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BIRD FLU VIRUS - EPIDEMIOLOGY AND CURRENT STATUS AT NATIONAL AND INTERNATIONAL LEVEL - A SYSTEMATIC REVIEW

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SHRI KANT YADAV

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In partial fulfillment of the requirements for the award of degree of

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In

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By

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I hereby declare that this dissertation entitled **"BIRD FLU VIRUS - EPIDEMIOL-OGY AND CURRENT STATUS AT NATIONAL AND INTERNATIONAL LEVEL - A SYSTEMATIC REVIEW"** is bonafide and genuine research work carried out by me under the guidance of **Dr. Mohd Saquib** Assistant Professor, Department of Microbiology and Co-guide **Dr. Ausaf Ahmad** Statistician & Associate Professor, Department of Community Medicine, Integral Institute of Medical Sciences and Research, Lucknow.

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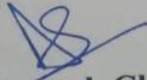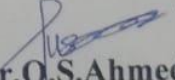### IIMS&R INTEGRAL UNIVERSITY, LUCKNOW

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The above mentioned research work has been approved by Institutional Ethics Committee, IIMS&R with consensus in the meeting held on **19 May 2022**.

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DEDICATED To

"TEACHERS"
"FAMILY"

&

"FRIENDS"

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INTRODUCTION

Bird flu infection can be particularly deadly compared to other viruses, and healthcare professionals may not be aware of the additional caution needed in evaluating possible cases of infection. Avian influenza is an umbrella term that describes the disease caused by several strains of the influenza A virus known to infect birds that occasionally cause viral disease outbreaks in humans.[1] Several known outbreaks of avian influenza include an outbreak of the H5N1 strain in Hong Kong in 1997 and H7N9 in eastern and southern China in 2013. Adapted to birds and often causing only mild illness, avian influenza viruses can be extremely dangerous with transmission successful in people with a high rate of confirmed cases requiring frequent hospitalization and intensive care (UTI).

Influenza A viruses are part of the Orthomyxoviridae family. Other viruses in this group include influenza B and C viruses. While influenzas B and C have been found in other species, only influenza A infects birds. The exact mechanism of bird-to-bird transmission is currently unknown. The virus is shed in large quantities in the feces and respiratory tract of infected birds. In birds, the strains of avian influenza are typically highly pathogenic avian influenza (HPAI) and low pathogenic avian influenza (LPAI). In birds, strains of LPAI are more common and usually cause limited disease. In humans, both HPAI and LPAI strains can cause fatal outbreaks of avian influenza, although HPAI strains are more likely to do so.

Influenza A virus divides into subtypes based on the antigen present on two virus surface glycoproteins, hemagglutinin (with 16 known potential antigens) and neuraminidase (with nine known potential antigens). [1] The virus is then described using the combination of antigens, such as H5N1. The hemagglutinin glycoprotein is produced as a precursor in this virus; this is important because the proteins needed to process and activate this protein in the LPAI strains of the virus are found only in specific parts of the body, such as the gastrointestinal tract and the respiratory tract, while the proteins needed for the HPAI strains are generally omnipresent in the host .[1]

Avian influenza viruses (AIVs) are found in most bird species, both wild and domestic. Generally, domestic birds are responsible for human disease outbreaks because they have more human contacts. However, some widespread diseases may play a role in migratory birds which can transmit diseases to various places where subsequent domestic bird infection leads to human transmission. [2] Bird flu is most often transmitted to humans through direct contact with live birds or through contact with raw poultry in factories and restaurants.[2]

Human pandemics are best documented in the 20th century, in 1918–19, 1957–58, and 1968–69. These pandemics are known to be caused by the influenza A subtypes H1N1, H2N2[3,] and H3N2[4,] respectively. Additionally, retrospective serological analysis showed that A/H2N2, which circulated from approximately 1889 to 1901, was likely responsible for a pandemic that began in 1889 and that a mild pandemic in 1900 may have been caused by A/H3N8.

Influenza A/H1N1 may have been circulating since around 1908.[5] It is therefore evident that at least two of the pandemics of the 20th century (1918 and 1957) have been associated with the re-emergence of viruses similar to those previously circulating, a process known as antigenic recycling. [6] According to this theory, there is a serious possibility that the next pandemic will come from an H2 subtype and not from HPAI A/H5N1. The majority of influenza deaths in interpandemic years occur in the elderly, with some reported in infants and young children.[7] A similar pattern emerged in England and Wales during the first quarter of 1918; However, in the fourth quarter of this year, during the second wave of the pandemic, this trend reversed and mortality was highest among people aged 25-29.[8] Similar trends were observed during the pandemics of 1957-1958 and 1968-1969, although to a much lesser extent. While the majority of excess deaths during these two pandemics occurred in the elderly, the relative increase in deaths was highest in young adults.[9] There is evidence that the very old were partially protected during the pandemics of 1957-58 and 1968-69, as they were in 1918-19.[10] This may be

because individuals in this age group were exposed to similar antigens as children or young adults and therefore retained partial immunity later in life, which is effectively the immunological consequences antigen recycling.[6]

The highly pathogenic avian influenza virus (HPAI) H5N1, which is panzootic in poultry, continues to spread and poses a major problem for human and animal health.[11] Since the pandemic influenza virus originates from avian influenza viruses[12] , the HPAI-H5N1 virus should be considered a potentially serious pandemic threat. New influenza virus pandemics in the 21st century are a certainty, but it is far from certain that H5N1 will be the next pandemic virus. What is already true, however, is that H5N1 viruses are wreaking enormous havoc on the poultry industry in many developing countries, and this directly or indirectly affects economic and social well-being.

The potential impact of the HPAI-H5N1 virus (and the human response to its spread) on wildlife and ecology has received less attention, but is also worth considering.[13] Although the H5N1 virus is zoonotically transmitted from infected poultry to humans, often with fatal consequences, this transmission remains ineffective. Although the virus replicates effectively in sick people, it has not yet adapted to efficient human-to-human transmission.

BIOLOGICAL PROPERTIES OF THE AVIAN INFLUENZA VIRUS

Influenza A viruses are enveloped RNA viruses with an eight-segment, single-stranded negative sense genome belonging to the Orthomyxoviridae family. Influenza virus type A (and type B) causes recurrent outbreaks almost every year, leading to significant morbidity and mortality in humans. However, only the influenza A virus has been associated with influenza virus pandemics, in which a new antigenic influenza virus emerges to rapidly spread around the world in an immunologically naive population. Past pandemics have infected 20 to 30% of

the world's population within the first year and, in this regard, influenza A viruses are unique human pathogens. The last century saw three pandemics of this type, in 1918 (the so-called "Spanish flu"), in 1957 ("Asian flu") and in 1968 ("Hong Kong flu"). The 1918 pandemic would have killed more than 40 million, while those of 1957 and 1968 would have killed more than 4 and 1 million respectively.[14]

The eight gene segments of the influenza A virus code for 10 proteins: hemagglutinin (HA), neuraminidase (NA), matrix proteins M2 and M1, non-structural proteins (NS) NS1 and NS2, nucleocapsid, and the three polymerases, PB1 (Polymerase Basic 1), PB2 and PA (Polymerase Acidic) proteins [15]. In some influenza viruses, it was recently discovered that the PB1 gene codes for an additional protein, the PB1-F2 protein [16].

