



## VIRUSES ASSOCIATED WITH HUMAN AND ANIMAL INFLUENZA - A REVIEW

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### ABSTRACT

*In this review, the most important viruses associated with human and animal influenza are reported. These include Influenza A,B and C. Influenza viruses are members of the family Orthomyxoviridae. Influenza A virus being the most pathogenic and wide spread with many subtypes has constantly cause epidemics in several regions of the world. Epidemiology and mechanism of infection were revealed from molecular basis. Classification of influenza A into subtypes are based on the type of hemagglutinin (HA) and Neuraminidase (NA) proteins present on the outer surface of the virus. The mode of transmission is through the air, contact with body fluids and surfaces contaminated with the virus. Clinical manifestation include a rise in the body temperature, cough pains through out the body and ruffled features in mild infections, myalgia and pneumonia are also presented in severe infections. Laboratory diagnosis of influenza are virus isolation, immunofluorescence and serological methods. In this review, the most effective treatment of influenza is by multidrug antiviral therapy (M<sub>2</sub> and N<sub>1</sub> inhibitors). Vaccination plays a major role in prevention though some have no or less safety guards such as the live attenuated influenza vaccine (LAIV) while the trivalent influenza vaccine (TIV) is more preferable.*

**Key words:** Viruses, influenza, humans, animals, safety.

### INTRODUCTION

Influenza, commonly known as the flu, is an infectious disease that affects birds and mammal caused by RNA viruses of the family orthomyxoviridae. The name influenza comes from the Italian. Influenza, meaning "influenza", (latin influential). The family has five genera but only 3 cause influenza, these are *influenza virus A*, *influenza virus B* and *influenza virus C* (Kawaoka, 2006).

According to Hay, *et al.*(2001) the type A viruses are the most virulent human pathogens among the three influenza types and cause the most severe disease. The influenza A viruses are sub divided into several serotypes based on the antibody response to these viruses.

Influenza B virus almost exclusively infects humans and is less common than influenza A. The only other animal known to be susceptible to influenza B is the seal (Osterhaus, 2000). In more serious cases influenza causes pneumonia which can be fatal, nausea and vomiting especially in children. In animals the disease may also either be mild or severe.

Influenza diagnosis to detect the specific subtypes are carried out by various methods with specimens collected from infected individual to treat the infection early because if left untreated, will lead to complications such as Reye's syndrome (Kerr, *et al.*, 1975).

Viruses associated with influenza are varied. Among, the 3 genera, Genus A are further subdivided by the HA (16) and NA (9) antigens present on the

surface of the virus, using the formular H<sub>x</sub>N<sub>y</sub> e.g H<sub>3</sub>N<sub>2</sub> (Hillemann 2002).

Influenza is caused by a variety of species and strains of viruses. In any given year some strains can die out while others create epidemics, while yet another strain can cause a pandemic. Typically, in a year's normal two flu seasons (one per hemisphere) there are between three and five million cases of severe illness and up to 500,000 deaths worldwide, which by some definitions is a yearly influenza epidemic (CDC, 2008). Although the incidence of influenza can vary widely between years, approximately 36,000 deaths and more than 200,000 hospitalizations are directly associated with influenza every year in America (CDC 2008). Every ten to twenty years, a pandemic occurs, which infects a large proportion of the world's population and can kill tens of millions of people. Indeed, if a strain with similar virulence to the 1918 influenza emerged today, it could kill between 50 to 80 million people.

The influenza viruses belongs to the genus *Orthomyxovirus* in the family of *Orthomyxoviridae*. They are single stranded RNA (ssRNA) enveloped viruses with a helical symmetry and are 80-120nm in diameter. The RNA is closely associated with the nucleoprotein (NP) to form the helical structure (7 for influenza C virus). The influenza viruses are roughly spherical, though filamentous forms can occur (ICTV, 2009). There are four main antigens present that elicit the production of antibodies in both humans and animals infected with the influenza viruses, these are hemagglutinin HA neuramidase (NA, nucleoprotein (NP) and the matrix (M).

