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Review article

Human infection caused by the avian influenza type A virus: a comprehensive update on its pathogenesis and recommendation for future re-occurrence

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ABSTRACT

Background: The emergence and re-emergence of the avian influenza virus in humans, particularly the A (H5) sub-types, have persistently presented a substantial danger to human well-being. Interestingly, the avian influenza virus has remained important despite various studies on the mechanism of inter-species transmission. In part, this is due to the insufficient understanding of the virus' pathogenesis, the diagnostic challenges, and the limited knowledge about the virus' genetic makeup, which enables it to keep evolving. Given the devastating nature of this disease and the possibility of the virus triggering a pandemic, this review aims to evaluate the current strains of Type A (H5) avian influenza virus, to better understand the mechanism of its interactions with humans, and to address critical questions related to its epidemiology. We further explored the factors contributing to the severity of the infection, which may improve the diagnosis and therapeutic options employed in the treatment of this disease.

Introduction

Human infection caused by avian influenza viruses, commonly known as "bird flu," is a transmissible respiratory disease that impacts individuals worldwide, regardless of age. This virus is classified into different types, of which Type A is highly pathogenic and is broadly discussed in this text. It predominately infects individuals with low immune defenses or chronic disease challenges and can trigger seasonal flu surges and occasional pandemics. Birds, especially those that inhabit aquatic environments, like geese, ducks, shorebirds, and gulls, are the primary carriers of Influenza Type A virus (IAV)[1]. Although it is commonly

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recognized as the “bird flu”, it adapts to humans via person-to-person transmission [2]. Type A (H5) is one of the predominantly recognized subtypes that can stimulate human infection, specifically the H5N1 strain. However, the risk factors, prevention, and control strategies of the virus, as well as the minimization of its effects on public health, animal welfare, and the worldwide poultry industry, are not fully explored in the existing works of literature. By offering a timely and thorough analysis, this study intends to close these gaps, making it easier to design evidence-based policies for efficient surveillance, prevention, readiness, and response to lessen the spread and effects of the virus. Ultimately, this review study aims to evaluate the current strains of the Type A (H5) avian influenza virus, to better understand the mechanism of its interactions with humans, and to address critical questions related to its epidemiology and associated risk factors. Furthermore, this study explored the factors that contribute to the severity of the infection, which may improve the diagnosis and therapeutic options employed in the treatment of this zoonotic disease.

Subtypes of the influenza type A virus

A (H5N1)

This strain is a potential pandemic hazard for influenza because of its high lethality and virulence, endemic presence, and major continuing mutations [2].

A (H5N2)

Influenza caused by this strain is relatively mild in comparison to other subtypes, which poses no obvious health issues to humans if infected.

A (H5N6)

Instances of humans being infected with this particular strain are rare; nonetheless, humans can be infected via direct exposure to infected birds, and the entry is usually through the eyes, nose, mouth, or even inhalation of the viral particle.

A (H5N8)

This strain has been reported to be highly fatal to poultry, but instances of human infections with this strain are relatively low, as its initial occurrence was documented in Russia in the year 2021 [3].

Influenza type A genetic makeup

The Orthomyxoviridae family includes the enveloped pleomorphic influenza A virus [4]. The viral strains contain helical capsids around their genomes; these structures enable them to assume diverse forms, spanning from small spheres to elongated filaments [5]. The virus particle incorporates a lipid enclosure that is attained from the membrane of the host cell during the viral process of forming buds, and the genetic material comprises eight segments of RNA, each single-stranded and possessing a negative sense [5]. Its envelope consists of three proteins known as neuraminidase (NA), hemagglutinin (HA), and matrix (M2). Among these, hemagglutinin and neuraminidase (HA and NA) are glycoproteins located on the surface. At present, there are 16 recognized subtypes of HA (H1–H16) and 9 recognized subtypes of NA (N1–N9) [6].