Influenza A viruses are subtyped on the basis of HA and NA antigens, which are surface proteins found on the viral envelope[17]Mutation in these genes is selected by herd immune selection pressures in the host, causing antigens to change direction over time ("antigenic drift"), which explains why the repeated outbreaks seen in the virus of influenza A or B can be observed.

The segmented genome of influenza viruses also allows for genetic rearrangement when two influenza viruses infect the same cell [18]. This provides influenza viruses with a powerful option to generate genetic diversity for transfer between species and to evade host immune responses through a broad antigenic shift ("antigenic shift").

Pandemics occur at irregular intervals when an influenza virus with an entirely new HA (and sometimes NA) acquires the ability for efficient and sustained human-to-human transmission in an immunologically naive population to the virus's surface proteins (HA and NA). The H2N2 influenza virus responsible for the 1957 pandemic arose through a genetic rearrangement, in which the prevalent human influenza A (H1N1) virus acquired the HA (H2), NA (N2) and PB1 genes from an avian virus[19] . Similarly, the 1968 pandemic arose from the

acquisition of a new HA (H3) and the PB1 gene from an avian source. In contrast, the 1918 pandemic is believed to have resulted from the direct adaptation of a pure avian virus to efficient human transmission [20] although the lack of genetic information on relevant avian precursors and human viruses prior to 1918 is a definitive conclusion. on this. [21]

Therefore, the pandemic influenza virus is a zoonosis and avian viruses play a fundamental role in its genesis [22] . Since the 1957 and 1968 pandemics occurred in southern China, this region has been identified as a hypothetical pandemic epicenter [23]

Highly pathogenic avian influenza virus

Two influenza A virus subtypes (H5 and H7) are known to cause HPAI virus in terrestrial poultry (broilers and turkeys). The HPAI virus phenotypes of these viruses are largely, but not exclusively, linked to mutations resulting in multiple basic amino acids in the connecting peptide between the HA1 and HA2 domains of the HA0 precursor protein [24]. In the viral life cycle, post-translational cleavage of the HA precursor molecule (HA0) into two subunits (HA1 and HA2) by host proteases is essential for productive viral replication, as this generates a domain fusogen which ensures the fusion between the viral envelope and the membrane of the endosome. This can occur extracellularly by trypsin-like proteases whose tissue distribution is restricted to the respiratory tract and gastrointestinal tract. However, when multiple basic amino acids are introduced into the HA cleavage site, the HA0 precursor becomes cleavable by a variety of proteases (eg, furins [PC6-like] [25] with ubiquitous tissue distribution. This allows for productive replication of the virus in organs outside the respiratory and gastrointestinal tracts, including the brain, resulting in fulminant disseminated disease with high mortality, leading to the HPAI virus [26]

Acquisition of a carbohydrate side chain near the cleavage site [27] can modulate the pathogenicity of a virus by masking the accessibility of proteases to the cleavage site. In the 31 years from 1959 to 1990, nine HPAI virus outbreaks were recorded in Europe, North America and Australia, and these outbreaks were contained by "wiping out" infected herds. In the 11 years since 1990, 10 new HPAI virus outbreaks have occurred, including in Asia. However, the current outbreak of the HPAI H5N1 virus (starting in 2003) is unprecedented in scale and geographic distribution. These viruses are now panzootic on three continents, causing huge economic losses and have been transmitted to humans with deadly consequences. The expansion of intensive poultry farming, the fastest growing livestock sector in the world, with around 16 billion chickens and 1 billion ducks worldwide, likely facilitating the increasing frequency and magnitude of HPAI virus outbreaks. In addition, the commercialized large poultry industry is now associated with the long-distance transport of live poultry and poultry products, which facilitates the transmission of infection.

BIRD- TO- HUMAN TRANSMISSION OF THE AVIAN INFLUENZA VIRUS

Avian influenza viruses do not effectively infect humans or non-human primates [28]. Conversely, human viruses do not replicate efficiently in ducks.[29]

The viral and host factors that determine host restriction are poorly understood [30] and are thought to be determined by several viral genetic determinants, including the viral HA and NA genes, as well as other internal genes such as nucleoprotein and PB2 genes. The HA of human influenza viruses binds to cell sialic acid bound by a -2,6 bond (SA -2,6) to galactose found on human cells, while avian viruses have a preference for the sialic acid linked by -2,3 linked to galactose is (SA-2,3) linkages found on avian epithelia (e.g. ducks).

This receptor specificity has been hypothesized to be one of the factors responsible for the species barrier that prevents avian viruses from easily infecting humans. Recently, lower respiratory tract epithelial cells (i.e., terminal bronchioles and alveolar epithelial cells) have been shown to possess both SA-2,3 and SA-2,6 receptors. In addition, fluorescein-labeled virus has been shown to bind effectively to epithelial cells of terminal bronchioles and alveoli, and avian-like H5N1 viruses have been shown to infect and replicate ex vivo cultures of lung fragments. .[31]

Although the putative SA-2,3 receptors of H5N1 viruses appear to be absent from the upper respiratory tract, H5N1 viruses are able to replicate in ex vivo cultures of upper respiratory tract organs. On the other hand, some H5N1 viruses isolated from humans seem to have acquired mutations in HA associated with a change in the affinity of the SA-2.3 and SA-2.6 receptors, although for these viruses these mutations alone were not effective for transmission from person to person. Therefore, the SA-2.3 and SA-2.6[32] receptor paradigm for explaining tissue tropism and host restriction of avian influenza viruses probably deserves re-evaluation. New technologies such as glycan arrays show that the situation is indeed complex, as different viral strains bind to new structures such as sulfated and sialylated glycans in addition to the traditional SA-2,3 and SA-2,6 . Additional information about host cell surface glycans, combined with data on virus binding preferences to these structures, is likely to provide new biological insights into the interspecific transmission of avian influenza viruses.

Transmission of avian influenza viruses to humans

The ability of avian influenza A viruses of the H1N1, H3N8, H3N2, H6N2, H6N1, H9N2, H4N8 and H10N7 subtypes to replicate in humans was studied by experimentally infecting 81 healthy volunteers[33]. Some volunteers experimentally infected with the H4N8,

H10N7, or H6N1 virus showed signs of viral replication in the nasopharynx, and some had mild upper respiratory tract symptoms. None of them had evidence of increased antibody titers using the conventional haemagglutination inhibition (HI) test. Neutralizing antibody responses were not evaluated. Attempts to artificially transmit H6N1 from one volunteer to another have failed. Volunteers infected with the H1N1, H3N2, H3N8, H6N2, or H9N2 avian virus had no evidence of virus replication in the nasopharynx, but some of them showed serological reactions to the infecting virus. It has been hypothesized that natural human virus infections of the H1 or H3 and N1 or N2 subtypes may have provided cross-reacting immunity that prevented the replication of the avian virus. These findings highlight the fact that avian influenza viruses can infect humans, at least after an experimental challenge, and also that conventional HI tests underestimate such infections. Human sera collected in southern China from the late 1970s to early 1980s had evidence of antibodies against a number of LPAI virus subtypes (e.g. H4, H5, H6, H7, H10 and H11), as assessed by the single radial hemolysis test [34] . Human seroprevalence was apparently related to virus isolation rates in ducks, with some exceptions (eg, H7). Seroprevalence for H5 viruses ranged from 0% (Hong Kong) to 2.3% (Jiangsu Province). It should be noted that this H5 seroprevalence probably reflects exposure to low pathogenic H5 viruses present in ducks; provides no evidence of continued exposure to the current HPAI H5N1 virus

Human avian influenza A (H5N1) infection - No new cases of human avian influenza A (H5N1) infection were reported to WHO in the Western Pacific between 24 December and 30 December 2021. As of 30 December 2021, a total of 239 cases of human infection with avian influenza A (H5N1) virus have been reported from four Western Pacific Ocean countries since January 2003 . Of these cases, 134 were fatal, representing a case fatality rate (CFR) of 56%. The last case was reported in Laos PDR from October 13, 2020 (one case, no deaths).