The NP possess no cross reactivity and is a type specific antigen which occur in 3 forms, A, B and C which provides the basis for the classification of influenza viruses into influenza A virus, influenza B virus and influenza C virus. Though it is only influenza A that is divided into subtypes of 16 haemagglutinin HA (1-16) and 9 neuraminidase NA (1-9) while B isn't divided into subtypes, but is further broken into different strains (CDC 2009a). The influenza A viruses are classified into subtypes based on antibody responses to HA and NA, forming the basis of the H and N distinctions in, for example H5N1 (Hilleman, 2002).

#### **VIRUSES ASSOCIATED WITH INFLUENZA IN HUMANS AND ANIMALS**

Influenza viruses infect many animal species, and transfer of viral strains between species can occur. Birds are believed to be the main animal reservoirs of influenza viruses (Gorman, 1990). All the 16 forms of hemagglutinin and 9 forms of neuraminidase have been found in birds but many subtypes are endemic in humans, dogs, horses and pigs; populations of camels, ferrets, cats, seals, mink and whales also show evidence of prior infection or exposure to influenza (Webster, 1998). Variants of flue virus are sometimes named according to the species the strain is endemic in or adapted to. The main variants named using this convention are: Birdflu, human flu, Swine flu, Horse Flu and Dog flu.

##### **Influenza virus A.**

This genus has one species, influenza A virus Wild aquatic birds are the natural hosts for a large variety of influenza A. Occasionally, viruses are transmitted to other species and may then cause devastating outbreaks in domestic poultry which in turn cause influenza pandemics to animals and humans in near contact. The influenza virus A is the most virulent pathogen among the 3 influenza types and cause the most severe disease. The influenza A virus can be sub-divided into different serotypes based on the antibody response to these viruses. The serotypes confirmed in humans ordered by the number of known pandemic death are: H<sub>1</sub>N<sub>1</sub>, which cause Spanish flue in 1918 ;H<sub>2</sub>N<sub>2</sub> H<sub>7</sub>N<sub>3</sub>, N<sub>3</sub>N<sub>2</sub> H<sub>10</sub>N<sub>7</sub>, H<sub>7</sub>N, H<sub>5</sub>N<sub>1</sub> and H<sub>1</sub>N<sub>2</sub> H<sub>9</sub>N<sub>2</sub> H<sub>7</sub>N<sub>2</sub>, which cause a pandemic threat in the 2007 and 2008 flu season. While all the remaining subtypes such as H3N8 are found in other animal species such as dogs.

##### **Influenza Virus B**

This genus has one species, influenza B virus. Influenza B almost exclusively infects humans (Hay, *et al.*, 2001) and is less common than influenza A. The only other animal known to be susceptible to influenza B infection is the seal (Osterhaus, *et al.*, 2000). This type of influenza mutates at a rate 2-3 times lower than type A (Nobusawa and Sato 2006) and consequently is less genetically diverse, with only one influenza B Serotype (Hay *et al.*, 2001). As a result of this lack of antigenic diversity, a degree of immunity to influenza B is usually acquired at an early

age. However, Influenza B mutates enough that lasting immunity is not possible (Webster, 1998). This reduced rate of antigenic change, combined with it's limited host range (inhibiting cross species antigenic shift), ensures that pandemics of influenza B do not occur (Zambon, 1999).

##### **Influenza Virus C**

This genus has one species, influenza C virus, which infects humans and pigs and can cause severe illness and local epidemics (Matsuzaki, *et al.*, 2002). However, influenza C is less common than the other types and usually seems to cause mild disease in children (Matsuzaki, *et al.*, 2006).

##### **Mode of transmission of the Influenza Virus**

Typically, influenza is transmitted from infected birds through their droppings and from infected mammals through the air by coughs or sneezes, creating aerosols containing, the virus. Influenza can also be transmitted by saliva, nasal secretions, feces and blood. Infections also occur through contact with these body fluids or with contaminated surfaces. Flu viruses can remain infectious for about 1 week at human body temperature, over 30 days at 0°C(32°F) and for much longer periods at very low temperatures (Mase, *et al.*, 2006). Poultry, especially those kept in small backyard flocks, are the main source of virus. These birds usually roam freely as they scavenge for food and often mingle with wild birds or share water source with them. Such situations created abundant opportunities for human exposure to the virus, especially when birds enter households or are brought into households during adverse weather, or when they share areas where children play or sleep (WHO, 2005), though most influenza strains can be inactivated easily by disinfectants and detergents (Suarez, *et al.*, 2003).

