vaccines against it may be a viable option for affluent countries [59].

CONCLUSION AND RECOMMENDATION

Highly pathogenic avian influenza is one of the most serious diseases in the poultry industry and in human population that causes public health problems and economic losses. And it had posed a continued threat on poultry and human health throughout the world.

Although another influenza pandemic in humans is inevitable, we cannot predict when it will occur. In the meantime, we must do everything in our power to avert this threat, which means improving our responsiveness to a pandemic alert through implementation of all possible preventive strategies. The impact of pandemic influenza outbreaks on individuals and societies can be reduced by being well prepared. This means having a comprehensive plan that has been tested and refined through conducting exercises, engaging the whole of society. National plans should be flexible enough to respond to outbreaks of various intensity. Communication will be one of the most challenging tasks during an outbreak and it should be planned well in advance.

Therefore, to prevent the possible public and economic effect of HPAI the following recommendations are forwarded:

- National level bio-security measures need to be developed and institutionalized to reach wider community.
- Performing disease surveillance on risky areas and establishing good and coordinated reporting system need to be considered.

- Creating public awareness on human health precautions like protective equipment, health monitoring, hand hygiene and other risk factors must be given due attention.
- Improving both regional and national capacities for efficient control and prevention must be a priority.

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