From January 2003 to December 30, 2021, 863 cases of human infection with the avian influenza A(H5N1) virus were reported in 18 countries worldwide. Of these 863 cases, 456 were fatal (53% fatality rate). The last case was reported in India in July 2021 [35]

Human infection with avian influenza A(H5N6) virus – No new cases of human infection with avian influenza A(H5N6) virus were reported to WHO in the Western Pacific region between 24 and 30 December 2021. To date, a total of 58 laboratory-confirmed cases of human infection with influenza A(H5N6) virus have been reported to WHO in the Western Pacific Region since 2014, of which 27 death. The last case was reported in China from December 3, 2021. [36]

Public health risk assessment of human infection with avian influenza A(H5) viruses – Whenever avian influenza viruses circulate in poultry, there is a risk of sporadic infection and small clusters of human cases due to exposure to infected poultry or contaminated environments. Therefore, sporadic human cases are not unexpected.[37]

Human infection with avian influenza A(H7N4) virus in China – No new cases of human infection with avian influenza A(H7N4) virus have been reported to WHO in the Western Pacific region between 24 and 30 December 2021. To date, only one laboratory-confirmed case of human infection with influenza A(H7N4) virus has been reported to WHO. This case was reported by China on February 14, 2018 [38]

The total number of 1,568 human laboratory confirmed avian influenza A (H7N9) infections, including 616 fatal cases (CFR: 39%) have been reported to WHO since early 2013. The latest case of human avian influenza A (H7N9) infection reported to WHO in the Western Pacific on February 14, 2017. [39]

Human Avian Influenza A (H10N3) Virus Infection - No new cases of human Avian Influenza A (H10N3) virus infection have been reported to WHO in the Western Pacific between

December 24 and December 30, 2021. To date , one case of avian influenza A (H10N3) virus

has been reported worldwide. [40]

REVIEW OF LITERATURE

In a study by Andrew M. Ramey et.al (2022)

Wild waterfowl, including waterfowl, shorebirds, gulls, and seabirds, are the primary or original reservoir hosts for the greatest genetic and antigenic diversity of influenza A viruses (Olsen et al. 2006, Lang et al. 2016). Influenza A viruses retained in wild birds are generally not associated with disease in these hosts; However, diseases sometimes occur when viruses from wild birds spread to other vertebrate species. For example, influenza outbreaks in wild harbor seals (Phoca vitulina) and farmed mink have been attributed to viruses derived from wild birds (Hinshaw et al. 1984, Klingeborn et al. 1985, Berg et al. 1990,

In rare cases, the viruses are again transmitted between species, this time from domestic poultry to humans, where they can cause clinical disease (Lam et al. 2013)

In the spring of 1996, domestic geese in Guangdong, China were affected by HPAI, associated with hemorrhagic and neurological diseases and a mortality rate of over 40%. The causative agent has been identified as an HPAI viral strain designated A / goose / Guangdong / 1/1996 (H5N1) (Wan 2012). In 1997, the viral progeny of A / goose / Guangdong / 1/1996 (H5N1) was identified in domestic chickens during HPAI outbreaks in Hong Kong and in 18 human patients, 6 of whom died (Guo et al. 1998 , Xu et al. 1999, Sims et al. 2003). From 2010 to 2013, sporadic Gs/GD-HPAI virus outbreaks continued to affect wild and domestic birds in Asia and Europe (Marchenko et al. 2011, Marinova-Petkova et al. 2012, Sakoda et al. 2012, Luo et al. 2018). During this period, a specific viral line of HPAI Gs / GD viruses emerged,

In a study by Irfan Irshad et.al (2020)

Analyzed virulent strains of AAvV-1 and low pathogenic avian influenza virus H9N2 currently endemic to Pakistan and repeated outbreaks with high mortality are continuously reported in poultry and non-poultry avian species. In this study, five AAvV-1 were pathotyped and genetically characterized from vaccinated birds collected between 201314. A phylogenetic analysis revealed that all isolates belonged to the VIIi subgenotype with a high similarity of 97.9 to 99.8% with similar viruses in this clade.

Analysis of hemagglutin in the gene sequences (HA) of the two AIVs was performed, and the phylogenetic analysis reveals genetically closely related H9N2 viruses classified in Middle Eastern group B and underlines B2. The two strains were classified as LPAIV in poultry based on the amino acid sequence at the proteolytic cleavage site of the HA gene with PAKSSR / G. Our results highlight the potential risk of ND and AI in poultry and ongoing active surveillance is required to control transmission of these viruses. [41]

Motamed N. et al., (2020)

Studied for avian influenza virus (AI) infections (subtypes H9N2 and H5) in birds due to great concern around the world. Most bird species, such as domestic, domestic and wild birds, are natural and experimental hosts of avian influenza viruses. There are worldwide concerns about members of the Columbidae family, namely pigeons or doves, due to their role as potential bridge species in the ecology of influenza A viruses. Scientific data obtained on this is not yet clear. as there are doubts about the transmission or not of viruses between susceptible populations and about the spread of viruses between companies during outbreaks. To monitor the infection status of the H5 and H9 influenza virus in rural, backyard and pet birds, an annual active surveillance program was conducted from September to October 2016. In December 2016,

an outbreak of highly pathogenic avian influenza virus (HPAI) subtype H5N8 was detected on a laying hen farm in Iran's Tehran province. Current research was conducted to study H9N2 or H5 infections in pigeons within the 2016 HPAI H5N8 outbreaks and annual national surveillance of AI in Iran. For this purpose, cloacal swabs and tissue samples (trachea, lung, brain, liver, heart, pancreas, and caecal tonsil) were collected and examined by the real-time reverse transcription polymerase chain reaction (RT-PCR) method.) and virus isolation. The results of tests performed on the swab and tissue samples were not negative for either H5 or H9N2 viruses. Real-time RT-PCR samples that still showed negative results in HA and molecular tests after three passes were considered negative. In addition, Newcastle disease virus has been isolated in most samples from dead pigeons after inoculation into encased chicken eggs. [42]

In a study of Belewu KY (2019)

The distribution and conservation of AIV in wild birds is important for understanding the factors contributing to the transmission of AIV from wild birds to poultry. This study looked at the impact of bird flu on chicken and egg consumption among employees of Ilorin University, Ilorin, Kwara state, Nigeria. A study was conducted by interviewing 110 employees of the University of Ilorin. Information was collected on the same economic characteristics of the interviewees, income and consumption of hens and eggs. The data were analyzed using descriptive statistics.

