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Review Article

Influenza A Virus: Cause of Multispecies Disease and Zoonoses

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Abstract

Influenza A viruses (IAV) in the family Orthomyxoviridae, including all avian influenza viruses (AIVs), are enveloped, pleomorphic, and possess eight separate RNA genomic segments ranging in size between 890 and 2341 nucleotides. As observed by, the persistent and sporadic outbreaks of various Influenza A viruses in poultry and humans, respectively, warns the likelihood of avian influenza viruses (AIVs) becoming the next influenza pandemic strain. Further, among the vast pool of AIVs in nature, the HPAI A/H5N1 virus is believed to represent the greatest threat for the next flu pandemic. Therefore, the pandemic potential of subtypes of AIVs should not be overlooked and the domestic and aquatic wild bird populations should be under surveillance to monitor interspecies transmission. Such monitoring would help in understanding the ecology of human influenza and controlling avian zoonoses. The HA and NA glycoproteins on the virus surface encoded by separate RNA segments are antigenically diverse, and divide the IAVs into 18 H and 11 N antigenic subtypes, respectively. Aquatic birds like wild water fowl and ducks are natural host for AIV subtypes of H-1 to H-16 and N-1 to N-9. Two new subtypes each of HA and NA (H17N10, H18N11) have been recently identified in bats. Isolation of new AIV subtypes from bats has added another angle, in addition to the role of wild aquatic birds, to the ecology and emergence of influenza/flu epidemics/pandemics that can affect both terrestrial birds and human beings depending upon availability of receptors on host cells. Bats are likely ancient reservoir for a diverse pool of influenza virus. Influenza A viruses naturally circulate in a range of avian and mammalian species, including in humans. The Influenza A serotypes that have been confirmed in humans are, H1N1, *H1N2* (endemic in humans, pigs and birds), H2N2, H3N2, H5N1, H6N1, *H7N2, H7N3, H7N7, H7N9, H9N2*, and *H10N7.* Although transmission of AIVs between pigs and humans have already been confirmed, direct transmission from avian to human beings and between human to human is seldom. Segmented nature of the viral RNA genome combined with its error-prone polymerase enzymes can produce novel virus strain(s) with expansion of host range, inter species transmission, higher virulence, multi organ involvement with potential to

cause influenza pandemics. Introduction of influenza A viruses into poultry can cause severe illness often leading to high mortality. According to degree of pathogenicity, the avian influenza viruses (AIVs) are divided into two pathotypes; high pathogenic avian influenza (HPAI) and low pathogenic avian influenza (LPAI) virus. Some HPAI strains of the H5 (H5N1) and H7 (H7N1, H7N3, and H7N7) subtypes are highly lethal in chickens with involvement of several organs other than the respiratory system. In contrast, LPAI strains mainly affect intestinal and/or respiratory tracts. Several AIV subtypes have caused zoonotic infections in humans (LPAIs H6N1, H7N2, H7N3, H7N4, H7N7, H7N9, H9N2, H10N7, H10N8, and HPAIs H5N1, H5N6, H7N3, H7N7, H7N9). Transmission of HPAI H5 and H7 viruses into humans in the recent past has been of significance from the point of zoonoses. First AIV zoonoses was caused by H5N1 virus in 1997 in Hong Kong, then spread to many parts of the World. Enzootic cocirculation of H5N1, H9N2, and H7N9 viruses in poultry birds has given rise to many novel reassortants with other viruses such as H10N8, H10N6, H5N8, H5N6, and H7N6. The present compilation is about interspecies transmission of Influenza A viruses.

Keywords: *H: Haemagglutinin; India; Influenza A Virus; N: Neuraminidase; Zoonoses*

Introduction

The influenza virus belongs to the family Orthomyxoviridae. The segmented nature of the viral RNA genome combined with its error-prone polymerase contribute to rapid evolution of the virus and adaption in new host species. There are four main influenza virus types (species): A, B, C and D. Wild aquatic birds are the natural hosts for a large species of influenza A virus [1] that may transmit to other terrestrial species. The influenza A virus may cause severe outbreaks in domestic poultry or give rise to human influenza having pandemic threat [2]. The IAV viruses are subdivided into different serotypes based on the antibodies elicited against these viruses following infection [3]. Influenza B virus has one serotype and almost exclusively infects humans and is less common than influenza virus A. Seals and Ferrets are also susceptible to it. Influenza virus C having one species infects humans, dogs and pigs, and Influenza virus D also with one species infects pigs and cattle.