The first segment of RNA (PB2) is the genetic code that contains information for synthesizing a subunit of the viral polymerase [7]. The PB2 protein takes advantage of the host mRNA to create cap primers and exhibits endonuclease activity. By employing a mechanism called "cap snatching", these primers are "stolen" from the 5' end of cellular mRNA and are employed in the synthesis of viral mRNA [7]. The second segment, which is the RNA polymerase constituent, codes for the polymerase PB1 subunit [6]. The tiniest component among the members of the RNA polymerase complex, the protein known as polymerase acidic (PA), is encoded in the third segment [8]. Due to the essential role of PA in transcription and viral replication, the PB1 constituents can build up within the nucleus. The hemagglutinin (HA) protein is synthesized from the fourth segment of the influenza virus genome; this is the factor that triggers the attachment of viral particles to host cell receptors that contain sialic acid [9]. The hemagglutinin (HA) protein originates from the polypeptide precursor HA0, which undergoes posttranslational cleavage to produce HA1 and HA2 [9]. HA cleavage is the primary determinant of virulence and an essential requirement for the infectivity of the viral particle [10].

The fifth segment of the viral genome encodes the nucleus protein (NP), which plays a vital role in viral transcription, replication, and transportation of the viral RNA (vRNA) within the nucleus [6,11]. According to **Matrosovich et al.** [12], the sixth segment of the genome is responsible for encoding neuraminidase (NA), a glycoprotein situated on the surface. Neuraminidase (NA) functions by cleaving the alpha-quetosidic ligand between a terminal sialic acid and an adjoining D-

galactose or D-galactosamine residue, resulting in the degradation of receptors.

The seventh segment contains the genetic instructions for the production of the M1 and M2 matrix proteins. During the assembly and breakdown of influenza A virus [9], the M1 protein engages with the viral RNA, vRNA, and RNP protein constituents within the viral particle [13]. Moreover, it produces a layer to separate ribonucleoprotein (RNP) from the viral envelope. In addition to attaching to cell membranes, M1 affects viral shape [6]. A crucial transmembrane protein called M2 houses an ion channel that is necessary for pH regulation. The viral particle's interior must become acidic for the cell's denudation process to proceed [6]. M2 serves as an essential constituent in the process of viral replication and is a probable focus for therapeutic intervention [7]. Furthermore, the viral particle relies on endosomal acidification for its replication, as this triggers the separation of virus ribonucleoproteins (vRNPs) from the M1 proteins that enter the nucleus. To preserve the natural shape of the newly formed hemagglutinin (HA) molecule during intracellular transport for viral assembly, maintaining a high pH within the Golgi vesicles is essential for the proper functioning of the M2 ion channel.

In the eighth segment, NS1 and NS2 are two proteins that are encoded. The single nonstructural protein of the influenza virus is called NS1. According to some researchers, NS1 may cause an imbalance in cytokines, which is likely a factor in the severe virulence of the avian influenza virus (AIV) when transmitted to humans [14].

Previous and recent outbreaks, strains implicated, and fatality rate

The A (H5) avian influenza virus has been linked to human infection, notably in people who were exposed to infected birds. Hong Kong experienced the first human surge of A (H5) in 1997, with 18 cases and six fatalities. Poultry sold for human consumption was found to be the main source of human infection [15]. Since 1997, H5N1 has expanded its reach from Asia to Europe, Africa, and the Far East through the trading of poultry and the migration of birds. Individuals of all ages appear to be vulnerable to it. This served as a signal for a potential worldwide outbreak of the virus [15]. While re-evaluating the early cases of human outbreaks of the virus, another case of H5N1 was recorded in Beijing in 2003. Consequently, there was a notable increase in cases in different areas of the world. Between 2003 and 2023, there were 868 instances of humans infected by H5N1 across 21 different nationalities, resulting in 457 deaths [16] **(Table 1)** and **(Figure 1)**.

The detection of human cases serves as the initial indication of an outbreak among poultry. Additionally, there appears to be a rise in human cases during the winter and spring seasons, correlating with the observed pattern of virus detection in poultry during these times [15]. Two distinct clusters of human avian influenza involving H5N1 were documented in February 2006, after the outbreak of the infection in many free-ranging avifauna in Azerbaijan [17]. A concerted effort of investigation by WHO and Azerbaijan later revealed eight cases with five fatalities **(Table 1)**. In May 2008, Bangladesh recorded its first human case involving H5N1. It involved a 15-month-old child from Dhaka, whose likely source of exposure was traced back to chickens that had been slaughtered in his household. Before this case in Bangladesh, there had been confirmed reports of H5N1 outbreaks in poultry dating back to March 2007 [18]. Similarly, isolated reports of human cases (53) with 38 fatalities have been documented in Cambodia that were associated with poultry-to-human transmission **(Table 1)**.