The results showed that the outbreaks and spread of avian flu in Nigeria pose a serious threat to the poultry industry, food security and livelihoods of urban communities. It was also noted that consumer confidence in poultry products (e.g. chicken and eggs) has decreased, as indicated by the respondents. People's perception of the bird flu pandemic accounts for 90% of respondents considered it a fatal, incurable and easily transmitted disease and therefore 77.27%

of the families in the sample stopped or drastically reduced the consumption of poultry products for fear of being infected by the disease.

The study concludes that since most people consider bird flu to be a deadly disease, the government is taking steps to prevent the spread of the virus, reduce the risk of infection, and ban the transport of poultry to the bird flu area.[43]

In a study by Sukanta Chowdhury et.al (2019)

Highly pathogenic avian influenza (HPAI) H5N1 has caused a large number of outbreaks in poultry in Asia, Europe and Africa [44].Chickens are susceptible to HPAI (H5N1), with high morbidity and a mortality rate of up to 100% [45]. Wild birds, including shorebirds, seagulls, and mallard ducks, are considered to be the natural reservoir for the virus. These animals can carry and shed HPAI viruses without showing signs of disease [46] Thus, they become silent vectors that maintain and perpetuate H5N1 and transmit the virus to other susceptible hosts.

In this study, we used data on H5N1 outbreaks between January 2006 and June 2019. We also collected molecular data on avian influenza viruses from published articles and abstracts. All reviewed articles and abstracts were published between January 1, 2006 and June 2019. We identified a total of 50 articles and abstracts for our review that were relevant to our research interest.

A total of 46 H5N1 virus isolates from Afghanistan, Bangladesh, Bhutan, India and Nepal were selected for phylogenetic analysis. The nucleotide sequences of the HA (hemagglutinin) gene of these selected H5N1 isolates were downloaded from GenBank. The HA gene sequences of the selected isolates were subjected to ClustalW multiple sequence alignment using the BioEdit 7.2 program [47].A phylogenetic tree was constructed with Kimura's 2-parameter model and neighbor joining methods (with 1000 bootstrap replicates) using MEGA 7 [48].

Of the eight countries in South Asia, six reported HPAI in poultry and wild birds during the

period of interest. To date, the Maldives and Sri Lanka have not reported any outbreaks of H5N1. Between January 2006 and June 2019, a total of 1063 H5N1 outbreaks from countries in South Asia were reported to the OIE (Figures 1 and 2). Bangladesh reported the highest number (n=561) of H5N1 outbreaks in poultry and wild birds from January 2006 to June 2019. Afghanistan, India and Pakistan reported outbreaks for the first time of H5N1 in 2006. Bangladesh reported its first outbreak in 2007, followed by Nepal in 2009 and Bhutan in 2010. Of all reported H5N1 outbreaks, 97% were reported in domestic poultry. Commercial poultry was three times more likely to be infected with H5N1 than backyard poultry (RR 3.47, 95% CI: 2.99-4.01)

In a study of Asmaa A Hussien (2017)

The spread of avian influenza A (H5N1) and swine influenza A (H1N1) infections in Egypt has increased exposure to a re-emerging virus that may increase human infection rates because it is unknown to the human immune system. This study was conducted from 2010 to 2016 to detect influenza virus in Assist Governorate among respiratory patients admitted to Assist Teaching Hospital by using real-time PCR (rRT-PCR) and to reveal factors associated with infection.

Four (5.8%) and 19 (27.5%) of 69 patients were infected with the H5N1 and H1N1 subtypes, respectively. Influenza virus activity increased in cold weather, leading to increased rates of influenza infection in poultry and humans. The clinical outcome in terms of patient recovery was also improved by early detection and treatment of viral infection. In addition, people who come into contact with poultry, patients with chronic diseases and people who come into contact with infected patients are of great importance for infection A (H5N1) and A (H1N1). Strict implementation of control measures to eradicate infection in both poultry and humans is essential to reduce the risk of zoonotic transmission and human infection from influenza diseases [49]

In a study by Fred Wabwire-Mangen et.al (2016)

In Uganda, influenza surveillance was conducted from October 2008 to December 2014 to identify and understand the epidemiology of circulating influenza strains in outpatients with influenza-like illnesses and to inform control strategies. In consultation with the Uganda Ministry of Health, sentinel stations in hospitals were selected through targeted sampling based on the following criteria: rural and urban environments, along trade routes, important landing sites for migratory birds and markets for birds alive. Five government hospitals, namely Mulago National Referral Hospital, Jinja and Gulu Regional Referral Hospitals, Kayunga and Bugiri District Hospitals, have been identified for influenza surveillance activities. The five locations selected are located in the three main geographic distributions of the country, namely central Uganda (Mulago and Kayunga), eastern (Jinja and Bugiri) and northern (Gulu). Samples were selected and subtyped using real-time reverse transcription polymerase chain reaction (RT-PCR) as previously described by Byarugaba et al. (2011) [50]. Aliquots of PCR positive samples were inoculated into Madin-Darby canine kidney (MDCK) cell lines for virus isolation and culture and further confirmed by immunofluorescence and PCR assays as well as haemagglutination (HA) and inhibition of blood tests. hemagglutination (HAI). Virus isolates were typed using RT-PCR for hemagglutination genes and hemagglutination inhibition (HAI) using guinea pig red blood cells, in accordance with CDC protocols and WHO recommendations. A detailed description of the influenza screening processes for influenza A and B viruses can be found in Byarugaba. et al. (2011) and Byarugaba. et al. (2013) respectively [51]

In a study of Vladimir Savic (2015)

Studied the three types of influenza viruses: A, B and C; and the latter two mainly concern human health. In contrast, influenza A viruses have been isolated from a variety of birds and mammals, despite natural ones the hosts of the virus are wild water birds, gulls and related

birds. Other species infected with the influenza A virus, particularly chickens, turkeys, pigs, horses and humans, are considered aberrant hosts.

Most influenza A viruses are fully adapted to natural hosts where they mainly reproduce in the gut and the infection causes no symptoms. Influenza A viruses in their natural hosts are in evolutionary stasis. On the other hand, infection in aberrant hosts usually results in rapid evolution due to the selective pressure driven by the adaptation of the virus to a new host. This rapid evolution can result in high virulence for the new host and sometimes for other species as well.

The emergence of highly virulent influenza A viruses is of particular concern to the poultry industry, as these viruses cause up to 100% mortality in chickens and turkeys. Few influenza viruses are well adapted and have established themselves in mammalian hosts, mainly causing respiratory diseases such as swine flu, equine flu and human flu. Pigs, as aberrant hosts, play an important role in the ecology and epidemiology of influenza A viruses, as this species is susceptible to virus infections of wild birds, domestic poultry and mammals. Such a universal host can act as a container for mixing the genetic material of different viruses, resulting in new influenza A viruses with unpredictable characteristics. [52]

1996-2003: emergence of HPAIV H5N1

The first HPAI H5N1 outbreak is believed to have occurred in 1996 on a commercial goose farm in Guangdong Province, China [Chen et al. 2004; Xu et al 1999; Alessandro 2007a]. This strain was probably introduced from wild birds as an LPAI virus and has undergone a subsequent mutation (Vijaykrishna et al. 2008). The resulting HPAIV was the first in a line that generated multiple genetic reassortments and is the precursor to all subsequent H5N1 HPAIVs. An H5N1 variant caused an outbreak on a farm in Hong Kong in April 1997, also showed potential for human infection, and brought the potential significance of this strain to public attention for the first time (de Jong et 1997; Subbarao et al 1998).

