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Mini Review

Highly Pathogenic Avian Influenza in Nepal

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Abstract

Avian Influenza is an economically important, highly contagious and fatal infectious disease of birds caused by Type A strains of the influenza virus of *Orthomyxoviridae* family. Avian Influenza is primarily a disease of domestic and wild birds however mammals may be affected. It can be classified as Low Pathogenic Avian Influenza (LPAI) and Highly Pathogenic Avian Influenza (HPAI) on the basis of pathogenicity. Highly Pathogenic Avian Influenza virus is circulating in various countries of Asia and World and causing huge economic loss. After first case of HPAI H5N1 in Kankarbhitta, Jhapa in 2009, several other cases have been reported from Kathmandu, Bhaktapur, Chitwan, Hetauda, Kavre and other places of the country. To date 255 outbreaks of HPAI in birds are reported from 21 districts of Nepal. After 10 years of outbreak of HPAI H5N1 in poultry, in March, 2019 first reported case of human casualty from H5N1 was reported, which shows passive surveillance of the disease. Poor biosecurity, lack of public awareness, few epidemiological investigation, insufficient quarantine and lack of vaccination are major factors in transmission and spread of disease in Nepal. The aim of this paper is to assess outbreak scenario, transmission, pathogenesis, signs and symptoms, diagnosis and prevention and control measures of Highly Pathogenic Avian Influenza.

Keywords: Highly Pathogenic Avian Influenza; H5N1; Nepal; Economic; Zoonotic

Introduction

Avian Influenza is primarily disease of domestic and wild birds but can also affect the mammals (Swayne & Suarez, 2000). It is extremely infectious systemic disease with the ability to transfer directly between poultry and humans and causes infection and mortality (Leigh Perkins & Swayne, 2002). Waterfowl, wild and domesticated sea bird are major reservoir host of avian influenza viruses and contact with these birds causes aerosol transmission of disease to commercial flocks (Chakrabarti, 2017; https://www.cidlines.com/en-UK/avian-influenza/introduction). Avian Influenza virus is classified into two pathotypes: Low Pathogenic Avian Influenza Virus (LPAIV) and Highly Pathogenic Avian Influenza Virus (HPAIV) (Chakrabarti, 2017). LPAI does not produce any significant clinical signs in poultry but some signs include ruffled feather, slight decrease in egg production and respiratory distress (Chakrabarti, 2017; Swayne & Pantin-Jackwood, 2006). Sudden onset and almost 100% mortality are the major feature of HPAI while other symptoms are respiratory distress, congestion and swelling of comb and wattle, nervous signs, purple discoloration of wattle, comb and legs (Chakrabarti, 2017; http://www.oie.int/doc/ged/D13947.PDF). Avian Influenza infection in humans is typically mild or subclinical with symptoms of conjunctivitis, high fever (38°C or above), cough, abdominal pain, chest pain and diarrhoea followed by lower respiratory tract infection including dyspnea (Kalthoff *et al.*, 2010; https://www.cdc.gov/flu/avianflu/avian-in-humans.htm). Infection may progress to pneumonia and neurological changes (altered mental status or seizures) and finally death of the person (https://www.cdc.gov/flu/avianflu/avian-in-humans.htm). Growth in consumption of poultry has

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emanated the rapid expansion of poultry industry in Nepal, which favors the susceptibility of avian influenza. Many Asian countries have reported outbreaks of disease in commercials birds since 2003 (Pant & Selleck, 2007). On January 16, 2009 Highly Pathogenic Avian Influenza (H5N1) was seen for the first time in Nepal from backyard poultry in Kankrarbhitta, Jhapa and subsequently seen in other parts of country like Kathmandu, Bhaktapur, Chitwan, Makawanpur, Kavre (Chaudhary & Pahwa, 2013; http://www.searo.who.int/nepal/documents/emergencies/Avian_Influenza_A_In_Human/en/). In March 2019 human casualty form H5N1 was seen in Nepal (http://www.searo.who.int/nepal/documents/emergencies/ Avian_Influenza_A_In_Human/en/) after 10 years since outbreak reporting in birds, this shows passive surveillance and poor vigilance of disease. The major aim of this paper is to review websites, journals, books, online article and literatures and propose present situation and outbreak incidence of poultry industry and avian influenza in Nepal.

