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Avian Influenza Infection: An Emerging Global Threat to Humanity

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Abstract

Avian influenza (AI), commonly called bird flu, is a viral infectious disease of birds. Most avian influenza viruses do not infect humans; however, some, such as A (H5NI) and A (H7N9), have caused serious infections in people. Outbreaks of AI in poultry may raise global public health concerns due to their effects on poultry populations, their potential to cause serious disease in people, and their pandemic potential. Reports of highly pathogenic epidemics in poultry, such as A (H5NI), can seriously impact local and global economics and international trade. Currently, the best way to prevent infection with avian influenza A virus is to avoid sources of exposure whenever possible. World Health Organization says that H5NI virus circulation in poultry is vital to reduce the risk of human becoming infected. Research regarding the background and transmission is ongoing. Data related to human infections with seasonal, pandemic and highly pathogenic avian influenza A (H5NI) viruses indicate that the earlier antiviral treatment is initiated the greater the clinical benefit as there is no vaccine at present.

Keywords: Avian Influenza; Pandemic; Poultry.

Background

Avian flu, also known as bird flu and more formally as avian influenza, refers to flu caused by viruses that infect birds and make them ill. It is an infectious disease of birds caused by type A strains of influenza virus. Avian flu affects several types of birds, including farmed poultry, i.e., chickens, geese, turkeys, and ducks [1]. Usually; bird flu is not passed from birds to people. But since 1997, some people have become sick with this serious, deadly kind of bird flu. Most of these infections have been in Asian countries among people who have had close contact with birds raised on farms. But experts believe that the virus may eventually spread to all parts of the world.[2] Influenza pandemics are unpredictable but recurring events that can have health, economic and social consequences worldwide. An influenza virus emerges with the ability to cause sustained human-to-human transmission, and the human population has little or no immunity against the virus. With growth of global trade and travel, a localized epidemic can transform into a pandemic rapidly, with little time to prepare a public health response [3]. There have been several bird flu outbreaks since the first one in December 2003.Wild birds and farmed livestock have died because of bird flu in Africa, Asia and Europe. Bird flu has a very high death rate, in some parts of the world over 50% of people who get ill die. If bird flu becomes a global pandemic, many people, possibly millions, could die [4]. Although millions of birds have become infected with the virus since its discovery, 359 humans have died in twelve countries accordingly to WHO data as of August 10, 2012 [4]. The avian flu claimed at least 300 humans in Azerbaijan, Cambodia, China Egypt, Thailand, Turkey, and Vietnam [5]. The Thailand outbreak of avian flu caused massive economic losses, especially among poultry workers. Infected birds were killed and slaughtered. The public lost confidence with the poultry products, thus decreasing the consumption of chicken products. This also elicited a ban from importing countries. There were, however, factors which aggravated the spread of the virus, including

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bird migration, cool temperature (increases virus survival) and several festivals at that time [6]. Epidemiologists are afraid, due to mutation of virus, it could pass from human to human. If this form of transmission occurs, several pandemic could result. Thus, disease-control centers around the world are making avian flu a top priority. These organizations encourage poultry-related operations to develop a preemptive plan to prevent the spread of avian flu. The recommended plans center on providing protective clothing for workers and isolating flocks to prevent the spread of the virus [5].

Etiology

Bird flu is caused by a type of influenza virus that rarely infects humans. More than a dozen types of bird flu have been identified, including the two strains that have most recently infected humans-H5NI and H7N9[7]. There are many subtypes of avian influenza viruses, but only some strains of five subtypes have been highly pathogenic in humans. These are types H5NI, H7N3, H7N3, H7N9, and H9N2 [8]. Avian influenza (AI) viruses are divided into 2 groups based on their ability to cause disease in poultry: high pathogenic or low pathogenic. High pathogenic viruses results in high death rates (up to 100% mortality within 48 hours) in some poultry species. Low pathogenic viruses also cause outbreaks in poultry but not generally associated with severe disease [3]. The A (H5NI) virus subtype, a highly pathogenic AI virus, first infected humans in 1997 during a poultry outbreak in Hong Kong SAR, China. Since its widespread emergence in 2003 and 2004, this avian virus has spread from Asia to Europe and Africa and has become entrenched in poultries in some countries resulting in millions of poultry infections, several hundred human cases, and many human deaths. The A (H7N9) virus subtype first infected 3 humans- 2 residents of Shanghai and 1 resident of Anhui province, China- in March 2013. No cases of A (H7N9) outside of China have been reported. Ongoing circulation of A (H5NI) and A (H7N9) viruses in poultry, especially where endemic, continues to pose threat to public health, as these viruses have both the potential to cause serious disease in people and may have the potential to change into a form that is more transmissible among humans. Other influenza virus subtypes also circulate in the poultry and other animals, and may also pose potential threats to public health [3]. Researchers are concerned that if either H5NI or H7N9 avian influenza virus strains mutate and acquire the ability to become easily transmissible, there would be a serious risk of a pandemic flu. There is strong evidence that the H7N9 bird flu virus strain is human transmissible, i.e., it can pass from person to person.[1] Another subtype of AI virus H10N8 infected and killed at least one person, an elderly woman in Jiangxi province, China in December 2013. Influenza A (H5NI) has evolved into a flu virus strain that infects more species than any previously known strain, is deadlier than any previously known strain, and continues to evolve, become more widespread and more deadly. This caused RG Webster, a leading expert on avian flu, to publish an article, titled, "The world is teetering on the edge of a pandemic that could kill a large fraction of population" in American Scientist. He called for adequate resources to fight what he sees a major world threat to possibly billions of lives [10].