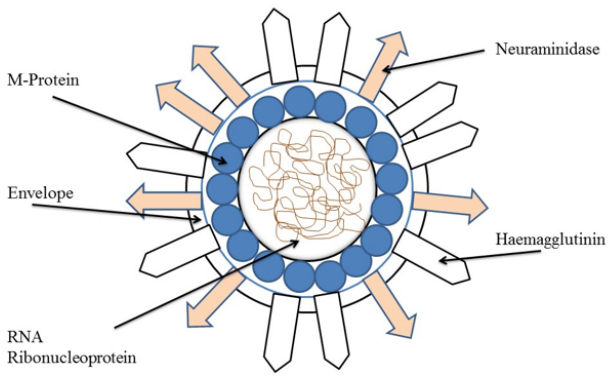

Figure 1: Structure of Influenza A virus.

Influenza A viruses, including avian influenza viruses (AIVs), are enveloped, pleomorphic, and possess eight separate RNA genomic segments ranging in size between 890 and 2341 nucleotides (Figure 1) [4]. Influenza viruses have a fast mutation rate, accumulating two to eight substitutions per 1000 sites per year [5]. Further, segmented genome enhances the evolutionary speed of the virus by exchange (reassortment) of RNA gene segments between virus strains infecting the same host. Both autologous and heterologous recombination are possible. Mutations facilitate antigenic drift, and reassortment of gene fragments lead to antigenic shift of the virus.

The HA and NA surface proteins encoded by separate RNA segments are antigenically diverse, and divide the IAVs into 18 and 11 antigenic subtypes, respectively. Apart from the recently discovered bat-specific H17, H18, N10 and N11 proteins (H17N10, H18N11) [6,7], all other subtypes are found in avian species, whereas only a

subset of the other subtypes have been detected in mammals [8]. Bats are likely ancient reservoir for a diverse pool of influenza viruses [7]. Bats are a major source of emerging infectious diseases, including coronaviruses, filoviruses, henipaviruses, and lyssaviruses [9,10]. Global distribution, abundance, diversity in the form of existence of more than 1000 species of bats emphasize the need to understand the ecology and properties of influenza A viruses, as well as the possibility of viral jumps across species barriers [7,11].

Influenza A viruses naturally circulate in a range of avian and mammalian species, including in humans [7]. The greatest diversity of these viruses is found in aquatic waterfowl that are natural reservoir of influenza A viruses [12]. Influenza A viruses H1N1, H2N2, and H3N2 are endemic in humans. The Influenza A serotypes that have been confirmed in humans are, H1N1 (Spanish flu in 1918, and Swine Flu in 2009), H2N2 (Asian Flu in 1957), H3N2 (Hong Kong Flu in 1968), H5N1 (Bird Flu in 2004), *H7N7, H1N2* (endemic in humans, pigs and birds). Influenza A/H5N1 has caused human infections associated with high mortality, and since 1998 the virus has evolved into many clades of variants with significant antigenic diversity. In 2013, three novel avian influenza viruses, A/H7N9, A/H6N1, and A/H10N8, which did not cause disease in poultry, were also transmitted from poultry to humans (avian zoonoses) in Asia [2]. These cases were mostly associated with direct contact with infected poultry.

Introduction of influenza A viruses into poultry can cause severe illness often leading to high mortality. According to degree of pathogenicity, the avian influenza viruses (AIVs) are divided into two pathotypes; high pathogenic avian influenza (HPAI) and low pathogenic avian influenza (LPAI) virus [13]. Some HPAI strains of the H5 (H5N1) and H7 (H7N1, H7N3, and H7N7) subtypes are highly lethal in chickens with involvement of several organs other than the respiratory system. In contrast, LPAI strains mainly affect intestinal and/or respiratory tracts [4]. Infection of human beings with HPAI H5N1 virus resulted in about 60% mortality worldwide. In recent years, the number of influenza A viruses crossing the animal-human species barrier has increased [2]. Unlike HPAI A/H5N1 viruses, which cause almost 100% mortality in affected poultry, A/H7N9 and A/H10N6 do not cause obvious symptoms in poultry thereby causing difficulty in virus tracking and surveillance. Enzootic cocirculation of A/H5N1, A/H9N2, and A/H7N9 viruses in poultry has given rise to many novel reassortants with other viruses such as H10N8, H10N6, H5N8, H5N6, and H7N6 [2]. Sporadic but severe infections of humans with avian influenza virus subtypes H5 [14], H6 [15], H7 [16,17], H9 [18], and H10 [19] have been directly from avian sources. There was no sustained human to human transmission.