Causative Agent

Avian Influenza is caused by Type A influenza virus which is segmented negative sense RNA virus of Orthomyxoviridae family (Swayne, 2009). This family have 5 genera, including Influenza Types A, B and C, Thogoto virus and Isa virus, Type A influenza affects avian and mammalian species; Types B and C affect human which rarely affect other species (Swayne, 2009). Isa virus affects salmon fish while Thogoto virus causes tick borne infection in both humans and livestock (Swayne, 2009). Type A Influenza virus genome consists of 8 single stranded RNA segments which encodes 11 proteins (Chakrabarti, 2017; Kalthoff *et al*., 2010). Haemagglutinin (HA) and Neuraminidase (NA) are two important surface antigenic proteins which form basic classification of virus into sixteen HA (H1–H16) and nine NA (N1–N9) subtypes (Chakrabarti, 2017; Kalthoff *et al*., 2010). Avian influenza is classified as Highly Pathogenic Avian Influenza (HPAI) and Low Pathogenic Avian Influenza (LPAI) on the basis of pathogenesis (Chakrabarti, 2017). Efficient replication of viruses with monobasic HA cleavage site are restricted to tissues of respiratory and gastrointestinal epithelia leading to mild disease in poultry and these viruses have low pathogenic effect (LPAIV) (Kalthoff *et al*., 2010). Viruses with a multibasic HA cleavage site have capacity to replicate in multiple tissues are called highly pathogenic avian influenza viruses (HPAIV) (Kalthoff *et al*., 2010). To date all outbreaks of HPAI arisen only from subtypes H5 and H7 (Kalthoff *et al*., 2010)

Antigenic Drift and Antigenic Shift

Antigenic drift and Antigenic shift are the mechanism in influenza virus which provide chance to change and adopt and initiate infection in new host (Swayne, 2009). Antigenic drift involves antigenic change through point of mutation in two genetic material coding for HA/NA and usually occurs in Type A & B influenza virus (Chakrabarti, 2017). A single cell if infected by two different virus subtypes, there may be direct or indirect genetic reassortment or exchange of genes between viruses which might give rise to new strain with keen change of antigenic determinants, and is termed antigenic shift (Chakrabarti, 2017; Kalthoff *et al*., 2010). Antigenic drift may cause localized outbreaks but not epidemic while antigenic shift might cause wide spread epidemic (Chakrabarti, 2017). Most catastrophic pandemic influenza to date (Spanish Flu (H1NI, 1918) was caused by virus resulting from antigenic shift (Kalthoff *et al*., 2010; Belshe, 2005)

Transmission

Sea birds, shore birds and waterfowl are major natural reservoir of influenza virus; contact of commercial birds with these birds results in outbreaks of disease (Chakrabarti, 2017). Most of the strains that circulate in these birds to domesticated birds are non-pathogenic or mild pathogenic, however virulent strain may arise from antigenic shift and antigenic drift (http://www.fao.org/avianflu/en/clinical.html).

Transmission occurs directly through faecal-oral pathways or indirectly through contaminated surface water (Kalthoff *et al*., 2010). Disease spread from one farm to other farms through movement of live domesticated birds, contaminated clothes, shoes, equipment's, vehicles, feed and cages (http://www.oie.int/doc/ged/D13947.PDF; Chakrabarti, 2017). Air borne transmission can occur when poultry are in close proximity with appropriate air movement (http://www.fao.org/avianflu/en/clinical.html). In laboratory viruses can be obtained from egg of infected hen at peak of the disease, but there are no evidences of egg transmission and possibility of vertical transmission in unresolved (Chakrabarti, 2017; http://www.fao.org/avianflu/en/clinical.html). A cluster of 8 human cases of HPAI (H5N1) was detected during late April and early May 2006 in Indonesia and investigation determined Human to Human transfer of AI (Yang *et al*., 2007). A cluster of 8 human cases of HPAI (H5N1) was detected in eastern Turkey but researcher did not find statistical evidence of human-to-human transmission of outbreak (Yang *et al*., 2007). Unmanaged poultry farms, large number of farms in small area, contact of poultry with wild-birds, poor biosecurity, slow government response, improper quarantine and lack of surveillance are the major factors for the transmission of HPAI among poultry farms in Nepal. Economic status of farmers is not very good which hinders the proper management and biosecurity of farms and this support disease transmission. In districts, like Chitwan and Bhaktapur large number farms are centralized in small area, after outbreak of disease in a farm there is high chance to spread in many farms. Poor surveillance of disease in wild-birds and lack of education and awareness among poultry are also favoring disease transmission in Nepal.

