The Journal of Animal & Plant Sciences, 29(3): 2019, Page: 629-644
ISSN: 1018-7081

REVIEW PAPER

EMERGENCE OF INFLUENZA A VIRUS IN DOGS AND COINFECTION WITH BACTERIAL SPECIES: A REVIEW

D. H. Kalhoro[1,2], M. S. Kalhoro[2], A. Kaka[2], N. Rapjut[2], M. Naeem[2], S. Kumbhar[2], G. M. Lochi[2], F. Parveen[2] and Y. J. Liu[*1]

[1]Joint International Research Laboratory of Animal Health and Food Safety, College of Veterinary Medicine, Nanjing Agricultural University, Nanjing, China; [2] Faculty of Animal Husbandry and Veterinary Sciences, Sindh Agriculture University, Tandojam-70060, Pakistan
[*]Corresponding Author E-mail: liuyongjie@njau.edu.cn

ABSTRACT

Dog is the most intimate companion animal of human, and the close contact between humans and dogs raises the possibility that dogs can transmit virus to humans as intermediate hosts. Canine influenza virus (CIV) belongs to *Influenza virus* A of *Orthomyxoviridae* family and is a highly emerging respiratory pathogen that can be adapted to new hosts by crossing interspecies barriers. In recent years, cases of dogs infected with various subtypes of influenza virus are reported continuously, including H3N2, H3N8, H5N1, H1N1, H3N1 and H9N2 viruses. Reports indicated that the influenza virus might further acquire the ability to infect dogs. The CIVs not only severely jeopardize the survival and health of dogs, but also bring tremendous risks to human health. During influenza pandemics secondary bacterial infection is the main cause of the mortality. There is dire need to know mechanisms involved in the interaction between Influenza and bacterial species to understand treatment procedures that fight viral and secondary bacterial infection.

Keyword: Influenza A Virus, Canine influenza virus, Subtypes, Co-infection, Pathogenicity, Transmission.

INTRODUCTION

Dogs are companion animals having close contact with humans and surrounding atmosphere, providing high health risk to human population (Su *et al.,* 2013a). Canine Influenza virus (CIV) belongs to *Influenza virus* A of *Orthomyxoviridae* family and is a highly emerging respiratory pathogen of canine (Lee *et al.,* 2010a). Influenza A virus is extremely pathogenic to humans and domestic animals including avian, swine, equine, canine and feline species. IAV is categorized into subtypes according to two viral proteins, hemagglutinin (HA) and neuraminidase (NA). By now, 16 HAs and 9 NAs have been identified. All subtypes of influenza virus can be isolated from birds. Hemagglutinin and neuraminidase can vary due to antigenic shift and antigenic drift (Shu *et al.,* 1994). Influenza A virus contains segmented genomes of eight single-stranded negative-sense RNA molecules, structural proteins such as PB1, PB1-F2, PB2 and PA, surface glycoproteins HA and NA, NP, M1, M2, and two nonstructural proteins NS1 and NS2 (Dangi *et al.,* 2012). Another viral protein N-40, a product of PB1, is identified but till now its function is yet to be understood (Wise *et al.,* 2009). It causes significant losses to animals and humans (Lee *et al.,* 2010a). Co-infection of different subtypes in canine may give an opportunity for the emergence of novel reassortant influenza viruses. Canine influenza virus (CIV) was first reported in 2004 from Florida racetrack Greyhounds and recognized as H3N8 subtype (Crawford *et al.,* 2005). CIV H3N2 was first emerged in South Korea in 2007 and subsequently spread to other countries, causing epidemic as well as endemic canine respiratory diseases. Virus can infect cats; however, no report is available of significant genetic evolution since its first emergence (Jeong *et al.,* 2013). Most of the clinical signs of CIV in infected dogs are low-grade fever, nasal discharge, and cough (Payungporn *et al*., 2008; Yoon *et al*., 2005; Song *et al.,* 2009).

Subtypes of influenza a virus in dogs: At present seven Influenza A Virus subtypes are reported from different parts of world that infect dogs: H3N2, H3N8, H5N1, H1N1, H3N1 and H9N2 (Table 1). Only IAV subtype H3N8 and H3N2 can cause continued transmission of infection among dogs. Whereas, remaining subtypes can cause infection but no significant evidences are available that show that these subtypes can be transmitted constantly in dogs.