Infection of the human respiratory tract is initiated by inhalation of avian influenza A viruses or by contact transmission to mucus membranes. The virus binds to receptors with sialic acid linked to galactose by alpha- 2,6 linkages (SA-alpha2,6Gal) found in the upper respiratory tract, and to sialic acid linked to galactose by alpha- 2,3 linkages (SA-alpha2,3Gal) in the lower respiratory tract [20].

The human H1N1 virus sequences of 1918 pandemic revealed genetic relationship with the contemporary classical swine H1N1 virus. Analysis have indicated that the polymerase gene sequences of the 1918 human H1N1 virus might have an avian origin [8,21]. The two human pandemics of 1957 (H2N2) and 1968 (H3N2) were not caused by completely avian-origin viruses. The H2N2 virus of 1957 Asian Flu was a reassortant virus with avian-origin NA segment, whereas the H3N2 virus of 1968 pandemic was a reassortant of HA and PB1 of avian origin [22-25]. The NA of the 1968 H3N2 strain was of avian origin introduced into the human population in 1957 [22]. The H1N1 virus of 2009 swine flu pandemic was a reassortment between different strains of IAV that were circulating earlier in swine and avian species [8,26,27]. The PB1 genes of the human (Asian Flu) pandemic virus H2N2 of 1957 and H3N2 virus of 1968 (Hong Kong flu) were from avian virus sources [23].

The emergence of highly pathogenic avian influenza viruses, and transmission of Avian H5 and H7 viruses into humans in the recent past has been of significance from the point of zoonoses. The threat of a new avian influenza virus causing a human pandemic is still present today, although control in domestic avian populations can minimize the risk to human health [8]. The majority of the virus diversity is seen in avian species which are the natural reservoir of IAV [4]. Bats also constitute a potentially important reservoir for a diverse pool of influenza viruses [7].

The haemagglutinin (HA) is synthesized on the endoplasmic reticulum as a precursor HA0 polypeptide that undergoes post-translational cleavage to separate the HA1 and HA2 domains. In LPAI

strains of virus, host proteases present on mucosal surfaces cause extracellular cleavage of HA0 after a single basic residue (PEIPK----GR). Whereas, HPAI strains have multi-basic amino acid sequence in HA0 (PEIPKRKKKGRG) that allows intracellular processing by universal furin-like proteases [28]. This multi-basic amino acid sequence in HA0 and its cleavage feature is responsible for expanded tissue tropism of the HPAI virus [8,29]. This phenomenon is well established for H5 and H7 HAs, but has not been seen for other HA subtypes [8]. The present compilation is limited to Influenza A virus including Avian Influenza virus and avian zoonoses.

Virus RNA segments and polypeptides

The genome segments of IAV encode 10-12 proteins, viz., three subunits of a viral polymerase (PB2, PB1, PA), a nucleoprotein, three transmembrane proteins (haemagglutinin (HA), neuraminidase (NA) and the M2 ion channel), a matrix protein M1 and non-structural proteins NS1 and NS2/NEP, as well as non-essential accessory proteins [30]. The viral polypeptides/proteins are, RNA polymerase complex composed of PB2 (segment 1; cap-binding), PB1+F2 (segment 2; polymerase), PA (segment 3; endonuclease), HA (segment 4), NP (segment 5), NA (segment 6), M1 and M2 (segment 7), and NS1+NEP (segment 8). Each RNA genome segment is encapsidated by a ribonucleoprotein (RNP) complex composed of RNA-dependent RNA polymerase (RdRP) and multiple copies of nucleoprotein (NP) [31]. The RNP complex plays a crucial role in virus replication by supporting and regulating transcription and replication of viral genome in infected cells. HA and NA are virus surface glycoproteins embedded in lipid bilayer that are major targets of neutralizing antibodies. The segment 7 encodes two matrix proteins, M1 and M2, transcripts of which are generated by RNA splicing. M1 is located internally below the lipid envelope of the virus, and M2 serves as an ion channel and is the target of the antiviral drugs amantidine and rimantidine. The RNA segment 8 codes for the non-structural proteins NS-1 and the nuclear export protein (NEP), the transcripts of which are generated by alternative RNA splicing.