Pathogenesis

Ability of any pathogens to survive, grow, replicate and establish infection or disease within various cells of host explain its pathogenicity (Finlay & Falkow, 1989). On the basis of pathogenicity, avian influenza can be classified as LPAI and HPAI but pathobiological effects differs in virus strain and host species within each category (Chakrabarti, 2017). Virus envelop have transmembrane proteins HA and NA also M2 protein which acts as an ion channel (Kalthoff *et al*., 2010). Eight ribonucleoprotein (RNP) complex are surrounded by matrix protein (M1) and each RNP complex have one nucleoprotein (NP) molecule along with three polymerase protein PB1, PB2, PB3 (Kalthoff *et al*., 2010; Noda *et al*., 2006). Trimerized HA proteins have spikes and act as viral receptor binding protein by recognizing definite sialic acid (SA) species situated on the cell surface (Chakrabarti, 2017; Kalthoff *et al*., 2010). Avian viruses bind specifically to a -2,3-linked SA whereas Human influenza A viruses ideally bind to a -2,6-linked SA (Chakrabarti, 2017; Kalthoff *et al*., 2010). Viruses bind to epithelial cells of upper respiratory tract, conjunctiva or the digestive tract (Chakrabarti, 2017) and enters the cells by endocytosis into an endosome (Chakrabarti, 2017; Kalthoff *et al*., 2010). HA facilitated fusion of endosomal membrane and viral envelop causes RNP complex release into cytoplasm (Kalthoff *et al*., 2010; Skehel & Wiley, 2000). In most of the avian influenza virus, cleavage site of HA protein is composed of one to two amino acid at specific position, for example, -1/-4 for H5 and -1/-3 for H7 subtypes (Kalthoff *et al*., 2010). With monobasic HA cleavage site, efficient replication of LPAI virus is restricted hence have low pathogenicity (Kalthoff *et al*., 2010). Viruses which can exhibit multibasic cleavage motif (minimal consensus sequence of -R-X-K/R-R-) are identified by subtilisin-like endo-proteases that are almost present in every tissue and hence replicate in multiple tissue, such viruses are HPAI viruses which causes systemic infection and up to 100% mortality (Kalthoff *et al*., 2010). To date all outbreaks of HPAI arisen only from subtypes H5 and H7 (Chakrabarti, 2017; Kalthoff *et al*., 2010). RNP complex when released into cytoplasm are transported into nuclease where viral transcription and RNA replication occurs (Kalthoff *et al*., 2010). After replication, newly formed infectious virus progenies are released and the host cell dies and finally infection occurs (Chakrabarti, 2017; Kalthoff *et al*., 2010). Antigenic drift and Antigenic shift may occur which causes localized outbreak and epidemic respectively (Chakrabarti, 2017; Kalthoff *et al*., 2010).

Clinical Findings in Birds

Free living shore birds, water fowls, sea birds may carry influenza viruses without any disease due to natural resistance (Chakrabarti, 2017). LPAI virus infection may manifest via clinically inapparent disease or may cause mild illness with signs of ruffled feather, drop in egg production and mild to moderate respiratory distress and symptoms (coughing, sneezing, nasal and ocular discharge, swollen infraorbital sinuses) (Chakrabarti, 2017; http://www.oie.int/doc/ged/D13947.PDF; https://www.cdc.gov/flu/avianflu/avian-in-birds.htm).

Others factors like age, species, exposure to stress, nature of virus, concurrent infection govern the severity of disease (Chakrabarti, 2017; http://www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/Disease_cards/HPAI.pdf). LPAI virus infection in some gallinaceous birds like quail, pheasant is asymptomatic (http://www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/Disease_cards/HPAI.pdf). HPAI virus infection (HPAI H5 or HPAI H7) causes sudden and huge outbreak with 90-100% mortality (Chakrabarti, 2017; http://www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/Disease_cards/HPAI.pdf).

Respiratory distress is the major clinical sign but ultimately mortality occurs due to multiple internal organs failure (Chakrabarti, 2017; http://www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/Disease_cards/HPAI.pdf).Others signs include edema of face and head, diarrhoea, ecchymoses on the feet and shanks, discoloration of legs, wattles and comb and nervous symptoms like incoordination (Chakrabarti, 2017).

Lesions in Poultry

Low Pathogenic Avian Influenza

Poultry exhibits signs of respiratory system such as sinusitis, rhinitis, inflammation in the upper respiratory tract and lower respiratory infection like pneumonia after secondary bacterial infection (Chakrabarti, 2017). Lesion like hemorrhagic ovary, involuted and degenerated in reproductive tract of laying hens may be seen along with air sacculitis and peritonitis (http://www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/Disease_cards/HPAI.pdf).