In December 2013, there was a report of a patient in Canada who contracted the H5N1 strain of the virus. The patient returned to Vancouver from Beijing and later died in January 2014 [19]. Chile also announced its first human case caused by H5N1, involving a 53-year-old Chilean who was hospitalized with an acute ailment and was immediately put in isolation. Later, in the Antofagasta region, the patient’s place of residence, H5N1 was found in wild birds and sea lions. This was the second human case reported on the South American continent. The first case was reported in Ecuador in 2022, involving a young girl from Bolivar Province. To confirm the infection, samples from the patient were dispatched to the Ecuadorian National Institute of Public Health to undergo an RT-qPCR examination, which later confirmed the presence of H5N1.

In April 2006, Djibouti announced that a young child had been admitted to the hospital with the H5N1 strain. Egypt experienced 292 human cases involving H5N1 from 2006 to 2015, with a 34% fatality rate. By 2023, the fatality outcome in Egypt had declined to 33.4% [16]. In India, the first human case involving H5N1 was announced in July

2021. The case occurred in Haryana state, in northern India. The infected individual was a boy below the age of 18, who had been residing with a family member who owned a butcher shop. He developed symptoms in June 2021, and consequently, the infection proved fatal, leading to his death in July 2021 [20]. Similarly, in July 2005, Indonesia recorded its first human case of H5N1. Following the incident, H5N1 has persistently circulated within Indonesia [21]. Likewise, in January 2006, the initial occurrence of H5N1 in Iraq was documented by a 15-year-old who passed away following an acute respiratory disease [22].

New strains of avian influenza (H5N8 and H5N6) emerged in 2014, spreading rapidly from South Korea to China, Japan, and Russia, and across Europe to Canada and the US. Two subtypes of H5N8, Buraan 2-like, and Cochang 1-like, were identified. In December 2020, seven poultry workers were reported to have contracted the H5N8 virus [23]. Multiple outbreaks of the H5N6 subtype virus occurred in China, Vietnam, and the Lao People's Democratic Republic in April 2014 and were associated with the first non-H5N1 virus in human infection [23]. In Myanmar, the only H5N1 infection in humans (non-fatal) was recorded in the province of Shan in December 2007, when there was also an outbreak of the disease among domestic birds during the same period [24]. The only verified human instance of H5N1 in Nepal was reported in April 2019. This case involved a 21-year-old male patient who exhibited symptoms and subsequently died on March 29 of the same year [25].

Nigeria witnessed the initial emergence of human cases of H5N1 in 2006, which continued until 2007. Nigeria is the third African country, following Egypt and Djibouti, to experience a human infection with H5N1. The case involved a woman who experienced symptoms after disemboweling an infected chicken, and she consequently died in January 2007 [26]. Similarly, the epidemiological investigation into the 2007 influenza (H5N1) outbreak in Pakistan's northwest frontier province revealed a total of 5 cases, of which 3 were verified by the WHO [27]. In another case, WHO was alerted by the Spanish Ministry of Public Health to an instance of H5N1 in a person working at a fowl ranch in the province of Guadalajara, Spain, in September 2022. This might be related to the H5N1 outbreak in poultry that was discovered earlier at the farm on September 20, 2022 [28]. Thailand has recorded 25 individuals who have been confirmed to have contracted H5N1 through laboratory testing, of whom 17 resulted in fatalities. The last confirmed human case in Thailand occurred in September 2006 in a North-eastern Thai Province [24].

