INFLUENZA VIRUS: BIOLOGY AND PUBLIC HEALTH SIGNIFICANCE

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Abstract

Annual influenza epidemics cause substantial morbidity, mortality and socio-economic tolls. According to WHO estimates, about three to five million infections and 250,000 – 500,000 deaths occur annually.Influenza pandemic, aglobal outbreak caused by a new strain of influenza virus, also occurs occasionally in populations with less pre-existing immunity. Zoonotic influenza A virus infections occurs when avian and swine influenza virus cross the species barrier and cause severe disease in humans and other mammals. Avian influenza viruses account for most, but not all cases of zoonotic influenza infection in humans.Most of the human infections of zoonotic influenza virus are acquired mainly through direct contact with infected animals/birds or contaminated environment. In this review, the biology of influenza virus infection with special reference to the avian zoonoses and its public health significance is discussed. Despite better awareness and preparedness towards seasonal, pandemic or zoonotic outbreaks, influenza virus still remains to be a major public health threat that warrants constant surveillance.

Influenza Virus- Biology and classification

Influenza virus belongs to the family *Orthomyxoviridae*, and is a single stranded, negative sense RNA virus which commonly causes seasonal outbreaks of upper respiratory tract infection (WHO., 2003)(Bouvier and Palese, 2008). These viruses infect humans, birds and a wide range of animal species (Wright et al. 2007). Influenzavirus has a segmented genome composed of eight segments encoding eleven viral proteins: hemagglutinin (HA), neuraminidase (NA), matrix protein 1 (M1), matrix protein 2 (M2), nucleoprotein (NP), non-structural protein 1 (NS1), non-structural protein 2 (NS2) polymerase acidic protein (PA), polymerase basic protein 1 (PB1), polymerase basic protein 2 (PB2) and polymerase basic protein 1 – F2 (PB1-F2)(Bouvier and Palese, 2008; Chen

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et al., 2001). Based on antigenic differencesin their matrix protein and nucleoprotein, influenza virus is broadly classified into three antigenic types, Type A, B and C(Palese and Shaw 2007; Swayne and Halvorson 2008). Influenza A viruses are the most important pathogen among the three since they cause morbidity and mortality in humans, animals and birds and are responsible for the major pandemics in the last century (Wright et al. 2007). Influenza B can cause the same spectrum of illness as Influenza A, but the frequency of severe illness is much lower, causing outbreaks every 2-4 years in humans. Influenza C is associated with sporadic and subclinical infections in humans and swine and is only rarely associated with severe lower respiratory tract infections (Sandrock and Kelly, 2007; Zambon, 1999;Wright et al. 2007).

Type A influenza viruses are divided into various subtypes based on their surface glycoproteins, HA and NA. There are eighteen HA (H1 through H18) and 11 NA (N1 through N11) subtypes and these subtypes are further divided into strains based on HA and NA present on the viral envelope (eg: H1N1, H3N2)(WHO., 2003)(Bouvier and Palese, 2008). HA is the principal antigen on the surface of the virus and it is responsible for virus binding to terminal sialic acid moieties present in host cell surface glycoproteins and glycolipids. Neuraminidase facilitates the release of the virions from infected cells (Wright et al. 2007; Swayne and Halvorson 2008). The virus replicates in the nucleus of the infected cell. Since the cells cannot copy the negative strand RNA, a positive strand mRNA is first synthesized by the viral RNA-dependent RNA polymerase. This mRNA is translated into viral proteins and it also acts as template for the synthesis of negative strand genome (Palese and Shaw 2007; Swayne and Halvorson 2008).

Influenza viruses undergo constant antigenic variation by two different mechanisms which help them to escape host immune response – antigenic drift and antigenic shift (Wright et al. 2007; Swayne and Halvorson 2008). Mutations may accumulate in the newly replicated viral populations that result in antigenic drift giving rise to new variants that evade immunity as they are immunologically distinct from the previous strains circulating in a population. Antigenic drift is minor, gradual point changes in HA or NA proteins as a result of point mutations. These antigenic drift variants escape neutralizing antibodies and are selected by sequential accumulation of point mutations. Similarly, the segmented genome may allow reassortment of viral segments resulting in the emergence of a new virus with novel proteins (Wright et al. 2007). Outbreak of Spanish influenza (H1N1), Asian influenza (H2N2), Hong Kong influenza (H3N2), Russian influenza (H1N1) and the 2009 H1N1 pandemic were the result of antigenic shift (Wright et al. 2007). Pandemic influenza result from this antigenic shift as the population may have no or little immunity against the virus with new HA (Wright et al. 2007).