High Pathogenic Avian Influenza

Oedema and cyanosis of head, wattle and comb, ulceration of combs, petechial hemorrhagic lesions in the serosal and mucosal surface, viscera and sometimes in muscle, edema and diffuse subcutaneous hemorrhages on the feet and shanks, fibrinous exudation in pericardial sac, air sac and protonium (Chakrabarti, 2017; http://www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/Disease_cards/HPAI.pdf)

Clinical Findings in Humans

To date Asian lineage H7N9 and HPAI Asian lineage H5N1 viruses are responsible for most human diseases including highest mortality and most serious illnesses (https://www.cdc.gov/flu/avianflu/avian-in-humans.htm). Infection with these viruses in human causes mild to severe infection which include conjunctivitis, respiratory symptoms (dyspnea, sore throat, pneumonia, acute respiratory distress, respiratory failure), influenza like illness (Cough, fever, malaise, muscle ache, sometimes nausea, abdominal pain, diarrhea, and vomiting), neurologic changes (altered mental status, seizures), and the involvement of other organ systems (https://www.cdc.gov/flu/avianflu/avian-in-humans.htm; Kalthoff *et al*., 2010)

Global Situation of Highly Pathogenic Avian Influenza

Poultry

Highly Pathogenic Avian Influenza is OIE listed and global panzootic disease and its situation over last six years is considered significant because of high number of affected countries and territories, substantial number of outbreaks and high diversity of subtypes, which make it complex for control and eradication. (http://www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/OIE_AI_situation_report/OIE_SituationReport_AI_August2018.pdf). HPAI H5N1 was first appeared in geese in Guangdong, China in 1996 and started spread in many countries mainly in Asia and started infect domestic and wild birds (Sturm-Ramirez *et al*., 2004; Alexander, 2000). From January 2013 to August 2018, 7122 outbreaks reported from 68 countries and territories with 12 different subtypes of HPAI which causes losses of 122 million birds while from January 2005 to December 2012, 8345 outbreaks reported from 65 countries and territories with 4 different subtypes of HPAI (http://www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/OIE_AI_situation_report/OIE_SituationReport_AI_August2018.pdf). In 2019 (January-July), many HPAI outbreaks occured in 6 SAARC countries (Afghanistan, Bangladesh, Bhutan, Pakistan, India and Nepal) and other 17 countries of the world (http://www.oie.int/animal-health-in-the-world/update-on-avian-influenza/2019/) this shows wide distribution of the disease and risky situation of South Asian countries.112 million deaths and destroyed poultry in 5.5 years shows the economic importance of the diseases and its challenges in the upcoming years. Status of HPAI outbreaks in domestic birds by region (Jan 2013- Aug 2018) is shown in Table 1.

Humans

To date HPAI H5N1 & Asian lineage H7N9 viruses are responsible for most human diseases including highest mortality and most serious illnesses (from https://www.cdc.gov/flu/avianflu/avian-in-humans.htm).

HPAI H5N1

In 1997, human infections with avian influenza H5N1 was reported in Hong Kong for the first time, out of 18 cases, 6 cases were fatal (Sturm-Ramirez *et al*., 2004),and then human cases started to appear from many parts of the world, from 2003 to date HPAI is reported from 17 countries including Nepal where 861 human cases are reported in which 455 are fatal cases, which indicate 52.8% Case Fatality Rate (https://www.who.int/influenza/human_animal_interface/2019_06_24_tableH5N1.pdf?ua=1). All this data shows the zoonotic importance of HPAI.

Table 1: Status of HPAI outbreaks in domestic birds by region (Jan 2013- Aug 2018)

Regions	Subtypes	Deaths and Destroyed
Asia	H5N1, H5N2, H5N3, H5N6, H5N8, H7N9	71,326,121 (58%)
Africa	H5N1, H5N2, H5N8,	8,291,669
Americas	H5N1, H5N2, H5N8, H7N3, H7N8, H7N9	28,224,324 (23%)
Europe	H5N1, H5N2, H5N5, H5N6, H5N8, H5N9, H7N7	14,260,122 (12%)
Oceana	H7N2	490,000
Total: 68 Countries & Territories, 7122 Outbreaks, 12 Subtypes		122,592,236 (122 Million)

Source: http://www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/OIE_AI_situation_report/OIE_SituationReport_AI_August2018.pdf

Asian lineage H7N9

Since March 2003, Type A Avian Influenza H7N9 virus started to infect human beings from China and started to spread all over the China (Wang *et al*., 2017). Since 2013 to July 2019 total confirmed human cases are 1568 in which 616 are fatal cases (http://www.fao.org/ag/againfo/programmes/en/empres/H7N9/situation_update.html) making Case Fatality Rate of 39.2 %. Among 1568 cases 1 case was exported to Malaysia in Jan 2014 and 2 to Canada in Jan 2015 and human to human transmission of H7N9 has not been reported yet (http://www.fao.org/ag/againfo/programmes/en/empres/H7N9/situation_update.html).