On December 31, 2005, Turkey reported its initial instance of human infection caused by H5N1. Two individuals from the same family living in the eastern province of Agri, near the borders of Iran and Armenia, succumbed to the infection [29]. On January 6, 2022, the United Kingdom announced the identification of a lab-verified human instance of H5N1. The individual affected lived with a considerable population of domestic birds that were infected. Although the patient remained asymptomatic, he exhibited symptoms starting in December and subsequently tested positive for H5N1 on December 24, 2021 [30]. In 2022, the CDC confirmed the only instance of human infection caused by H5N1 in the United States. The case involved an individual who had interaction with birds and was engaged in the slaughter of birds with presumed H5N1 bird flu [2]. In December 2003, the first case of H5N1 was documented in Vietnam, in the vicinity of Hanoi province. Subsequently, the virus spread to other provinces, and since then, intermittent outbreaks have frequently arisen [31].

Complications and clinical manifestations associated with A(H5) avian influenza virus in humans

The avian influenza A (H5) virus typically shows its initial symptoms within 2-4 days after last contact with infected poultry, although longer incubation periods of up to 8 days have been documented, however, it remains unclear whether the virus is shed during this time, and to what extent it is been shed. Infected patients commonly exhibit fever, cough, shortness of breath, and radiographic signs of pneumonia [28]. In fatal cases of H5N1 human infections, significant histopathological observations present extensive lung infiltrates, disseminated intravascular coagulation, and multiple organ failure. The virus primarily targets the alveolar cells in the lung, leading to various manifestations, such as diffused alveolar injury with interstitial fibrosis, the formation of hyaline membranes, patchy interstitial lymphoid infiltrates, and inflammation of bronchioles with squamous metaplasia. Additionally, the lung may experience varying degrees of pulmonary congestion and

hemorrhage [32]. Diverse complications including dyspnea may commonly be observed in 42-72 % of A (H5) infected patients, also extrapulmonary symptoms like abdominal pain, diarrhea, and vomiting may sporadically occur. Most patients develop severe pneumonia followed by Acute Respiratory Distress Syndrome (ARDS) after 4-13 days, leading to multiple organ failure and death. Moreover, lethal cases of highly pathogenic avian influenza (HPAI) H5N1 infection are associated with lymphopenia, thrombocytopenia, leukopenia, elevated Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), and Creatine Kinase (CK) levels [33]. Autopsy findings from a patient who succumbed to A (H5N1) infection revealed that highly pathogenic avian influenza (HPAI) H5N1 infection could lead to multiple organ failure, not only affecting the lungs but also causing edema, degeneration of cardiomyocytes, extensive hepatic centrilobular necrosis, and brain lesions. Furthermore, a fatal case of A (H5N1) observed in a pregnant woman revealed avian influenza viral infection in the brain, placenta, and fetus. The infection also resulted in systematic cytokine activation, leading to hemophagocytic syndrome, lymphocyte depletion, and skeletal muscle fiber necrosis [34.]

Pathogenesis of H5N1

The virus' process of pathogenesis requires several steps, and it is very contagious. Understanding its pathophysiology will therefore aid in developing a prevention and treatment plan. By inhaling respiratory droplets from an infected person, the organism enters the body. These can be caught by an infected person's speech, sneezes, coughs, or by touching their face [35]. The respiratory epithelium lining of the upper airways, which include the nose, bronchi, and throat, has been exposed to the organism through inhalation. The host respiratory epithelial cells' sialic acid receptors connect with the hemagglutinin (HA) glycoprotein on the virus surface, allowing the virus to attach to the surface and be taken inside the host cell through receptor-mediated endocytosis [14]. The eight segments of the viral genome, which is a negative-sense single-stranded RNA, are transmitted into the cytoplasm when the virus enters the host cell. The viral RNA segments are copied and multiplied by viral RNA polymerase in the nucleus of the infected cell. The newly created viral RNA segments then serve as a template for the creation of the viral proteins [14]. Later, in the host cell's cytoplasm, the neuraminidase, hemagglutinin, viral proteins, and matrix proteins are translated. The viral genome segments and proteins are subsequently put together at the cell membrane to form new viral particles [36]. A lipid envelope containing viral glycoproteins is acquired by all the formed viral particles from the host cell [11]. Since the sialic acid residue on the cell surface hinders viral aggregation, the neuraminidase will therefore make it easier for new viral particles to be released. The subsequent viral propagation within the respiratory system is caused by the discharged virions' ability to infect nearby cells [11].