##### **Clinical Manifestations**

In pigs, horses, and dogs, influenza symptoms are similar though frequency of animal diseases are not as well studied as human infection. Following a typical incubation period of 48 hours, the typical symptoms of influenza appears. The onset is abrupt with a marked fever with body temp ranging from 38-39°C (approx 100-103°F) headache, photophobia, shivering, a dry cough, malaise, myalgia and a dry tickling throat. The fever is continuous and lasts around 3 days. Influenza B infection is similar to influenza A, but infection with influenza C is usually subclinical or very mild in nature (Webster, 1998). On the other hand, outbreaks in pigs are common and do not cause severe mortality.

Flu symptoms in birds are variable and can be unspecific. The symptoms following infection with low pathogenicity avian influenza may be as mild as ruffled feathers, a small reduction in egg production, weight loss combined with minor respiratory disease (Capua and Mutinelli 2001) while some strains such as Asian H<sub>9</sub>N<sub>2</sub> are highly virulent to poultry and may cause more extreme symptoms and significant mortality.

In its most highly pathogenic form, influenza in chickens turkeys produce a sudden appearance of severe symptoms and almost 100% mortality within two days (Swayne and Suarez 2000).

In humans the flu could be difficult to distinguish with the common cold in the early stages but a flu can be identified by a high fever with a sudden onset and extreme fatigue, gastro-intestinal symptoms such as nausea and vomiting (more common in children than adult) much more severe and last longer than those of the common cold. Recovery takes about one to two weeks. Influenza however, can cause deadly complications, especially for the weak (very young children old or chronically ill individuals). People with emphysema, chronic bronchitis or asthma may experience shortness of breath while they have the flu and influenza may cause worsening of coronary heart disease or congestive heart failure. Smoking is another risk factor associated with more serious disease and increased mortality from influenza (Murin and Bilello, 2005).

#### **Prevention and Control of Influenza**

The most effective way to manage influenza is to prevent the illness with a yearly administration of influenza vaccine. The vaccines are usually given in developed countries to people and to farm poultry. The vaccine is estimated at 70%-90% effective for healthy adults and children (CDC, 2009) while October and November are the best times to receive a flu shot. It is never too late in the flu season to be vaccinated. The Advisory Committee on Immunization Practices (ACIP) of the CDC recently expanded recommendations to include 5-to 18-year-olds. Because of the necessity for widespread planning to ensure vaccination of all appropriate children, the ACIP has targeted the 2009-2010 season for full implementation of the new recommendation. It's anticipated that full-scale campaigns, such as school-based vaccine clinics, may be necessary to implement the goal of vaccinating children. The trivalent influenza vaccine (TIV) contains purified and inactivated material from three viral strains. Typically this vaccine includes material from two influenza A virus subtypes and one influenza B virus strain (Horwood and Macfarlane, 2002). The TIV carries no risk of transmitting the disease and it has very low reactivity.

In infected animals, the control measure leads to massive disruption of infected farms. During the epidemic of H<sub>5</sub>N<sub>1</sub> in Hong Kong in 1997, the virus was eradicated by the slaughter of all poultry in the country (Li, *et al.*, 2005). Also quarantine and wearing of protective clothing when handling birds and other animal may reduce or control the spread of the virus. The use of disinfectants and detergents inactivate most influenza strains.

#### **DISCUSSION**

Influenza infect many animal species and transfer of viral strains between species can occur, though all the known subtypes are found in birds but many subtypes are endemic in other animal (Gorman 1999).

Generally, the influenza virus A subtype H<sub>5</sub>N<sub>1</sub> is the most pathogenic among all the influenza viruses isolated in different areas around the globe during influenza pandemic. Genetic analysis revealed those human isolates of H<sub>5</sub>N<sub>1</sub> subtype to be indistinguishable from a highly pathogenic avian influenza that was endemic in the local poultry population. This outbreak provided the first evidence that avian viruses could be

transmitted directly to humans without prior reassortment in a mammalian host or with a human virus and could cause severe disease (Li, *et al.*, 2005).