The same virus reappeared in Hong Kong in December 1997 and was found to be wide-spread in live bird markets (LBM) (Shortridge 1999), where it may have circulated for several months without effective surveillance (Guan et al. 2009) . The first outbreaks in Hong Kong were controlled by slaughtering all of the island's poultry, although further outbreaks were reported in 2001 and 2002 (Sims et al. 2003a, b).

From 1999 to 2003, multiple H5N1 virus genotypes were isolated from domestic waterfowl in southern China and from birds imported from China to Hong Kong for slaughter (Chen et al. 2004; Sims et al. 2003a, b; Cauthen). et al. 2000; Guan et al. 2002; Lee et al. 2004; Martijn et al. 2006; Wang et al. 2008a). H5N1 viruses have also been isolated from duck meat imported from China to South Korea (Tumpey et al. 2002) and Japan (Mase et al. 2005).

In Vietnam, two LBMs in Hanoi were tacitly infected with the H5N1 virus in 2001 (Nguyen et al. 2005). In addition, two human cases were reported in Hong Kong in 2003 by a family who had recently traveled to China (Piris et al. 2004). These results suggest that the H5N1 viruses spread after their emergence in southern China (Sims et al. 2003a; Guan et al. 2002; Martin et al. 2006; Duan et al. 2008).

Furthermore, the large genetic variation of the isolates suggests that the AI virus pool in the region is large and that a large number of H5N1 genotypes have emerged in a relatively short period of time. Southern China, and in particular Guangdong Province (Wallace et al. 2007), therefore appears to be the main source of emergence of HPAIV H5N1, which then spread both regionally and internationally (Wallace et al. . 2007; Che et al. 2006).

Among multiple reassortants, genotype Z has become the dominant genotype since 2002 (Li et al. 2004; Duan et al. 2008). This virus, first discovered in Guangxi, China, in 2001 (Guan et al. 2009), is more virulent than its predecessors and infects a wider range of species (Eagles et al. 2009).

2003: Major outbreaks in Southeast Asia

From November 2003 to February 2004, eight countries (Vietnam, Thailand, Indonesia, South Korea, Japan, Cambodia, Laos and China) reported outbreaks of HPAI H5N1 to the OIE (Li et al. 2004). However, it is very likely that the virus circulated in many of these countries, including Vietnam and Indonesia, several months before official reporting (Vijaykrishna et al. 2008). Thailand and Vietnam were particularly affected, with the infection spreading to most provinces by the end of January 2004. A second wave of outbreaks began in June 2004 and culminated in Thailand in late 2004 and Vietnam. early 2005 (Guan et al. 2009). Malaysia reported its first cases in August 2004 but later eradicated the disease through mass culling (Martin et al. 2006). The viruses circulating in Vietnam, Thailand, Malaysia, Cambodia and Laos at the time belonged to group 1 and were descended from viruses previously identified in Yunnan province, China. In contrast, the viruses circulating in Indonesia belonged to clade 2.1, believed to have originated in Hunan Province, China (Guan et al. 2009; Wang et al. 2008b). China therefore seems to have been the epicenter of the spread of the disease, with the countries of Indochina acting as sinks (Wallace et al. 2007). However, within this countries, geographic diversity was already emerging with viruses circulating in northern Vietnam more closely related to those in Thailand and viruses in the Mekong region related to those in Cambodia (Smith et al. 2006a)

2005-2006: Western virus spread The deaths of more than 6,000 wild birds from HPAIV H5N1 in May 2005 in Qinghai Lake in western China raised fears of increased spread of the virus through bird migration (Liu et al. 2005; Chen et al. al. 2005). This was the first appearance of the 2.2 H5N1 clade variant, whose lineage spread rapidly from China to Europe, Africa and the Middle East (Guan et al. 2009). Shortly after the virus was first detected in wild birds in China, infection was found in wild birds in Mongolia (Gilbert et al. 2006a).

In July 2005, several outbreaks were reported across Siberia (Feare 2007) and wild bird deaths were recorded around the Caspian and Black Seas from October. HPAI H5N1 outbreaks in

poultry were subsequently reported in Crimea (Feare 2007). Although HPAI H5N1 viruses had been detected in Europe before 2006, previous cases were rare and isolated (Van Borm et al. 2005; Alexander 2007b). As of February 2006, dead birds, mainly mute swans, were found in several countries, including Austria, Croatia, Denmark, France, Germany, Greece, Scotland, Sweden and Switzerland. Outbreaks in domestic poultry have also been detected in some of these countries, but have generally been controlled quickly and transmission between sites has been limited (Brown 2010).

Although the disease has spread only to a limited extent in Europe, the clade 2.2 variant has also spread among domestic poultry populations in the Middle East, particularly Iran, Azerbaijan, Afghanistan, Pakistan, as well as Africa (Feare 2007; Brown 2010) and first hit Nigeria in January 2006 (Cattoli et al. 2009), and shortly after Egypt, Niger, Cameroon, Burkina Faso, Sudan, Ivory Coast and Djibouti. From February to December 2006, a total of 1,024 outbreaks were reported in Egypt, both in commercial groups and in backyard herds (Aly et al. 2008). The disease further spread to Africa in 2007, with Ghana, Togo and Benin all reporting outbreaks (Cattoli et al. 2009). Phylogenetic studies suggest that there have been several independent introductions of H5N1 viruses in Europe (Salzberg et al. 2007; Gall-Recule et al. 2008; Starick et al. 2008) and in Africa (Ducatez et al. 2006, 2007; Fasina et al. al. .already. 2009). However, all viruses are closely related and viruses circulating in Russia in 2005 have been proposed as presumed precursors of this Euro-African lineage (Cattoli et al. 2009; Ducatez et al. 2007)

From 2007: virus maintenance and genetic diversification

Although outbreaks are now reported less frequently than the first outbreaks in 2003-2006, HPAI H5N1 has become endemic in several regions of Asia and Africa. LBM surveys in southern China from January 2004 to June 2006 (Chen et al. 2006; Smit et al. 2006a) and

from 2007 to 2009 (Jiang et al. 2010) showed that H5N1 viruses continue to circulate in a variety of poultry species. In this period, a new variant also emerged: the Fujian-like variant (clade 2.3.4), related to genotype V. Since 2005, this variant has gradually replaced the formerly dominant leader in China (Duan et al. 2008; Smith et al. 2006a; Read para. 2010a), and in North Vietnam (Wan et al. 2008; Dung Nguyen et al. 2008), where the disease also appears to be endemic. This variant has also been detected in Laos, Malaysia and Thailand (Smith et al. 2006a; Saito et al. 2008). In addition to 2.3.4, several clades continue to circulate in China, including clade 7 and clade 2.3.2 (Jiang et al. 2010). Clade 7 has also been introduced in Myanmar (Saito et al. 2008) and North Vietnam (Nguyen et al. 2009). Furthermore, clade 2.3.2 has been isolated in many other Asian countries and in Europe, in both poultry and wild birds, following a new wave of transcontinental distribution from Asia to Europe (Jiang et al. 2010; Boltz et al. 2010; Kim et al. 2010).