Mode of transmission and spread of H5N1

H5N1's mode of transmission and spread pattern can vary based on specific conditions. Nonetheless, the following are the primary methods by which it can be passed on: direct contact with infected birds; indirect contact with surfaces that are infected with the virus; ingestion of contaminated chicken items, including poultry meat that is either undercooked or raw; and eggs from birds that have been infected with the H5N1 virus.

Environmental risk factors

In 1878, avian influenza viruses were initially documented in Italy and subsequently segregated from chickens in 1934. Studies have shown that wild migratory birds and waterfowl are frequently seen as the natural carriers of avian influenza viruses (AIVs). Through their movements, the viruses are disseminated worldwide [37]. Due to poor biosecurity in places like backyards and multi-species farming, viruses can readily pass between various hosts, primarily between various bird species or between birds and pigs, occasionally resulting in transmission from bird to human. Similarly, local live bird markets (LBMs) serve as environments where a variety of bird species, such as songbirds, minor domestic birds like quail and pheasants, as well as large domestic birds from both large-scale industry and small-scale farming across various geographic areas, have close interactions and potentially transmit viruses among each other. Moreover, if infected items such as cages, droppings, feed, and deceased animals are brought back to local farms, they can serve as breeding grounds for infections even in distant areas that are geographically separated from the live markets.1. Furthermore, unlike land-dwelling wild birds, migratory birds that are infected, such as waterfowl (Anseriformes) and shorebirds (Charadriiformes),

have a greater propensity to spread viruses over extensive distances [1].

A(H5) diagnosis and treatment

Human influenza is classified into three types, with Influenza A being the most prone to pandemics due to its heightened susceptibility to antigenic changes. According to a Barcelona study, it is challenging to clinically diagnose less than 40% of children with confirmed influenza solely based on clinical symptoms. In children aged 7-13, the sensitivity of clinical diagnosis and the positive predictive value is elevated during the peak of influenza season [38]. The RT-PCR test, which is the gold standard for diagnosing influenza, demonstrates high sensitivity and efficiency in distinguishing between different types and subtypes of influenza. Although serology testing is valuable for research and retrospective diagnosis, it is not advised for treating acute illnesses [38].

The main advantage of influenza treatment is that it shortens symptom duration by approximately 24 hours if administered within 36 hours, along with decreasing the severity of the disease. However, anti-influenza drugs do not seem to lower the risk of hospitalization or death in adults or children in the outpatient setting, as indicated by systematic reviews of both published and unpublished randomized trials. Moreover, three observational studies in hospitalized patients found a link between the use of neuraminidase (NA) inhibitors and lower mortality rates [39]. For the treatment of influenza, four antiviral drugs—Oseltamivir (Tamiflu), Zanamivir (Relenza), Peramivir (Rapivab), and Baloxavir (Xofluza) have been authorized. These medications are suitable for treating outpatients with uncomplicated influenza, given that they meet the criteria of being of appropriate age, in good health, and having no contraindications. Baloxavir and oseltamivir are specifically recommended for patients aged 12 years and older with uncomplicated influenza, as they can reduce the duration of flu symptoms by about one day [39]. However, due to their high cost, limited benefits, and side effects (most notably nausea and vomiting with oseltamivir), these medications are not usually recommended for otherwise healthy people with influenza [38,39]. To impede influenza infection, adults are advised to inhale zanamivir at a recommended dosage of 20mg/50kg/day, administered twice daily with half of the dose in each inhalation. To manage influenza in adults, the recommended dosage of oseltamivir is 75mg, taken twice a day for a duration of 5 days [40]. Oseltamivir's effectiveness diminishes when used more than 48 hours after influenza infection. For preventive purposes during a community outbreak, the usual dose is 75mg taken once a day for at least 10 days or up to 6 weeks. In contrast to zanamivir, oseltamivir is associated with a higher occurrence of adverse effects and a propensity to induce viral strains that are resistant [40].

Peramivir is administered via a single intravenous drip diffusion at a 300 mg dose over 15 minutes for influenza treatment. It serves as a highly effective inhibitor against both influenza A and B viruses, displaying favorable safety profiles [40]. Baloxavir operates in a unique mechanism, combining baloxavir and oseltamivir have demonstrated enhanced protection against lethal influenza infection, surpassing the effectiveness of either drug used alone. Surprisingly, a significantly lower dose of baloxavir, just 30 times lower than the protective dose of 15mg/kg, provided ample protection when used in conjunction with oseltamivir [41].