Avian Influenza

Avian Influenza or Fowl plague is a contagious disease in poultry caused by Influenza A viruses. Only type A influenza virusesare known to cause natural infections in birds and all different possible combinations of HA and NA subtypes have been isolated from them (Alexander, 2000, 2008;Wright et al. 2007). Depending on the ability to cause disease, influenza A viruses in poultry are divided into highly pathogenic avian influenza (HPAI) and low pathogenic avian influenza (LPAI) (Alexander, 2000, 2008). Some viruses of the subtypes H5 and H7 cause HPAI and the mortality rate may reach up to 100% (Alexander, 2000). All other Influenza A viruses infecting poultry cause LPAI, characterized by a mild respiratory infection and drop in egg production, which can be exacerbated by other conditions (Swayne and Halvorson 2008; Pantin-Jackwood and Swayne, 2009). Wild birds of the order Anseriforms and Charadriiforms are the natural hosts and asymptomatic carriers of avian influenza, and hence are not usually affected by HPAI (Wright et al. 2007). However, influenza viruses can be transmitted from wild aquatic to domestic birds, which usually results in LPAI (Alexander, 2007). After circulating in domestic poultry, a few H5 and H7 LPAI viruses may mutate into HPAI causing severe systemic disease(Alexander, 2007).

The HA gene is the primary determinant of virulence in avian influenza virus (Wright et al. 2007; Swayne and Halvorson 2008). The cleavage of HA0 into HA1 and HA2 is essential for the virus to be infectious. In HPAI, the HA cleavage site has multiple basic amino acids that can be recognized and cleaved by ubiquitous proteases like furin and

PC6 and hence the virus can enter and replicate in organs throughout the body causing severe clinical disease and death (Stieneke-Grober et al., 1992; Wright et al. 2007; Swayne and Halvorson 2008). In LPAI, the HA can be cleaved only by trypsin like proteases which are present in restricted sites such as respiratory and digestive tracts and hence the clinical signs are limited to these sites(Bosch et al., 1979; Steinhauer, 1999; Wright et al. 2007; Swayne and Halvorson 2008).

Public health significance

Wild aquatic birds are the reservoirs of influenzavirus and the virus can cross the species barrier and can infect and cause disease in chickens, humans and other mammals, and are hence classified under avian zoonosis (Alexander, 2007; Wright et al. 2007; Swayne and Halvorson 2008). The species specificity is determined by the HA glycoprotein binding to the sialic acid residues of the host cell. Human and swine H1N1 influenza viruses preferentially recognize receptors with saccharides ending in sialic acid (SA)α 2,6 galactose mainly expressed in tracheal epithelial cells whereas avian and equine viruses prefer those terminating in SAα 2,3 galactose located mainly on tracheal and intestinal epithelial cells (Rogers and Paulson, 1983; Wright et al. 2007). Initially it was thought that avian influenza cannot cause infection in humans due to the differences in receptor specificities and their location. However, that thinking has changed since the Hong Kong outbreak of avian influenza in humans in 1997 with 18 proven cases of which six were fatal.This is likely due to the presence of a minor population of ciliated cells in human tracheal and bronchial tissues (Matrosovich et al., 2004)and non-ciliated cuboidal bronchiolar cells (Shinya et al., 2006) that contain SAα 2,3Gal oligosaccharides. Transmission of influenza A virus from birds to humans may also be associated with the ability of HA to switch its preference from SAα 2,3Gal to SAα 2,6Gal (Yamada et al., 2006). Since the respiratory epithelium of pigs expresses both SAα 2, 3 Gal and SAα 2, 6 Gal, pigs can be infected by both avian and human influenza virus (Kida et al., 1994)and is considered as the mixing bowl of infection (Ito et al., 1998; Wright et al. 2007). The pandemic influenza H1N1/2009 outbreak originated from swine in Mexico was generated by multiple reassortments and the precursors include classical swine, human and avian viruses(Vijaykrishna et al., 2010).

Multiple subtypes of avian influenza have infected and caused disease in humans and several human outbreaks have been reported in recent years from countries around the world. The ability of H5N1, H7N7 and H9N2 to infect humans makes them the most likely avian candidates to cause pandemics(Katz et al., 2009; Lazzari and Stohr, 2004). Human infection due to avian influenza viruses mainly occurs due to close contact with infected birds especially through the direct contact with the excreta from infected birds and mucous membrane with infected secretions (Hayden and Croisier, 2005; Koopmans et al., 2004; Tran et al., 2004). Personnel involved in processing the birds for consumption have occasionally been infected. The virus may also enter through respiratory tract or conjunctivae (Fouchier et al., 2004). Human-to-human transmission may occur with low efficiency which may involve close contact during the early phase of infection (Koopmans et al., 2004; Ungchusak et al., 2005).

Conclusion

Influenza virus continue to evolve genetically and cross the species barrier and cause disease in humans. The WHO global surveillance system (Global Influenza Surveillance and Response System (GISRS)) constantly monitors influenza outbreaks and provide recommendations on diagnostics, treatment and preventive measures. The 1918 influenza pandemic (Spanish flu) which affects half of the world population was the most devastating of all pandemics. Even after 100 years, influenza virus continues to be a major threat to public health that warrants constant surveillance and rapid response. Further understanding on influenza virus transmission and pathogenesis as well asdevelopment of more efficacious vaccination strategies will reduce the economic burden of seasonal outbreaks and help to prevent the occurrence of another pandemic.

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