Nepal being neighboring country of China, it has a great risk of human infection with H7N9. As H5N1, it may cause infection in human in Nepal. So, everyone related to poultry industry must be alert and Nepal government, farmers and veterinarians must adopt preventive measures to stop transfer of disease. High number of outbreaks of Avian Influenza H5N1 since 2009, causes high economic loss and recently human casualty was seen, under this prevailing situation of H5N1, outbreak of H7N9 will be havoc.

Situation of Poultry Industry and Outbreaks Incidence of Highly Pathogenic Avian Influenza in Nepal

Poultry

Situation of Poultry Industry

Poultry industry started about 30 years ago in Nepal and started to grow rapidly, to date Nepal is almost self-sustainable in egg and poultry meat (Anonymous, 2018). Agriculture based poultry sector is emerging as cheap protein source for Nepalese people. In 2018, Nepal had 72 million chickens and 4 hundred thousand ducks' population which were contributing in production of 60 thousand MT chicken meat, 241 MT duck meat, 1 billion 498 million chicken eggs and 14 million duck eggs (Krishi diary 2076 B.S.). In Nepal Per Capita Meat (Commercial Poultry) Availability (Kg/Year) is 4.1 and Per Capita Egg (Commercial Poultry) Availability (No. of egg/year) is 43.7 ("Nepal Commercial Poultry Survey 2015", 2015). There are 21956 total poultry farms in Nepal which include 20483 broilers farms, 1337 layers farms, 128 hatcheries and Giriraj/koiler farms where as Chitwan is major broiler and egg producing district. ("Nepal Commercial Poultry Survey 2015", 2015). Kavre, Dhading, Kathmandu, Kaski respectively follow Chitwan in broiler production and Makawanpur, Nawalparasi, Dang, Bhaktapur respectively follow Chitwan in egg production ("Nepal Commercial Poultry Survey 2015", 2015). Value of production (Rs. '000) for meat is 20528891, 9133736 for egg, 3607674 for chicks and 453722 for manure and gross value added (Rs in Million) is Rs 684 ("Nepal Commercial Poultry Survey 2015", 2015). As a whole in country, Mortality rate of broiler is 12.8%, layer is 9.2 % and parent is 7% while hatchability of layers egg is 74.2 % and 55871 permanent and 103035 temporary people are engaged in poultry sector ("Nepal Commercial Poultry Survey 2015", 2015)

Outbreaks incidences from 2009-2018

Highly Pathogenic avian influenza (H5N1) was seen in Jhapa district and was confirmed on January 16, 2009; for the first time in Nepal (Chaudhary & Pahwa, 2013; https://www.reuters.com/article/idUSDEL133818) .Total 2 outbreaks in 2009 in Jhapa in Nepal caused death of 164 poultry, where 2560 poultry were destroyed (http://www.oie.int/animal-health-in-the-world/update-on-avian-influenza/). After 2009, 8 outbreaks were reported in 6 districts in 2010, 13 outbreaks were reported in 6 districts in 2011-2012 and 210 outbreaks were reported in 16 districts in 2012-2013 while only one outbreak was reported in 2014 from Sunsari district (http://www.oie.int/animal-health-in-the-world/update-on-avian-influenza/). No outbreaks were reported in 2015 & 2016 whereas 4 outbreaks reported from Kaski and Sunsari in 2017 and 3 outbreaks reported from 3 districts in 2018 (http://www.oie.int/animal-health-in-the-world/update-on-avian-influenza/). Total 241 outbreaks reported from 2009-2018 in 20 districts which causes deaths of 224,881 poultries and 2,162,269 poultries were destroyed, total loss of 2,387,150 (2 million) poultries occurred in 9 years which include commercials broilers, layers, parents and backyard poultries along with ducks (http://www.oie.int/animal-health-in-the-world/update-on-avian-influenza/). In the country where poultry farmers are in very risk and facing many problems daily, disease like avian influenza is nightmare. Initially from Jhapa it is spreading all over the country, government negligence and lack of quarantine in every district may be reason behind spread of disease. In these outbreaks, deaths of 6 crows, 1 Asian openbill and 14 whopper swans were reported and in 2017, outbreak in Sunsari was due to HPAI H5N8 which was new subtype for the country (http://www.oie.int/animal-health-in-the-world/update-on-avian-influenza/). Outbreaks in wild birds and their deaths makes situation more serious in the country with 40% forests, prevention must be applied to stop transmission of disease from such wild birds to domestic birds. Outbreaks of new subtype is matter of concern, there are possibilities of outbreaks with new subtype which make avian influenza more dangerous and complex (Table 2).