Virus and host cell receptors and Interspecies transmission of Influenza A virus (IAV)

Influenza A viruses have potential to infect different animal species, but are not readily transmissible from one species to another until facilitated by environmental, viral, and host factors [2]. Avian and human influenza viruses differ in their specificity for host cell receptors that creates barrier for efficient transmission of avian viruses to human hosts. Over the last century, each influenza virus pandemic has coincided with the emergence of virus with an immunologically distinct hemagglutinin (HA) with human receptor specificity, distinct from HA of the viruses circulating in zoonotic/reservoir species [32]. Natural mutations in H5N1 may lead to increased affinity to human receptors. The receptor specificity is linked to interaction of HA glycoprotein on the virus surface with sialic acid receptors on host epithelial cells [33,34]. The HA of human influenza virus strains preferentially bind to oligo- saccharides that terminate with sialic acid linked to galactose by α(2,6) linkages (Sia [α2,6]Gal), whereas the HA of avian influenza virus strains prefer oligosaccharides that terminate with a sialic acid linked to galactose by α(2,3) linkages (Sia [α2,3]Gal) [35,36]. Cells in the respiratory tract of some laboratory strains of mice express both these receptors, therefore susceptible to both human and avian influenza A viruses. A synonymous mutations leading to amino acid substitutions in and around the receptor binding domain of HA alter the receptor binding preference of influenza viruses that define virus transmissibility [37]. The specific amino acid residues responsible for receptor-binding specificity vary among the different HA subtypes. The NA also contributes to transmissibility of the virus [38,39]. An optimal balance between HA and NA activities is critical for efficient transmission of H1N1 virus in ferrets [40]. Viral proteins other than HA and NA, have role in Influenza virus transmission. The polymerase basic protein 2 (PB2) has been found associated with transmission via respiratory droplets between ferrets, and replication in human cells [2,9,33,41]. Avian origin PB1 gene in the H3N2 virus causing Hong Kong flu in 1968 could be a crucial factor in the emergence of reassortants having advantage over seasonal influenza viruses in respect of replication and virulence [42]. The HA glycoprotein not only determines the species specificity of the virus, but also tissue specificity; thereby facilitates inter-species transmission and also spread within the host [2]. The AIVs recognize specific sialic acid receptors in the cells lining the intestinal gut of avian species [43].

Several avian influenza A virus subtypes have caused zoonotic infections in humans (LPAIs H4N8, H6N1, H7N2, H7N3, H7N4, H7N7, H7N9, H9N2, H10N7, H10N8, and HPAIs H5N1, H5N6, H7N3, H7N7, H7N9) [2,12,44]. Humans also possess AIV-susceptible cells in the lower respiratory tract. The receptors in the lower respiratory tract are not expressed by upper respiratory tract tissues

[35,36,45]. Continuous exposure to infected poultry increases the chances of interspecies transmission [2]. Specific amino acid substitutions in HA can shift receptor recognition. By consecutive passages in chickens, a highly virulent AIV was isolated from a virulent-swan virus that normally replicates poorly in chickens [2]. The HPAI strains of H5 and H7 antigenic subtypes are associated with accumulation of basic amino acid residues (arginine and lysine) in HA0 cleavage sites [29,33]. This polybasic amino acid stretch facilitates growth in various organs outside the respiratory tract [29,28,46].

The AIV subtypes H5N1 and H7N9 have caused the highest impact with severe disease. The first instance of AIV virus causing severe disease in human being was by H5N1 in 1997 in Hong Kong [47]. Human cases were preceded by outbreaks in poultry. Since 2013, H5N1 viruses of clade 2.3.4.4 have undergone reassortment with other avian influenza A viruses to generate H5N6, H5N8, and other related subtypes [48]. In 2003, an outbreak of HPAI H7N7 occurred in the Netherlands affecting both poultry and humans, with limited human-to-human transmission [49]. The LPAI H7N9 virus caused zoonotic disease in eastern China during 2013-17 [50,51]. This LPAI virus (H7N9) caused little or no illness in poultry and spread in China, and human cases corresponded with a seasonal increase in virus circulation among poultry [12]. In 2016, the H7N9 virus acquired properties of an HPAI virus and caused disease in poultry. AIV H7 viruses have tropism for ocular receptors. Conjunctivitis has been reported in persons with H7N2, H7N3, and H7N7 virus infections [52]. In regions with enzootic poultry infections, human exposures to AIVs H5N1, H5N6, and H7N9 have been extensive with rare zoonoses [12].