Recommendation against the future (H5N1) re-occurrence

Preventative measures:

The H5 strain of avian influenza has attracted considerable interest because of its capacity to induce serious diseases and fatalities in both avian and human populations. It is of utmost importance to avoid its reoccurrence and mitigate its potentially devastating consequences. Influenza viruses change and adapt primarily by acquiring genetic mutations in their genomes and exchanging genetic material with other strains [42]. This process is known as reassortment. Additionally, the resurgence of Avian Influenza A (H5) presents numerous risks and difficulties. To begin with, it can cause considerable financial setbacks within the poultry sector and also has the potential to present substantial danger and pose a significant threat to global health if ignored [43]. One effective method to prevent the future resurgence of avian Influenza A viruses is to strengthen surveillance and early warning systems. Countries must establish strong monitoring systems for both animals and humans to identify any strange patterns of illness, particularly those related to respiratory tract infections, and if any are detected, immediate testing for avian influenza virus (AIV) A (H5) is advised [42].

Additionally, it is important to steer clear of any instances where one may come into direct contact with diseased birds, their droppings, or objects that have been contaminated by birds suspected or confirmed to be infected with the avian influenza virus (AIV) A (H5). In 2022, the United States Department of Agriculture (USDA) advised that individuals responsible for flocks and those working with poultry should refrain from unprotected direct physical interaction with deceased birds and encouraged them to wear the approved PPE when in direct contact with infected poultry, then perform thorough hand washing after contact [44]. Furthermore, in the case of suspected symptoms, one might consider using influenza antiviral drugs, such as neuraminidase inhibitors or oseltamivir, as a preventive measure against infection.

Vaccination

Various nations have devised multiple approaches to managing the spread of pathogenic avian Influenza viruses. These include segregating infected birds from poultry and refraining from engaging in wet markets, and some countries, e.g., China, have adopted the use of vaccination strategies [42]. To date, authorized influenza vaccines have generated antibodies that target the virus hemagglutinin (HA) protein, which facilitates the entry of the virus into cells. Antibodies generated against the hemagglutinin (HA) strains counteract the virus and prevent infection. Administering vaccines to poultry can be an effective measure to decrease the spread of infection; nevertheless, there have been documented instances where the vaccines did not match the presently prevalent virus, as reported by **Shi et al.** in 2022 [42]. Furthermore, certain strains of the avian influenza virus (AIV) H5 virus have demonstrated resistance to the vaccines, indicating the need for formulating and employing vaccinations that align with the currently circulating virus strains [45]. Overall, enhancing the efficacy of vaccines and implementing regular monitoring measures can aid in resolving the menace of vaccine failures [37].

Figure 1. Comparison of the total number of cases and fatality rate for each country from 2003-2023, as of April 24, 2023, using WHO updated outbreak data.