Since 2001, nine different genotypes have been discovered in Vietnam, of which at least four seem to originate in the country, others have been introduced (Wan et al. 2008). New variants in Vietnam appear to have been discovered first in northern regions and then spread south (Wan et al. 2008), although clade 1 is still found in southern Vietnam (Wan et al. 2008; Dung Nguyen et al. 2008). In Indonesia, the disease has been officially declared endemic since 2006 (OIE 2010a) and outbreaks in poultry are frequent, especially in the islands of Java, Bali, Sulawesi and Sumatra (Henning et al. 2010). Clade 2.1 is still the predominant variant in that country (Eagles et al. 2009), although new reassortments with different transmission and evolution dynamics seem to continually emerge in Java, the main endemic focus, and then spread to other regions. to the. 2008, Takano et al. 2009).

Therefore, the co-circulation of multiple sublines and their continued evolution in both China and Southeast Asia has led to the generation of new variants that can spread widely in the region. It has been suggested that HPAI H5N1 is unlikely to be endemic to Cambodia or Laos

(Buchy et al. 2009; Boltz et al. 2006), where outbreaks appear to be the result of virus reintroduction from nearby endemic areas, rather than from continuing transfer. In Thailand, the disease appears to have been effectively controlled, with interventions to control the sporadic emergency. This is also the case in South Korea and Japan (Eagles et al. 2009).

The genetic diversity that exists in African virus isolates appears to be due to the prolonged circulation and evolution of viruses in a separate area rather than the reintroduction of new variants (Cattoli et al. 2009; Salzberg et al. 2007). In Nigeria, for example, the co-circulation of several sub-lines led to the emergence of new variants which gradually replaced the introduced viral strains (Owoade et al. 2008; Fusaro et al. 2010; Monne et al 2008). However, some new introductions are likely to have occurred as genotypes closely related to those circulating in Europe and the Middle East were detected in 2007 (Fusaro et al. 2009). No outbreaks have been reported in Nigeria since 2009 (OIE 2010b). The disease has been officially declared endemic in Egypt (Aly et al. 2008) and surveillance campaigns have shown a high prevalence in farms and VODs (Abdelwhab et al. 2010; Hafez et al. 2010). Several sub-lineages have established themselves, circulate in the country and continue to evolve (Arafa et al. 2010; Abdel-Moneim et al. 2009) as they have been reclassified as a new third-order clade, 2.2.1 (Balish et al. 2010).

Outbreaks have occurred regularly in Bangladesh since 2007, suggesting that the disease may now be endemic in the country (Ahmed et al. 2010; Biswas et al. 2008; ProMED-mail 2010a, b). Additionally, several waves of outbreaks have been reported in India since 2006. The viruses associated with these waves belonged to clade 2.2 and the outbreaks are considered to be the result of new introductions as interventions have been reported to mitigate successive outbreaks (Chakrabarti et al 2009, ProMED-mail 2009, 2010c, Ray et al., 2008, Mishra et al. 2009; Murugkar et al. 2008).

The first low pathogenicity H9N2 (LPAIV) and high pathogenicity H5N1 (HPAIV) avian influenza viruses in Asia were isolated in 1994 and 1996, respectively, in Guangdong Province, China [53]. Currently, H9 and H5 are the most common VIA subtypes and can be found in most parts of China. Interestingly, VIA H9N2 and H5N1 are prevalent in unvaccinated and vaccinated poultry flocks, often causing sporadic outbreaks [54]. Besides the high prevalence of VIA H9 and H5 in poultry, new VIA are also emerging in China. In March 2013, a new H7N9 LPAIV appeared in the Yangtze River Delta region and quickly spread to more than 18 provinces and municipalities. As of April 2015, at least 630 laboratory-confirmed human H7N9 infections (CFR >30%) have been documented in China. In December 2013, a new LPAIV H10N8 appeared in Jiangxi province, China, resulting in 3 human infections and 2 deaths. Unlike the H5N1 strains, the H7N9 and H10N8 strains are classified as LPAIV. Therefore, poultry show few symptoms of H7N9 and H10N8 infection, but these viruses retain the ability to cause severe disease in humans. A high prevalence of AIV H9 and H5 can be found in poultry species regardless of location, but viruses H7 and H10 are rarely detected in poultry farms and appear to be particularly amplified in birds in live poultry markets (LPM) [55]. New strains of HPAIV H5N1, H5N2, H5N6 and H5N8 have been found in China since 2000, and the overall prevalence of H5 viruses appears to have increased since 2010.

H5N6 and H5N8 AIVs have been more common among Chinese water birds in recent years; However, H5N6 AIVs caused several outbreaks in chickens in China, Vietnam and Laos in 2014 and 2015. H5N8 AIVs caused outbreaks in poultry in several countries in Asia, Europe and North America. Variants H5N1 and H5N2 have also been isolated from chickens and waterfowl, and H5N2 AIV was the cause of a chicken outbreak in Hebei Province, China in December 2013, and is currently a major problem in the United States

The first human disease caused by H5N1 was reported in Hong Kong in 1997, with 18 cases and six deaths [56].The source of human infection was found to be live poultry markets where

chickens, ducks, geese and other types of minor poultry (e.g. quail, pheasant, chukka, pigeons, etc.) were sold for human consumption. In February 2003, as the world prepared for severe acute respiratory syndrome, H5N1 was diagnosed in Hong Kong in a father and son who had just returned from a vacation in Fujian Province, the People's Republic of China. [57] . These two patients were infected with a virus of genotype Z, except that it had no deletion in the stem region of the NA (called genotype Z). This virus had an amino acid substitution at position 227 (numbering H3) in the HA receptor binding pocket which altered its receptor binding profile to recognize both avian and human SA-2,3 receptors. 2.6. By itself, however, this did not appear to alter human-to-human transmission capacity. In retrospect, another case of H5N1 occurred in Beijing, People's Republic of China, in November 2003. Subsequently, with the increasing spread of the H5N1 disease in poultry, further human cases have been reported in Vietnam, Thailand, Cambodia, Indonesia and somewhere else. In a number of cases, the detection of a human case in a region was the first indication of the presence of poultry contamination in that locality. Taken together, human cases appear to increase in the winter and spring months. This correlates with the seasonality observed in virus detection in poultry. [58] Since the HPAI H5N1 virus in poultry is associated with the presence of infectious viruses in many organs, as well as with the secretion of large amounts of the virus in poultry feces and other secretions, sick poultry is a major source of human infection. Most human cases of H5N1 infection have been associated with direct handling of infected poultry, slaughtering or preparing sick poultry for consumption, consumption of uncooked poultry products such as raw blood, or in close contact with poultry I live. As H5N1 infection is not always clearly symptomatic, especially in ducks, even asymptomatic poultry can pose a risk of infection, for example in wet markets, in areas with endemic properties. Contact with a contaminated environment, such as water and poultry feces used as fertilizer or fish feed, is believed to be a source of infection in cases of H5N1 in humans who have not had direct exposure to poultry.