Outbreak incidences from January 2019- July 2019

In short span of 7 months, 14 outbreaks of HPAI H5N1 in poultry are reported from 9 districts of Nepal with loss of 107,084 poultries from (http://www.oie.int/animal-health-in-the-world/update-on-avian-influenza/) High number of outbreaks in Kathmandu district (Capital) may be due to haphazard transportation of poultry from other part of the country, large numbers of farms in small area with dense human population. In this precarious situation every individual related to poultry sector and government must come in one place and make strategy to eradicate Highly Pathogenic Avian Influenza; otherwise, poultry industry is in great risk and chaos may happen in near future. Loss of economy of the country is in one place, small farmers may lose everything in aspect of economy. In the month of march 2019, 1 outbreak with 200 deaths of crows was reported from Launchaur, Kathmandu (http://www.oie.int/animal-health-in-the-world/update-on-avian-influenza/), this shows beside poultry and gallinaceous bird HPAI is infecting other birds too, therefore surveillance among wild birds, home crows and other susceptible birds have to be done which may help to prevent the disease transmission and to determine the source of outbreak.

Table 2: Outbreak statistics of Highly Pathogenic Avian Influenza from 2009 to 2018 in Nepal

Years	Outbreak Numbers	Districts	Susceptible poultry (Backyard & Commercial)	Disease Cases in Poultry	Death	Destroyed	Strain of Virus
2009	2	Jhapa	27724	164	164	2560	H5N1
2010	8	Kaski, Banke, Chitwan, Dang, Kailali, Nawalparasi	29149	1114	1114	28037	H5N1
2011/12	13	Bhaktapur, Kathmandu, Sunsari, Jhapa, Ilam, Lalitpur	43639	31429+4 crows	31429+4 crows	12210	H5N1
2012/13	210	Lalitpur, Bhaktapur, Kathmandu, Dhading, Nuwakot, Kaski, Jhapa, Taplejung, Nawalparasi, Chitwan, Kailali, Rupandehi, Sindhuli, Kavre, Makawanpur, Sindupalchowk	2076755	184776+2 crows	184776+2 crows	1891879	H5N1
2014	1	Sunsari	2000	570	570	1430	H5N1
2017	2	Kaski	2557	98	98	2459	H5N1
2017	1	Sunsari (Asian openbill, Whopper swan)	1,14	1,14	1,14	-	H5N1
2017	1	Sunsari	6200	3650	3650	2550	H5N8
2018	3	Chitwan, Kathmandu, Lalitpur	25224	3110	3080	221144	H5N1
Total	241 Outbreaks	20 Districts	2213248	224911	224881	2162269	-
Total Deaths and Destroyed= 224881+2162269= 2,387,150							

Source: from http://www.oie.int/animal-health-in-the-world/update-on-avian-influenza/

Table 3: Outbreak statistics of Avian Influenza in poultry 2019 (Jan-June) in Nepal

Total outbreaks	**14**
Districts	Makawanpur, Kathmandu*5, Kaski, Morang, Sunsari, Bhaktapur*2, Lalitpur, Nawalpur (Susta Purba), Rasuwa
Susceptible	1,07,084
Cases	20,386
Deaths	20,386+ 200 Crows
Killed and Destroyed	86,698
Total (Deaths, Killed, Destroyed)	1,07,084