Virology

Avian influenza A virus belongs to family-Orthomyxoviridae, genus- Influenza A (Single species). The multiple partite genome of the virus is encapsulated with each segment in a separate nucleocapsid in which different segments of negative-sense, single-stranded RNA are present; this allows for reassortment in single cells infected with more than one virus and result in multiple strains that are different from the initial ones. The genome consists of 10 genes encoding for different proteins (8 structural and 2 nonstructural proteins). The virus envelop glycoproteins (HA&NA) are distributed evenly over the viron forming characteristic spike-shaped structures. Antigenic variations in these proteins are part of the influenza A virus subtype definition. There are 16 different HA antigens(H_1 to H_{16})and nine different NA antigens (N_1 to N_9). Until recently,15HA types had been recognized [11]. Human disease historically has been caused by three subtypes of HA (H1, H2, and H3) and two subtypes of NA (N1 and N2). H1 and H2 are the subtypes that currently cause seasonal influenza in human populations around the globe each year. More recently, human disease has been recognized to be caused by additional HA subtypes including H5, H7 and H9. Such cases have predominantly been associated with exposed/ infected birds. Person-to-person transmission has occurred in a few isolated situations. Antigenic strain nomenclature of influenza A is based on (i) host of origin (if other than human) (ii) geographic origin (iii) strain number (iv) year of isolation and (v) HA and NA types. Influenza A nomenclature for human strain include: A/Hong Kong/03/68 [H3 N2], A/ swine /Iowa/15/30. As with other influenza A subtypes, standard nomenclature is used to name avian strain A/chicken/HK/5/98 [H5N1] [12].

Genetic factors in distinguishing between human flu viruses and "avian flu" viruses include PB2 (RNA polymerase) position 627 in the PB2 protein encoded by the PB2 RNA gene. Until H5NI, all known avian influenza viruses had a Glu at position 627, while all human influenza viruses had a Lys. Avian HA viruses bind alpha 2-3 sialic acid receptors, while human influenza HA viruses bind alpha 2-6 Sialic acid receptors. Swine influenza viruses have the ability to bind both types of sialic acid receptors. Hemagglutinin is the major antigen of the virus against which neutralizing antibodies are produced, and influenza virus epidemics are associated with changes in its antigenic structure. This was originally derived from pigs, and should technically be referred to as pig flu [13].

Transmission

A known subtypes of influenza A can be found in birds, and wild aquatic birds are the reservoir of influenza A viruses [14]. Birds become infected when they are in contact with contaminated excrements or secretions, or tainted surfaces. Domesticated poultry becomes infected via direct contact with infected waterfowl, other infected livestock, or tained surfaces of cages and other farming equipments and installation. Humans can become infected and ill with avian influenza after coming into contact with infected birds. The following circumstances have been linked to human illness [1]:

- Touching infected birds.
- Defeathering infected birds.
- Touch secretions from infected birds (saliva or fluids, feces).
- Inhaling dried feces dust from infected birds.
- Preparing poultry for cooking, if the bird was infected.
- Slaughtering or butchering infected poultry.

There is currently a large threat in Asia with infected poultry due to low hygiene conditions and close quarters. Although it is easy for humans to become infected from birds, it is much more difficult to do so from human to human without close and lasting contact [2]. At the moment, it is very hard for a human to become infected with bird flu, and extremely rare for one human to pass avian influenza onto another human. Experts fear that if a human who is already ill with seasonal human flu, becomes infected with bird flu, the H5NI virus may exchange genetic information with the human flu virus (HINI) and acquire its ability to spread from human-to-human. An easily human transmissible avian flu virus strains could have devastating consquenses [1].