It was observed that that the HPAI H5N1 virus that caused human outbreaks in 1997 (in Hong Kong) and onwards acquired most of its gene segments from avian A/H9N2 subtypes [53]. Human infection with LPAI H9N2 virus was first diagnosed in Hong Kong in 1999 [54]. Direct avian-to-human transmission of H7N7 virus was first diagnosed in 1996 [55]. The LPAI viruses are able to spread in domestic poultry undetected, posing risk to humans. Unlike H5N1 and H9N2 AIVs, the H7N9 virus, deficient in polybasic amino acid residues, replicates efficiently in poultry without inducing remarkable disease [56,57]. Unlike highly and rapidly fatal (in chicken) H5 and H7 HPAI viruses, H7N9 virus infection may lead to silent infection in poultry birds that may go undetected and can infect and cause disease in human beings in direct contact with these birds [58]. The first human case of H6N1 virus infection was recorded in Taiwan in 2013. Genetic analyses revealed homology of this virus to chicken H6N1 virus of Taiwanese origin, except with a G228S substitution in the HA protein that might increase the affinity for the human sialic acid α (2–6) galactose (Sia [α2,6] Gal) receptor [59]. Occurrences of H10N7 virus infection in humans were recorded in Egypt and Australia [60]. Human infection with H10N8 virus was recorded in China in 2013, and the virus derived some of the gene segments from H9N2 virus subtype prevailing in Chinese poultry with no remarkable disease in birds like H7N9 virus [19].

Role of pigs is important in the evolution and ecology of influenza A viruses as pigs are susceptible to both human and animal influenza viruses due to availability of both N-acetylneuraminic acid α (2,3)-galactose (preferred by AIVs) and N-acetylneuraminic acid α (2,6)-galactose (preferred by mammalian influenza viruses) in their respiratory tract [36,43]. Due to availability of receptors for both AIVs and human A influenza viruses, in addition to directly transmitting the virus to humans, pigs also act as mixing vessels promoting reassortment of RNA genome fragments/segments between influenza viruses of various origin [61,62]. Such mixing and reassortment may result in antigenic shift; antigenically away from the parent viruses contributing different gene segments during reassortment. Due to the significant role of pigs in the ecology of influenza viruses including generation of new antigenic types/variants, transmission events between pigs and humans and the other way need to be monitored and minimized to prevent generation of reassorted viruses with greater human health concerns [2].

Pathogenesis

Pathogenicity is defined as the ability to cause disease in the host. Influenza A viruses of different HA and NA subtypes are present asymptomatically in the gastrointestinal tract of wild birds [63] but may cause disease in domestic birds, humans and pigs when infected, classified as avian zoonoses [64]. Virulence and host range of AIVs are mostly linked to the HA and NA glycoproteins on the virus surface and host cell receptors. In addition, the other gene segments also contribute to virus adaptation, pathogenesis, transmission, and immune evasion [2]. The HA glycoprotein helps the virus to attach to the terminal sialic acid residues on host cell glycoproteins and glycolipids. After entry of the virus in to the endosome, the HA facilitates fusion of virus envelope with the cell membrane

and virus contents are released in to the cell. HA is synthesized as HA0 precursor and presented on the virus surface, and it is cleaved by host proteases at a conserved arginine amino acid residue to HA1 and HA2, linked by a single disulphide bond. This cleavage is required for productive infection. The NA cleaves terminal sialic acid residues of cellular receptors and is involved in the release of mature virions. The NA may also contribute to initial viral entry [65]. NA is also the target of inhibitor drugs like oseltamivir and zanamivir. The NS-1 protein is a virulence determinant of HPAI H5N1 virus that interferes with the host interferon response [66] by sequestering viral genomic RNA from intracellular receptors. The NS gene also codes for the nuclear export protein (NEP), generated by alternative RNA splicing of NS transcript, is involved in the nuclear export of RNA and assembly of new virion particles [67]. In the viral polymerase PB2, ^{627}E→K (glutamic acid to lysine is most commonly observed in HPAI H5 and H7 viruses [68]. The ^{701} D→N (aspartic acid to asparagine) has been shown to be associated with susceptibility of human beings to H5N1 virus [41]. Mutation of ^{627}E→K in the PB2 protein and the ^{66} N→S mutation of the PB1-F2 protein, is associated with an impaired adaptive immune response and increased host cell apoptosis, which may contribute to enhanced viral replication and infection of non-respiratory organs [2,69,70]. The PB1-F2 protein (by RNA segment 2) has been shown to contribute to pathogenicity. Reports demonstrated that PB1-F2 promotes cell death, causes immunopathology and increases pro-inflammatory responses [70-73]. A single point mutation from asparagine (N) to serine (S) at position 66 in the PB1-F2 protein highly increased the virulence of highly pathogenic avian H5N1 influenza virus and the 1918 H1N1 pandemic virus [69]. The pathogenic functions of PB1-F2 protein in detail has been worked out by [74]. The IAV PB1-F2 protein translocates to mitochondria, accelerates the mitochondrial fragmentation and impairs innate immunity [75]. PB1-F2-induced mitophagy was critical for the degradation of MAVS (mitochondrial antiviral signalling protein) and led to suppression of the type I IFN production. The C-terminal LIR motif of PB1-F2 protein was demonstrated to be essential for its mitophagy induction and attenuated innate immunity. The PB1-F2-induced mitophagy strongly correlated with impaired cellular innate immunity, and it can be a potential therapeutic target.