Source: ("OIE - World Organisation for Animal Health", 2019

Humans

After 10 years of outbreak of HPAI H5N1 in poultry, on March 29, 2019; a 21-year-old male patient from Kavre district died in hospital due to Type A Influenza H5N1 which was confirmed on April 30, 2019 in National Influenza Center (NIC) of Japan (http://www.edcd.gov.np/news/download/press-conference-by-mohp-on-influenza-a-h5n1-translated-version1).He was admitted in hospital with symptoms of cough and fever in March 24, 2019 later throat swab sample was sent to National Influenza Center (NIC) of Nepal to confirm suspected influenza on March 25, 2019 (http://www.edcd.gov.np/news/download/press-conference-by-mohp-on-influenza-a-h5n1-translated-version1). After this outbreak Government of Nepal as member of International Health Regulation (IHR) shared the details of events via World Health Organization (WHO) and Ministry of Agriculture and Livestock Department, WHO south east Asia regional office, WHO Nepal country office and related stakeholders are working together to enhance surveillance, epidemiological investigations and risk assessment for to control Avian Influenza in humans (http://www.edcd.gov.np/news/download/press-conference-by-mohp-on-influenza-a-h5n1-translated-version1). This is the just the beginning of human case, if responsible person and organization still does not take it as serious, many human casualties may occur in near future. Lack of knowledge about avian influenza and zoonotic diseases among poultry workers and improper handling may be the reason behind disease transmission and outbreak. Trainings and awareness among poultry workers and butchers and surveillance may decrease susceptibility among them.

Avian Influenza Control Project (Id P100342) was launched in Nepal by the world bank after approval in Jan 19 2007 to July 31, 2011 to minimize the threat of Highly Pathogenic Avian Influenza and other zoonotic diseases in humans by controlling such disease in poultry and to respond influenza outbreak and other zoonotic disease in humans (http://projects.worldbank.org/P100342/avian-influenza-control-project?lang=en&tab=overview) Behavioral changing programs among poultry farmers, health workers, general population in respect to knowledge, attitude and practices, national monitoring of domestic poultries, surveillance among humans, awareness programs and other related programs were done and $ 18.20 million was spent in the course of the project (http://projects.worldbank.org/P100342/avian-influenza-control-project?lang=en&tab=overview). Although implementing such a grand program, HPAI H5N1 infected human and also caused death, this is the where all related organizations and individuals have to work and investigate what is lacking behind and make strategies for upcoming days.

Diagnosis

Diagnosis of avian Influenza can be done on the basis of history and epidemiology, clinical signs symptoms and lesions, rapid kits and laboratory findings. Signs and symptoms along with outbreak history and epidemiology can guide towards disease diagnosis.

In most of the cases of per acute infection with HPAI there is death of the bird with no visible signs while in acute infection chickens have ruffled feathers, swollen head, congestion and/or cynosis of wattle and comb, hyperemia, edema of eyelids, conjunctiva and trachea (Swayne & Suarez, 2000; Chakrabarti, 2017). Inflammation and necrosis are lack in parenchymal cells of most of visceral organs, brain and skin in per acute death caused by HPAI virus while in acute infection major lesions are necrosis, apoptotic cell death with inflammation hemorrhage and edema (Swayne & Suarez, 2000). Homogenates from trachea, lung, internal organs and faeces of infected bird or human is inoculated directly in 9-11 day old embryonated egg for virus isolation (Swayne & Suarez, 2000; Swayne 1998). Virus isolation, serological tests, and direct antigen detection are combinedly use for virus detection and after virus isolation HA and NA test can be done to identify subtypes (Swayne 1998). Detection of specific antibody is done by Agar Gel Immunodiffusion (AGID) and the Enzyme-Linked Immunosorbent Assay (ELISA) (Swayne & Suarez, 2000; Chakrabarti, 2017). Reverse Transcription Polymerase Chain Reaction (RTPCR), real-time reverse transcription PCR and nucleic acid sequence-based amplification are tools for rapid molecular diagnosis of avian influenza virus (Swayne & Suarez, 2000; Chakrabarti, 2017).

Treatment

Poultry

There is no any specific treatment for Highly Pathogenic Avian Influenza (Chakrabarti, 2017). Outbreak of HPAI in any place or farm, depopulation or stamping out is carried out and surveillance of nearby poultries and quarantine of exposed flocks is done to control and eradicate disease (https://www.cdc.gov/flu/avianflu/avian-in-birds.htm).

Humans

Hospitalization

Suspected person with HPAI should be hospitalized in isolation for clinical monitoring, diagnosis and antiviral therapy (Beigel *et al*., 2005). Supportive care with oxygen supplement and ventilatory support are the base of management (https://www.cdc.gov/flu/avianflu/avian-in-humans.htm).

Antiviral Agents

Suspected patients of HPAI H5N1 are treated with neuraminidase inhibitor until laboratory diagnosis, dose and duration is generally uncertain (Beigel *et al*., 2005). Oral oseltamivir (Leneva *et al*., 2000) and topical zanamivir are effective in animal models of H5N1 Influenza A (Beigel *et al*., 2005; Gubareva *et al.*, 1998).