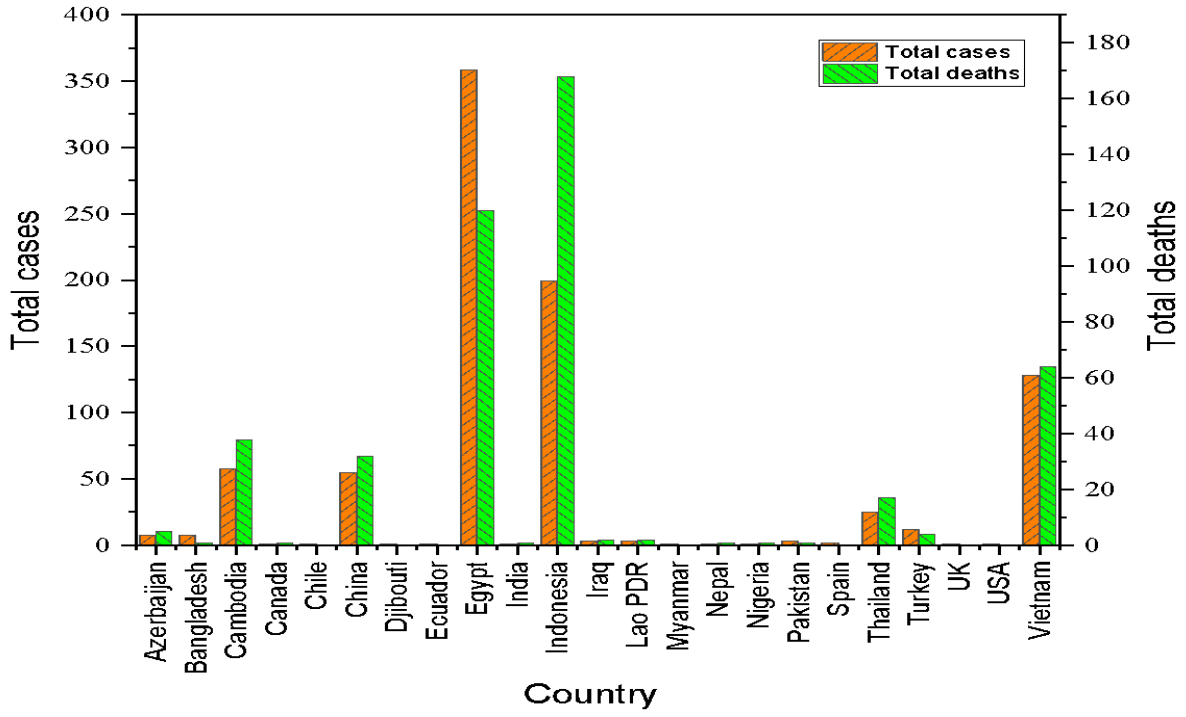

Table 1. Total count of verified human cases of AIV A (H5N1) officially reported to the World Health Organization

Country	2003-2009		2010-2014		2015-2019		2020		2021		2022		2023		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	6	1	1	0	0	0	0	0	0	0	0	0	8	1
Cambodia	9	7	47	30	0	0	0	0	0	0	0	0	2	1	58	38
Canada	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Chile	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
China	38	25	9	5	6	1	0	0	0	0	1	1	1	0	55	32
Djibouti	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Ecuador	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Egypt	90	27	120	50	149	43	0	0	0	0	0	0	0	0	359	120
India	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1
Indonesia	162	134	35	31	3	3	0	0	0	0	0	0	0	0	200	168
Iraq	3	2	0	0	0	0	0	0	0	0	0	0	0	0	3	2
Lao Peoples's Democratic Republic	2	2	0	0	0	0	1	0	0	0	0	0	0	0	3	2
Myanmar	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Nepal	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	1
Nigeria	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	0	0	0	0	3	1
Spain	0	0	0	0	0	0	0	0	0	0	2	0	0	0	2	0
Thailand	25	17	0	0	0	0	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	0	0	0	0	12	4
United Kingdom of Great Britain and Northern Ireland	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
United States of America	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Vietnam	112	57	15	7	0	0	0	0	0	0	1	0	0	0	128	64
Total	468	282	233	125	160	48	1	0	2	1	6	1	4	1	874	458

Conclusion

Avian Influenza Type A (H5) virus has been discussed; its subtypes, genetic make-up, previous and recent outbreaks, modes of transmission, risk factors, and its diagnosis and treatment. The endemic nature, virulence, and mutant capacity brought by the reassortment of this virus have posed a critical threat to human life. Investigation shows the virus is highly contagious and has been detected in birds, domestic poultry, and humans. However, there is a glimpse of hope as some countries have tried in alleviating the spread of the disease through the guidelines of the National Immunization Program and the intervention of the World Health Organization. Hence, more cutting-edge research on the disease's prevention, diagnosis, and treatment is essential.

Recommendation

Due to the enormous sporadic outbreaks and constantly evolving nature of the Influenza virus among animal populations, there should be an urgent need for global surveillance to monitor and detect virological changes attributed to the circulation of the avian Influenza A (H5) virus that may affect human or animal health. Emergency vaccination against all subtypes of influenza viruses should be developed for preparedness purposes. The World Health Organization should be notified of all human-infected cases, and public awareness about the causes of the avian influenza A (H5) virus should be raised.

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