In bird-to-human transmission, the probable entry of the virus is via the respiratory tract, gastrointestinal tract or conjunctiva. Cats experimentally infected with the H5N1 virus after eating infected chickens showed evidence of viral replication in the gastrointestinal plexuses. However, this is not seen in people infected through the respiratory tract. In humans, the possibility of intestinal infection is supported by reports of patients with H5N1 infection showing diarrhea as their only first symptom, as well as by patients reporting consumption of raw duck blood as the only exposure to poultry. Additionally, the presence of infectious viruses in fecal material may indicate replication of the virus in the human gastrointestinal tract. [59]

There are a number of puzzles regarding human H5N1 infection and disease. Despite large-scale H5N1 virus outbreaks among poultry in densely populated areas and allegedly massive human exposure to the virus, the number of H5N1 patients reported to date has been relatively small. In Hong Kong in 1997, with excellent surveillance of the symptomatic influenza virus, there were still only a small number of cases despite the extraordinarily heavy viral load on the poultry retail markets, where 20% of poultry were infected. Sero-epidemiological studies following the 1997 H5N1 outbreak in Hong Kong showed that mild or asymptomatic infections had occurred in some individuals exposed to infected patients or poultry.

Similar studies in individuals at risk of H5N1 exposure during recent H5N1 outbreaks revealed little or no evidence of human-to-human transmission in unprotected healthcare workers exposed to H5N1 patients. Similarly, villagers, poultry workers and poultry slaughterers in Vietnam, Thailand, Indonesia and Cambodia who are heavily exposed to infected poultry rarely have clinical or asymptomatic (serological) evidence of infection.

In contrast, about 10% of poultry farms in Hong Kong in 1997 had serological evidence of H5N1 infection without presenting as overt H5N1 disease, although it is unclear whether sero-positivity was a recent HPAI H5N1 virus infection or a previous infection. by LPAI H5 the subtype represented viruses known to be present in ducks. Although more serosurveillance data

are needed to address the possibility that the number of true cases may be underestimated, observations to date suggest inefficient transmission of current H5N1 viruses from infected poultry to humans. Therefore, the question is not why people get H5N1 disease, but why so many people with high exposure to the virus in areas where the virus is endemic are not symptomatically or asymptomatically infected with a virus that is infected appears to be ubiquitous. Conversely, while the cases affected in Hong Kong in 1997 had significantly more exposure to live poultry markets, around 30% of them had no obvious source of infection. Similar observations have been made elsewhere.[60].

There are a significant number of familial clusters among human cases of H5N1. It is difficult to determine whether these clusters represent infection from a common environmental source or from limited human-to-human transmission. Excluding a common source of infection is epidemiologically extremely difficult, and only unusual circumstances allow definitive proof. The lower incidence and mortality rates of H5N1 in people over 40 remain unexplained. Overall, it appears that while exposure to a source of H5N1 infection is necessary, such exposure alone is insufficient to explain the observed epidemiology of H5N1 disease. Other yet undetermined factors appear to be crucial in determining who gets infected and gets sick. Among other possibilities, the role of host genetic susceptibility factors and hitherto unrecognized host resistance mechanisms deserve investigation [61]

AIM AND OBJECTIVES

AIM-The aim of this study is to analyze the epidemiology and source of avian influenza virus in humans

OBJECTIVES- To perform a systematic review of English language articles found via pubmed, google scholar taking into consideration of following question

1.What are the risk factors which contribute significantly in avian influenza virus

2.What are the preventive measure to decrease the incidence of avian influenza virus

<u>METHODOLGY</u>

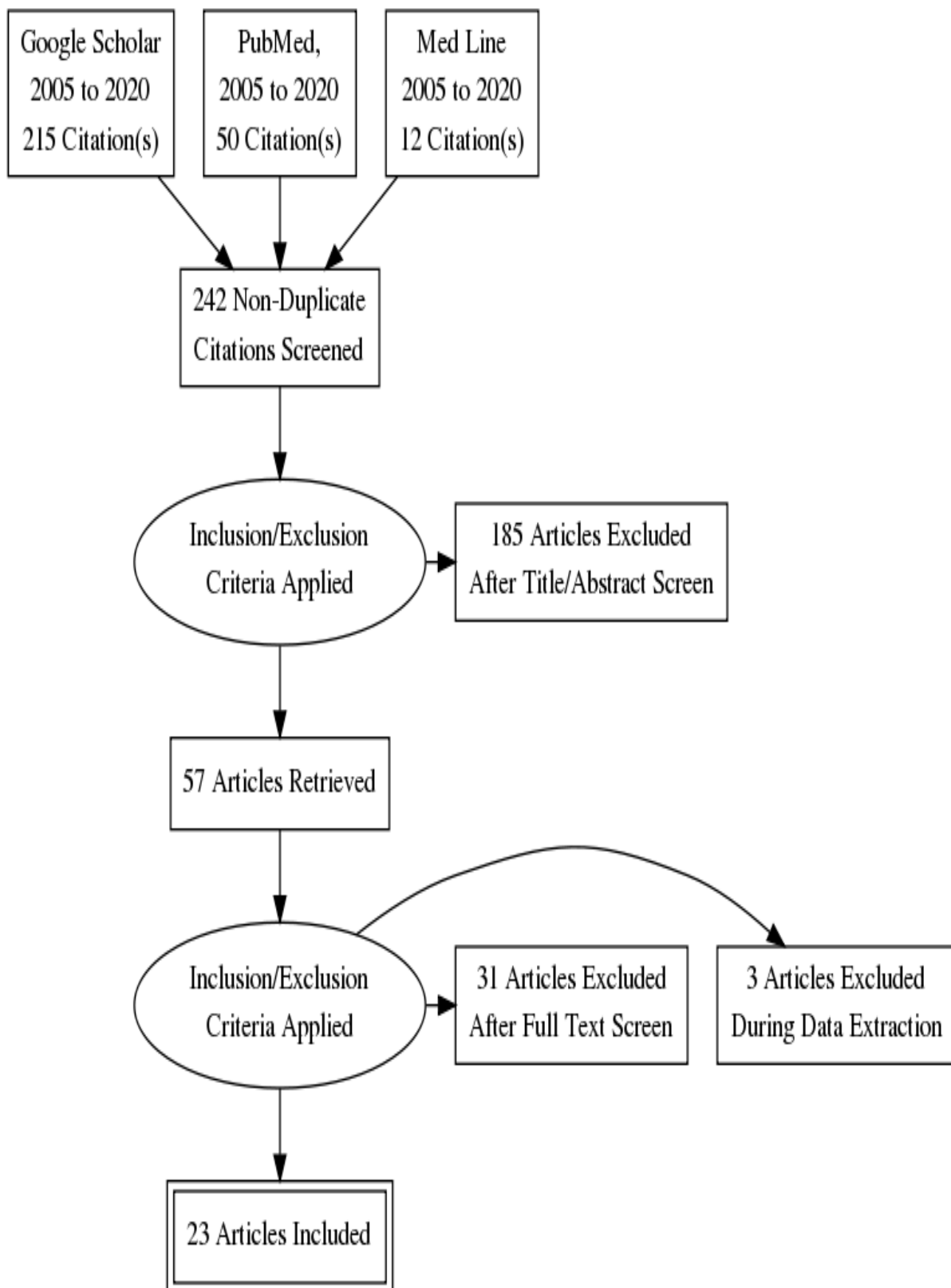**RESEARCH OF DESIGN-Qualitative and Quantitative**