Risk Factors

The primary risk for human infection appears to be direct or indirect exposure to infected live or dead poultry or contaminated environments. Controlling circulation of A (H5NI) and A (H7N9) virus in poultry is essential to reducing the risk of infection. There is no evidence to suggest that the A (H5NI) and A (H7N9) viruses can be transmitted to humans through properly prepared poultry or eggs. A few A (H5NI) human cases have been linked to consumption of dishes made of raw, contaminated poultry blood. However, slaughter, defeathering, handling carcasses of infected poultry, and preparing poultry for consumption, especially in household settings, are likely to be risk factors [3].

Influenza Pandemic

Pandemic flu viruses have some avian flu virus genes and usually some human flu virus genes. Both the H2N2 and H3N2 pandemic strains contained genes from avian influenza viruses. The new subtypes arose in pigs coinfected with avian and human viruses, and were soon transferred to humans. Swine were considered the original "intermediate host" for influenza because they supported reassortment of divergent subtypes. However, other hosts appear capable of similar co-infection(e.g., many poultry species), and direct transmission of avian viruses to humans is possible [15]. The Spanish flu virus strain may have been transmitted directly from birds to humans [16]. In spite of their pandemic connection, avian influenza viruses are non infectious for most species. When they are infectious, they are usually asymptomatic, so the carrier does not have any disease from it. Thus, while infected with an avian flu virus, the animal does not have flu. Typically, when illness (called flu) from an avian flu virus does occur, it is the result of an avian flu virus strain adapted to one species spreading to another species (usually from one bird species to another bird species). So far is known, the most common result of this is an illness so minor as to be of not worth noting (and thus less studied). But with the domestication of chickens and turkeys, humans have created species subtypes (domesticated poultry) than can catch an avian flu virus adapted to water fowl and have it rapidly mutated into a form that kills over 90% of an entire flocks in days, can spread to other flocks and kill 90% of them, and can only be stopped by killing every domestic bird in the area [10]. The A (H5NI)

and A (H7N9) AI viruses remain two of the influenza viruses with pandemic potential, because they continue to circulate widely in some poultry populations, most humans likely to have no immunity to them, and they can cause severe disease and death in humans [17].

Clinical Manifestations

The incubation period for A (H5NI) avian influenza may be longer than that for normal seasonal influenza, which is around 2 to 3 days. Current data for A (H5NI) infection indicates an incubation period ranging from 2 to 8 days and possibly as long as 17 days. Current data for A (H7N9) infection indicates an incubation period ranging from 2 to 8 days with an average of five days. WHO currently recommends that an incubation period of 7 days be used for field investigations and monitoring of patient contacts [18]. Humans with avian flu may have the following features: a cough-usually dry, a high-temperature over 38°C, aching-bones, joints and muscles, bleeding from the nose, blocked nose, chest pain, cold sweats and chills, fatigue, headache, loss of appetite, runny nose, sleeping difficulties, stomach upset-sometimes diarrhea, bleeding from gums, some patients develop the symptoms of lower respiratory tract infections, breathing difficulties which occurs around day five of the first symptoms, hoarse voice and sometimes sputum is bloody. Patients with avian influenza can deteriorate rapidly, resulting in pneumonia, multiple organ failure, and death. In a large number of patients, flu caused by H5NI virus develops unusually aggressively [1]. Complications of avian bird flu include: hypoxemia, multiple organ dysfunction, and secondary bacterial and fungal infections [21].

Diagnosis

Bird flu needs to be diagnosed early on during the disease's cycle. It may be diagnosed by evaluating the hallmark signs and symptoms of patient with history of recent travel as well as any contact with birds.

A respiratory specimen to be collected and sent to the laboratory; this should ideally occur within four to five days of appearance symptoms. A Rapid Test for Avian influenza A virus in humans in 2009, the FDA, USA approved the Advantage A/H5NI Flu test, which detects influenza A (bird flu) from nose or throat swabs collected from patients with flu-like symptoms. The test takes less than 40 minutes to identify a specific protein (NS) that indicates the presence of influenza A virus subtype [1].