Table 1. Subtypes of Influenza A Virus in dogs

S. No	Subtypes of IAV in dogs	Susceptible animals/birds	Country	Year	Reference
1.	H3N2	Canine, Feline, Poultry	South Korea	2007	Jeong *et al.,* 2016
2.	H3N8	Canine, Equine	USA	2004	Crawford *et al.,*2005
3.	H5N1	Canine , Porcine, Poultry	Thailand	2004	Abdelghafar *et al.,* 2008
4.	H5N2	Canine, Poultry	China	2009	Lee *et al.,* 2009
5.	H1N1	Canine, Feline, Porcine, Poultry	China	2009	Dundon *et al.,* 2010
6.	H3N1	Canine	South Korea	2010	Song *et al.,* 2012
7.	H9N2	Canine, Feline, Poultry	China	2013	Sun *et al.,* 2013

Subtype H3N2: After first case of avian origin CIV H3N2 reported in 2007 from South Korea, several cases have been reported from canine populations from other countries (Li *et al.,* 2010b). Canine influenza virus H3N2 was isolated from canines in Jiangsu province, China and was almost similar to the Korean isolate from cats; sequencing and phylogenetic analysis of the virus show its resemblance to the Korean feline isolate. Phylogenetic analysis is summarized in (Fig. 1) in which HA sequence of H3N2 strains were compared, phylogenetic results revealed that feline, avian and swine influenza A viruses have close relation with canine. Most of the cases of virus outbreaks were reported from Animal Clinics (Lin *et al.,* 2012b). Clinical signs due to H3N2 are coughing, sneezing, nasal discharge, fever, and the shedding of the virus in the nasal discharge (Lee *et al.,* 2010a; Song *et al.,* 2008; Song *et al.,* 2009), decreased body weight, and interstitial pneumonia. Histopathological sings are mainly associated with respiratory infection causing severe and long-persistent suppurative bronchointerstitial pneumonia (Kang *et al.,* 2013). Cytokines level is elevated that may play a role in the pathogenesis of canine influenza virus H3N2 (Jung *et al.,* 2010). Whereas, transcriptional genomic study in lungs of dogs infected with H3N2 have shown highly active genes associated with immunity, inflammation and apoptosis as compared to the mock-infected dogs (Kang *et al.,* 2013).

First reported case of AIV H3N2 transmitted to the canines in South Korea was reported in 2007 and localization of SAα 2, 6-gal and SAα 2, 3-gal linkages in the respiratory tracts were evaluated. The causative agent was transmitted to the canine through direct contact by nasal route in experimental trials in miniature schnauzer, cocker spaniel, and Jindo dogs (Song *et al.,* 2008). Subsequent follow-up studies have demonstrated spread of virus through direct contact from canine to canine; virus can be recovered from nasal swabs (Song *et al.,* 2009). Furthermore, interspecies transmission of H3N2 to the feline was firstly reported at an animal shelter in Seoul, South Korea causing 100% morbidity and 40% mortality (Song *et al.,* 2011). Sialic acids is a primary receptor play an important role in the direct transmission of H3N2 to dogs, with SAα 2, 3-gal shown on epithelial cells of the upper and lower respiratory tracts of dogs (Song *et al.,* 2008). Recently, H3N2 was isolated from nasal swab sample of a dog having flu like symptoms in an animal hospital in Bangkok, Thailand, showing similar genetic characteristics to the isolates from Jiangsu and Zhejiang, Eastern China but not from Guangdong, Southern China and Korea (Bunpapong *et al.,* 2014). In China, interspecies transmission of H3N2 to canine was reported at animal clinics in Guangdong province showing> 94.7% homology to Asian H3N2 AIV (Li *et al.,* 2010b) and Jiangsu province of Southern China (Lin *et al.,* 2012b). It was assumed that dogs eating infected poultry meat and products or aerosols are playing vital role in the transmission of the infection (Gibbs and Anderson, 2010). Due to ecological changes in China, there are increased cases of H3N2 CIV infection in dogs; this may be due to change in the socioeconomic circumstances and use of dogs as companion animals and for food in densely populated areas (Li *et al.,* 2010b).