DATA TYPE-Secondary mode of data collection

    a) **Data from various journals**

    b) **Data from books**

    c) **Data from various literature reviews**

RESEARCH TOOL-Secondary data from published report of article

TIME FRAME-All the study in indexed journel from January 2003 to 11 november 2021

RESEARCH ENGINE- Pubmed, google scholar

Google Scholar
2005 to 2020
215 Citation(s)

PubMed,
2005 to 2020
50 Citation(s)

Med Line
2005 to 2020
12 Citation(s)

242 Non-Duplicate
Citations Screened

Inclusion/Exclusion
Criteria Applied

185 Articles Excluded
After Title/Abstract Screen

57 Articles Retrieved

Inclusion/Exclusion
Criteria Applied

31 Articles Excluded
After Full Text Screen

3 Articles Excluded
During Data Extraction

23 Articles Included

OBSERVATIONS

AND RESULTS

S.NO.	AUTHOR	YEAR	PLACE	FINDING
1.	Andrew M.Ramey et.al	2022	North Amer-ica	the detection, investigation, and mitiga-tion of emerging viruses at the human-do-mestic animal-wildlife interface. viruses develop the propensity to cause mortality in chickens as assessed through a stand-ardized pathogenicity index involving ex-perimentally inoculated 6-week-old spe-cific pathogen-free chicken
2.	Irfan Irshad et.al	2020	Pakistan	Virulent strains of AAvV-1s and low-pathogenic H9N2 avian influenza viruses are presently endemic. reported with high mortality in poultry and non-poultry avian species. highlight the potential risk of ND and AI in poultry and continued active surveillance is needed to monitor the transmission of these viruses.
3.	Motamed N et. al	2020	Iran	the tests performed on the swab and tis-sue samples were negative for neither H5 nor H9N2 viruses. The samples in real-time RT-PCR that after three passages still showed negative results in HA and molecular tests were considered negative-Newcastle disease virus was isolated in most of the samples taken from dead pi-geons, after inoculation in embrocated chicken eggs. Belewu K.Y. (2019) was taken the dissemination and maintenance of AIV in wild birds is import
4.	Belewu K.Y et.al	2019	Nigeria	It revealed that avian flu outbreaks and spread in Nigeria have caused serious

				threat to the poultry industry, the food security and livelihoods of urban communities. most of people perceived avian influenza as deadly disease, government enact measures to prevent the virus from spreading and to reduce the risk of infection
5.	Sukanta Chowdhury et.al	2019	South Asia	the reported H5N1 outbreaks, 97% were reported in domestic poultry. Commercial poultry were three times more likely to be infected with H5N1 than backyard poultry (RR 3.47, 95% CI: 2.99–4.01)
6.	Asmaa A Hussien	2017	Tamil Nadu	detect influenza viruses in Assist Governorate among respiratory patients admitted to the Assist University hospital using Real time PCR (rRT-PCR), as well as exhibit the factors associated with infection. Four (5.8 %) and 19 (27.5 %) out of 69 patients were infected with H5N1 and H1N1 subtypes respectively. Influenza virus activity was increased in cold weather resulted in increased influenza infection rate in both poultry and humans
7.	Fred Wabwire-Mangen et.al	2016	Uganda	influenza virus infection was detected in 10.4% (n = 687/6,628) of the specimens. Several trends were observed: influenza circulates throughout the year with two peaks; the major one from September to November and a minor one from March to June. The predominant strains of influenza varied over the years: . The peaks generally coincided with times of higher

				humidity, lower temperature, and higher rainfall.
8.	Vladimir Savic et.al	2015	Serbia	influenza A viruses have been isolated from a variety of birds and mammals, nevertheless the natural hosts of the virus are wild waterfowls, gulls and related birds. universal host can serve as a vessel for mixing of the genetic material of different viruses which can result in new influenza A viruses with unpredictable features.

DISCUSSION

According to the OIE(World Organization For Animal Health), a total of 7122 HPAI outbreaks were reported in domestic birds across 68 countries from January 2013 to August 2018. Asia, Africa and Europe were the regions most affected by these outbreaks. Between January 2006 and June 2019, South Asian countries reported more than one thousand H5N1 outbreaks to OIE. South Asia detected the first H5N1 outbreak in poultry in 2006, with the highest number of outbreaks in the region reported in 2008.

Though few H5N1 outbreaks were reported after 2014, circulation of H5N1 viruses continues. Findings from surveillance and other studies suggest that both HPAI and LPAI viruses continue to circulate among birds in South Asian countries

In this analysis, we found that HPAI (H5N1) outbreaks in the region occurred most frequently in the winter season (January to March), with the largest number of outbreaks occurring specifically in March. This finding is similar to the results from Southeast Asian countries where H5N1 outbreaks were frequently detected during winter in poultry.

HPAI (H5N1) outbreaks globally showed a clear seasonal pattern in poultry, humans and wild birds; most human cases (50%) were reported during January to March. This seasonality could be due to the lower ambient temperature (average minimum temperature 13.9 ∘C). Lower temperatures are suitable for the survival of avian influenza viruses. Avian influenza viruses persist in cold water for a long time and this may be associated with a higher chance of transmission. One study suggested that lower ambient temperatures may cause decreased immunity in poultry and thus make the birds more susceptible to infection with the H5N1 virus.

The circulation of avian influenza viruses is also related to the migration of wild birds, particularly during the winter season, as reported by some global studies . This analysis noted that the high incidence of H5N1 outbreak in commercial poultry farms in Bangladesh, Nepal and Pakistan. India, Afghanistan and Bhutan reported more outbreaks in backyard poultry flock. This geographical diversity for H5N1 outbreaks within South Asia could be due to the variation in farm biosecurity system, proximity to the migratory bird flyway, wild bird-domestic poultry interaction, animal health infrastructure and strength of outbreak reporting system. Avian influenza viruses continue to evolve and infect a wide range of poultry species and humans. In South Asia, multiple clades of the H5N1 virus were detected in poultry from 2006 to 2019.

Conclusions

This analysis provides an overall update on HPAI (H5N1) outbreaks in South Asia. The emergence of diverse genetic clades of H5N1 viruses in poultry in South Asia indicates the continuing evolution of HPAI viruses with the potential to become of public health interest. Despite the low number of reported human cases, people in this region are highly vulnerable to HPAI viruses due to their close and frequent interaction with poultry.

Continuous monitoring is necessary to identify both existing and novel avian influenza viral strains circulating in poultry, wildlife and humans using a One Health approach. Individual country experiences on poultry production system, farm biosecurity, and outbreak reporting system may be useful to develop and design avian influenza control strategies. Strong regional collaboration and cooperation is essential for pandemic influenza preparedness planning and response in South Asia

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