Early treatment with oseltamivir is highly recommended if patient is confirmed or highly suspected with H5N1; and zanamivir might be recommended in such case (https://www.who.int/medicines/publications/WHO_PSM_PAR_2006.6.pdf).

Immunomodulators

Corticosteroids are frequently used in treatment with uncertain effects (Beigel *et al*., 2005) but should not be used frequently or routinely (Clinical management of human infection with avian influenza A (H5N1) virus, 2007) while its treatment has not been effective in HPAI H5N1 virus infection (Beigel *et al*., 2005).

Prevention and Control Measure

As there is no specific treatment of HPAI, prevention and control measure plays a great role to suppress disease outbreak. Various strategies are applied all over the world for the prevention and control of disease. Strategies should be focused to preclude exposure of poultry to HPAI H5N1 virus, if disease occur then depopulation is the most viable option. Essential elements for effective prevention, control and containment of disease from Nepal are listed below.

Epidemiological investigation and Surveillance

A comprehensive epidemiological investigation, integrated surveillance and disease diagnostic programmes in various parts of country are necessary to determine enormity of the HPAI virus infection in wild birds, backyard poultry, commercial poultry and humans. Transparency of the data from such programme is very necessary to establish prevalence of disease in districts, province and country and also for national and international trade of poultry and related products. Surveillance among wild birds and home crows is very necessary in recent context. Early reporting of disease helps in taking rational decision either to stamp out or isolation of infected flocks.

Public Awareness and Education

Public awareness is key tool in prevention of any disease as it helps to create understanding of different aspects of disease. Awareness, education and flow of information among poultry farmers, farm owners, workers, veterinarians, stakeholders and government is necessary for acceptance, execution and successful outcome of prevention and control programme (Swayne & Suarez, 2000). Public must be aware about zoonotic and economic impact of the diseases and need to understand the spread and transmission of disease among poultries and to humans.

Biosecurity

Enhanced biosecurity plays very important role in prevention and control of disease and its main purpose are bio exclusion and bio containment (Swayne & Suarez, 2000). The practice of biosecurity must be applied in every sector of poultry farm, poultry industries and all by every personnel involved. Prevention of contact of poultry with wild bird, proper disinfection and decontamination of all farm's equipment, personal hygiene of employee are the basics of biosecurity. Workers of one poultry farm should be restricted in another farm, veterinarians working in different farms must change all clothes and shoes before entering poultry farms.

Stamping Out/ Depopulation

In case of outbreak of HPAI H5N1, stamping out or depopulation is the best way to prevent spread and to eliminate disease. Depopulation program should be initiated as soon as possible to make it effective and to prevent huge economic loss. Disposal must be done either by burial or incineration according to law and environment situation. In Nepal from January to July 2019, 86,698 poultries are killed after death of 20,386 poultries in 14 outbreaks of HPAI H5N1, resulting in huge economic loss (http://www.oie.int/animal-health-in-the-world/update-on-avian-influenza/). Early detection of disease and early stamping out will prevent huge economic loss.

Quarantine

Containment of the disease through restriction movement of poultry, workers and equipment is necessary to prevent spread HPAI to non-infected farms and locations (Swayne & Suarez, 2000). Depopulation and disposal of poultry after outbreak is very essential. Every district of Nepal must have quarantine to examine the bird during transportation of poultry from another district and India. It helps to limit the disease in certain place only and prevents spread in large geographical area.

Vaccines

Inactivated whole virus vaccines and recombinant fowl pox vaccine with an H5 AI HA gene insert have been used in the control or eradication of HPAI in different part of world (Swayne & Suarez, 2000). There is no provision of vaccination of HPAI in Nepal. Complete efficacy of vaccines remains doubtful because of different subtypes, antigenic drift and antigenic drift of HPAI virus.

Conclusion

As in many countries in the world, situation involving highly pathogenic avian influenza is very serious in Nepal. Extensive study and research on the epidemiology, zoonotic and economic impact of avian influenza is urgently necessary. Efforts should be made to stop transmission of disease from wild birds to domestic birds along with surveillance among gallinaceous birds and crows. Every poultry farmer, chicken handlers, transporters, chicken suppliers, regular visitors to live bird markets, butchers, veterinarians and every related individual should be conscious about disease and apply all preventive measures to stop transmission in humans from birds and among birds. Screening of HPAI H5N1 among these personals is necessary on a regular basis. Awareness among every individual working with live poultry and carcass should be straightened and knowledge about disease transmission and food security should be provided. Government of Nepal and stakeholders in coordination with different origination like WHO, FAO should work more efficiently to enhance epidemiological investigation, surveillance and risk analysis.

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