An epidemiological study was carried out to determine prevalence of CIV H3N2 viruses in the Liaoning province of China. Serum sample (158) and nasal swab specimens (510) were collected from Sept-2010 and May-2012, showed respiratory signs in dogs. Serological study identified two viral strains A/canine/Liaoning/27/2012 and A/canine/Liaoning/H6/2012 with a prevalence of 10.8 % in pet dogs. Genes of both strains have genotype (K, G, E, 3B, F, 2D, F, 1E) and were (99.2–99.8 %) similar to the strains commonly circulating in H3N2 CIVs in Asia (Yang *et al.,* 2014). Recently, two H3N2 canine isolates were identified by RT-PCR from pet dogs. Phylogenetic results indicated that genes were clustered with Moscow/10/99 and H3N2 swine influenza viruses, high homology with human/swine influenza viruses and some amino acid substitutions in NA, polymerase basic protein 1 (PB1), and nucleoprotein (NP) was also observed that play an important role in the interspecies transmission of the virus (Chen *et al.,* 2015). Studies have been done recently, indicated that CIV H3N2 is circulating in Chinese dogs (Lin *et al*., 2016). Whereas, serological studies in South Korea and southern China showed seroconversion of IAV H3N2 as 3.3% and 10% respectively in the dogs, so these results suggested that Avian-origin CIV H3N2 has become endemic in the dogs

in South Korea and China (Lee *et al.,* 2009; Su *et al*., 2013a). Recently, one strain of CIV H3N2 was isolated from dogs in Nanjing and phylogenetic analysis showed its similarity to the newly isolated H3N2 viruses from dogs in China (Kalhoro *et al.,* 2018). Above described epidemiological results strongly suggested that CIV H3N2 had been circulating in the canine population in China and Korea.