The high pathogenicity of H<sub>5</sub>N<sub>1</sub> is attributed to the constant emergence of new antigenic variants, giving rise to yearly epidemics of strains to which most humans have no immunity and the resulting pandemics vary from serious to catastrophic (Webster, 1998).

According to Tam (2002), many factors may have contributed to the sudden outbreak of H<sub>5</sub>N<sub>1</sub> influenza infection in Hong Kong these may include:

- The close proximity of various poultry in traditional markets and wholesale markets where different species of birds were kept.
- The overcrowding conditions of areas and close proximity of live birds to residential complexes
- The traditional Chinese requirement of purchasing live chicken for various cultural activities and the believe in the freshness of recently slaughtered birds.

Under such conditions, the virus can easily spread from one species to another species of bird and eventually to man.

Natural infection with influenza A viruses have been reported in a variety of animal species including humans, pigs, horses, sea mammals and birds. As such influenza A viruses are zoonotic agents recognized as continuing threat to both veterinary and human public health, since eradication of the virus completely is not possible (Shortridge, *et al.*, 2003).

During epidemics, PCR tests are adopted because they yield faster and more accurate diagnosis than the other test methods with results in 30 minutes and are 85-95% sensitive (CDC 2008).

The two groups of antiviral drugs should be used in combination since the amantines show resistance to some strains of the influenza A virus (CDC, 2008) and also the NP inhibitor oseltamivir, resistance was detected in A (H<sub>2</sub>N<sub>1</sub>) viruses in several outbreak and those viruses remain sensitive to Rimantadine and amantidine (Waknine, 2009).

Vaccines against influenza have been around for 50 years. Despite this, the efficacy of influenza vaccine is still questioned, and the availability of vaccines to limit epidemic has not been proven. But research into new vaccines is certainly important as current vaccines are limited to a specific subtype.

The sequencing of the influenza genome and recombinant DNA technology may accelerate the generation of new vaccine strains by allowing scientist to substitute new antigens into a previously developed vaccine strain. Used influenza vaccine is the trivalent influenza vaccine (TIV) and not live attenuated influenza vaccine (LAIV) because of the risk associated with LAIV and also it is estimated that if the safeguards are to be satisfied, 2 years would be needed for the development of an attenuated vaccine.

#### **Conclusion and Recommendations**

Influenza infections constitute a major health problem both in humans and other mammals around the globe especially during pandemics. Influenza virus subtypes H<sub>7</sub>N<sub>7</sub>, H<sub>3</sub>N<sub>2</sub>, H<sub>4</sub>N<sub>5</sub>, N<sub>7</sub>N<sub>2</sub>, H<sub>1</sub>N<sub>1</sub>, H<sub>5</sub>N<sub>1</sub>, H<sub>2</sub>N<sub>2</sub>, H<sub>9</sub>N<sub>2</sub>, H<sub>4</sub>N<sub>6</sub>, H<sub>7</sub>N<sub>3</sub>, H<sub>1</sub>N<sub>2</sub> and H<sub>10</sub>N<sub>7</sub> have all been found circulating in the world but at present H<sub>5</sub>N<sub>1</sub> is the most pathogenic causing highly pathogenic Avian influenza (HPAI) in both humans and birds.

Complications such as pneumonia and myositis are responsible for many of the deaths in children and the elderly. These complications can be prevented or managed without difficulty if adequate preparation is made to handle them. To decrease mortality rates and retard infectiousness, uncomplicated cases of influenza must be treated early and adequately. The public must be aware during epidemics and patients must be managed in the nearest health centres. Availability of simple, rapid and reliable laboratory test at the health centres should be ensured, so as to assess and manage infections of influenza.

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- To avoid infection (in healthy individuals) and complications in infected individuals, vitamin D from the sun should be properly utilized
  - Infected animals should not be eaten even if well cooked to avoid the reassortment of the viral particles with other human viruses.
  - Quarantine should be observed by the government to prevent pandemics
  - Due to high poverty level, state and local governments in Nigeria should also incorporate free management of severe influenza.
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