Influenza virus cross-species transmission is restricted by the host, but viruses overcome this restriction by accumulating mutations which allow them to adapt to a new host. Polymerase basic protein 2 (PB2) 627 plays an important role that facilitates virus-host adaptation [76]. Histone H1.2 (encoded by HIST1H1C) regulates human or avian influenza virus replication in different ways [76] found that levels of HIST1H1C expression, phosphorylation and methylation levels decreased upon infection with H1N1 influenza virus, but increased when infected with H5N1 virus. Overexpressing the eight gene segments of the influenza virus, they found that only PB2 significantly affects HIST1H1C expression and modifications. Further analysis showed that influenza virus PB2-627 regulates HIST1H1C expression via Sp1; PB2-627K down-regulates Sp1 and HIST1H1C whereas PB2-627E up-regulates Sp1 and HIST1H1C. The Clade 2.2 Eurasian-lineage H5N1 HPAI viruses were first detected in Qinghai Lake, China, in 2005, and subsequently spread through Asia, Europe, and Africa. These viruses had lysine at PB2- 627 (PB2- 627K) that supports mammalian adaptation. Previous avian influenza virus isolates had PB2 627E that restricts virus polymerase function in the mammalian host [77].

Beside the viral virulence factor described earlier, host factors are also responsible for the pathogenesis of AIV infection. Unlike H5N1, the AIVs H7N9 and H10N6 infection in poultry do not elicit prominent clinical symptoms and may go undetected. Such sub clinical infections may yield new reassortants. Cocirculation of H5N1, H9N2, and H7N9 viruses has been found to yield many new reassortants, viz. H10N8, H10N6, H5N8, H5N6, and H7N6 with participation of other enzootic AIVs [19,78-81]. Asymptomatic infections in humans with different avian influenza A viruses have been identified by serology and virology. Clinical symptoms like conjunctivitis, respiratory failure, refractory shock, and multi organ failure etc have been reported in humans associated with many AIV LPAI and HPAI virus strain (H5/7/9/10 and N1/2/3/6/7/8/9) infections[12].

Prevention and control

Currently there is no policy to vaccinate against bird flu in India and control is by culling infected birds including in-contact ones following the guidelines laid down by government.

Conclusion

Interspecies transmission of IAVs has been a regular feature since long in the history of human and animal influenzas. Avian zoonoses has been detected world wide involving several antigenic H and N types of IAVs. Segmented nature of the RNA genome has

facilitated antigenic shift by means of exchange of gene segments between co-infecting/co-circulating antigenic types of the virus, and expanded host susceptibility. Worldwide, emergence and re-emergence of AIVs has been found associated with the practices of rice cultivation and duck rearing/farming. Transmission of HPAI virus strains between countries and continents has been made possible by long distance migratory birds as well as contaminated poultry feed. The emergence of H5N1 bird flu was traced to migratory birds in the Qinghai lake, China. The proximity of humans with birds and pigs has helped in avian zoonoses. In spite of several avian zoonoses, human to human transmission of AIVs has been inefficient. In India, bird flu caused by H5N1 was detected during February-March 2006 that caused enormous economic loss to the poultry industry, depopulation of indigenous poultry birds, and threatened in contact human populations. Chemical nature of the HA receptors in the respiratory tract differentiates avian and human influenza viruses. Asynonymous mutations leading to amino acid substitutions in and around the receptor binding domain of HA alter the receptor binding preference of influenza viruses that define virus transmissibility. Wild aquatic birds, ducks and pigs play significant role in the ecology of human and avian influenza (Bird flu). Asymptomatic circulation of several antigenic types of AIVs in domestic birds including poultry usually go undetected and is of concern to avian and human health. Regular surveillance for AIVs in aquatic and terrestrial birds is important to prevent avian zoonoses.

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Conflict of Interest

No conflict of interest is declared.

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