Management

According to World Health Organization (WHO), antiviral medications, such as oseltamivir can suppress viral replication and improve outcome for patients, especially survival prospects. Oseltamivir (Tamiflu) should be administered within 48 hours after the onset of symptoms for best effect. However, as avian influenza mortality rates are high, doctors should consider prescribing oseltamivir for patients who were diagnosed later. For those with severe symptoms, doctors may have to increase the recommended daily dose, as well as treatment duration. Physicians should bear in mind that drug absorption may be severely impaired in patients with severe gastrointestinal symptoms. Patients diagnosed with avian flu or who are suspected of having avian flu will be told to either remain at home or will be hospitalized (in isolation from other patients). In addition, patients should drink lots of fluid, receive proper nutrition and medications for pain and fever. The use of corticosteroids is not recommended [1,20]. Clinical cases of severely ill patients should be focused on evidence based supportive management of complications such as acute respiratory distress syndrome (ARDS). Adherence to recommended infection control measures in clinical settings to reduce the risk of nosocomial transmission can not be overemphasized. Secondary invasive bacterial infections associated with influenza can cause severe and fatal complications and appropriate empirical antibiotic treatment may be indicated [7]. Analysis of available avian influenza viruses circulating worldwide suggests that most viruses are susceptible to oseltamivir, peramivir and zanamivir. However, some evidence of antiviral resistance has reported in HPAI Asian-origin H5NI viruses and influenza A (H7N9) viruses isolated from some human cases. Monitoring for antiviral resistance among avian influenza A virus is crucial and ongoing [21].

Prevention

Currently, the best may to prevent infection with avian influenza A virus is to avoid sources of exposure whenever possible. People who work with poultry or who respond to avian influenza outbreaks are advised to follow recommended biosecurity and infection control practices; these include use of appropriate personal protective equipment (PPE) and careful attention to hand hygiene. In addition, highly pathogenic avian influenza (HPAI) poultry outbreak responders should adhere to the guidance from CDC and WHO and receive seasonal influenza vaccination annually and take prophylactic antiviral medication during response. They should also be monitored for

illness during and after responding to HPAI outbreaks among poultry. Seasonal vaccination will not prevent infection with avian A virus, but can reduce the risk of co-infection with human and avian influenza A viruses [21]. A person will not be infected if eats cooked poultry. WHO and several national authorities in Europe say poultry should be cooked to at least 74°C (165°F). According to experts, humans cannot become infected by eating eggs. Even so, the FDA (Food and Drug Administration) of the United States says eggs should be cooked until both the white and yolk are firm. It is currently impossible to stop avian influenza from spreading- it is a virus that is carried by birds, including wild birds that migrate. Understanding the bird migration and agricultural authorities with vital data so that they can prepare and protect live stock [1].

Vaccination

There is vaccination for human seasonal flu, but not for bird flu. Various public health laboratories around the world, as well as pharmaceutical companies are working towards producing avian flu vaccines. Vaccines for poultry have been formulated against several of the avian H5NI influenza varieties. Vaccination of poultry against the ongoing H5NI epizootic is widespread in certain countries. Some vaccines also exist for use in humans, and others are in testing, but none have been made available in civilian populations, nor are produced in quantities sufficient to protect a tiny fraction of the Earth's population in the event of an H5N1 pandemic outbreak. The WHO has compiled a list of known clinical trials of pandemic influenza prototype vaccines [22,23].

World Health Organization (WHO) Response

WHO, in its capacity for providing leadership on global health matters, is monitoring avian influenza very closely, developing and adjusting appropriate interventions in collaboration with its partners. Such partners include animal health agencies and national veterinary authorities responsible for the control and prevention of animal diseases, including influenza. WHO is monitoring the situations as it evolves, and as more information becomes available, will revise its guidance and actions accordingly [17].

Bangladesh's Preparedness

Bangladesh is well capable of diagnosis of influenza A HINI/H3N2/H5NI/H9N2/H7 at laboratory of Institute of Epidemiology and Disease Control and Research (IEDCR) and ICDDR, B with Real time RT-PCR to provide confirmatory results within 24 hours. Arrangements have been made with CDC (USA) and WHO for further analysis of the virus. Biosafety level 3(BSL3) laboratories of IEDCR and ICDDRB are in function. IEDCR is presently involved in monitoring, surveying, training and making awareness of the disease. It has been campaigning "Street wise" hygiene through promoting 4 actions as follow [24]:

1. Wash hands thoroughly with soap frequently.
2. Cover coughs and sneezes.
3. Wear a mask if symptomatic.
4. Don't spit.

Conclusion

The impact of pandemic influenza outbreaks on individual and societies can be reduced by being well prepared. This means having a comprehensive plan that has been tested and refined through conducting exercises, engaging the whole society. National plans should be flexible enough to respond to outbreaks of various intensity. Communication will be one of the most challenging tasks during an out break, and it should be planned well in advance. More research is necessary to understand the pathogenesis and epidemiology of the virus in humans. Exposure routes, disease transmission characteristic genetic and immunological factors that may increase the likehood of infection to be more clearly understood.

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