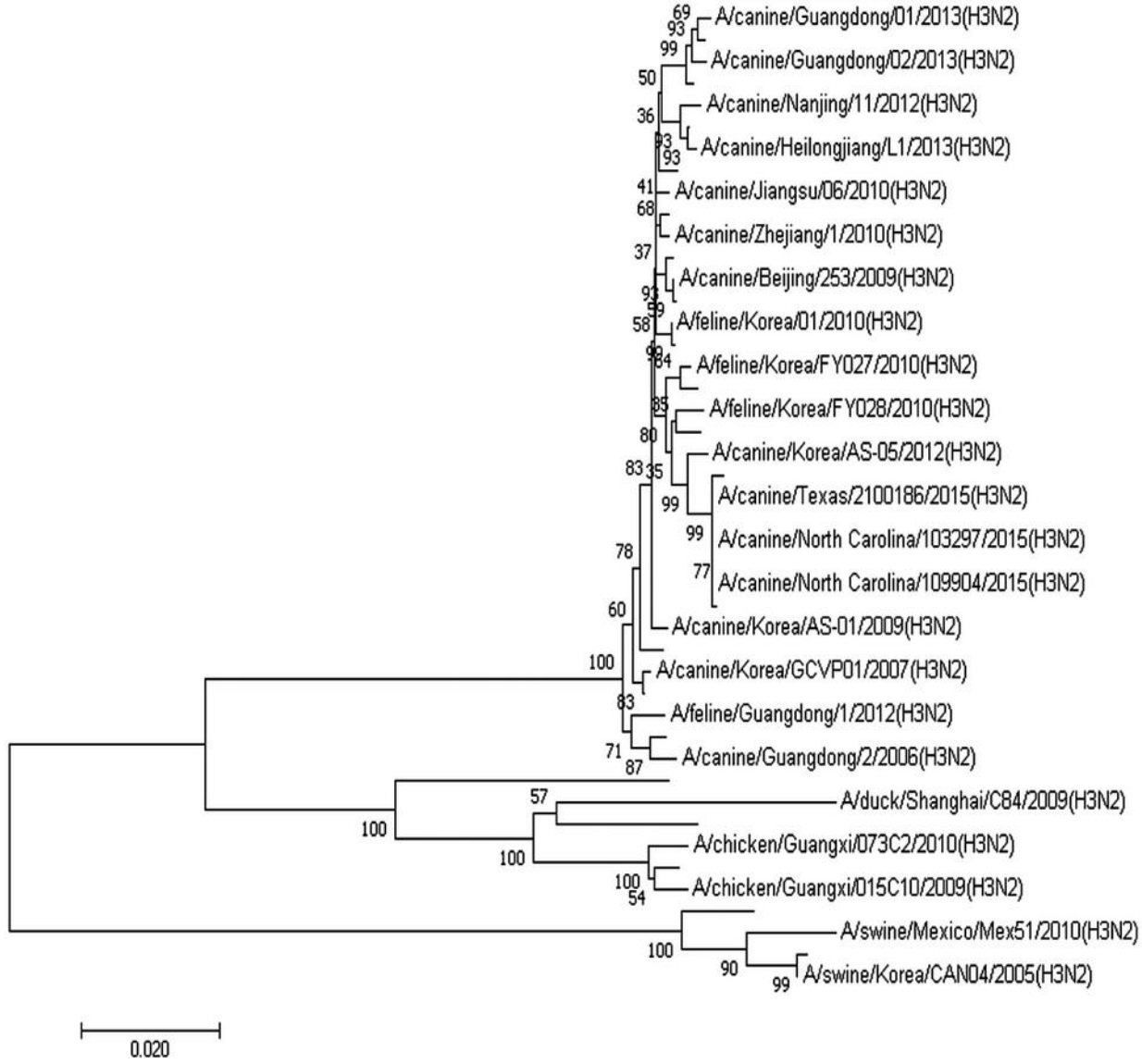

Fig 1. The Phylogenetic tree of H3N2 influenza A viruses based on HA gene was generated with the MEGA program (version 7.0) by using neighbor-joining analysis and bootstrap test (1000 replicates).

Subtype H3N8: Earlier studies showed that EIV H3N8 viruses did not cause acute respiratory disease in other animals and man (Kasel *et al..,* 1965) but in January 2004, CIV sub type H3N8 was firstly detected from lungs of racing greyhound dogs kept near infected horses, causing severe clinical signs such as high fever, nasal or ocular discharge, hemorrhagic tracheitis, bronchopneumonia, vasculitis and finally death. An outbreak of Canine influenza virus was reported in 22 racing greyhound dogs, nucleotide sequence revealed its similarity with equine influenza virus (EIV) H3N8 (Crawford *et al.,* 2005; Dubovi and Njaa, 2008). H3N8 was isolated from dead greyhound dogs in Florida and Texas, seroepidemiological survey indicated that the CIV H3N8 was also prevalent in the greyhounds that can be transmitted to the companion dogs in USA (Payungporn *et al.,* 2008). Again in 2004 and 2005 outbreaks due to H3N8 has been reported in dogs including pet dogs from animal shelters, humane societies, rescue groups, pet stores, boarding kennels, and veterinary clinics in USA (Yoon *et al.,* 2005). Phylogenetic analysis is summarized

in (Fig. 2) in which Subtype H3N8 may be diverging into lineages: New York, Colorado and Pennsylvania.

CIV H3N8 can be transmitted by direct contact of dogs (Jirjis *et al.,* 2010) with respiratory secretions and fomites. Due to early shading of virus before showing clinical signs, outbreaks can occur when clinically normal dogs come into contact with naïve dogs. Virus is mostly transmitted to other dogs in dense populations where susceptible can enter in as ideal place for transmission (Wiley *et al.,* 2013). H3N8 canine influenza virus has been serologically investigated in different parts of the world. In Ontario, Canada, 225 dogs were serologically investigated, only one greyhound dog originated from Florida was positive so it was concluded that this virus was either not present or rarely circulate in the province (Kruth *et al..,* 2008). In 2002, a retrospective study in dogs was done and confirmed by different techniques showing respiratory outbreaks in UK among English foxhounds. It may be transmitted through direct contact with infected horses or ingestion of infected material from horses (Daly *et al.,* 2008). In the spring of 2003, in UK, transmission of H3N8 EIV was also reported in dogs that were fed for a week on raw meat and offal from horses (Newton *et al.,* 2007). During 2007 epidemic of H3N8 EIV in Australia, dogs developed influenza-like illness after direct contact with infected horses. Through serologically and RT–PCR sequencing, multiple cases were confirmed and genes were identical to the H3N8 equine influenza; however virus was not isolated from affected dogs and it could not be transmitted from dog to dog (Kirkland *et al.,* 2010). Recently, low prevalence of CIV H3N8 in dogs was investigated in Germany. Samples were taken from clinically healthy dogs (n-272) and dogs with acute respiratory signs (n-35) were tested by different assays. Antibody prevalence was 0% (0–1.24%, 95% CI), so it was concluded that the risk for CIV H3N8 infection is very low in Germany (Schulz *et al.,* 2014).

Recently studies were conducted from May 2015-November 2015 in Guangzhou, Shanghai, Beijing and Shenzhen. A total of 600 sera from pet dogs were collected and analyzed by hemagglutination inhibition (HI) assays and microneutralization (MN) assays. Fifty two (8.66%) of the 600 sera were positive for H3N2, while five (0.83%) were positive for H3N8, that is the first report of H3N8 virus infection among dogs in China (Zhou *et al.,* 2016).

Subtype H5N1: Canine influenza virus was isolated nearly 10 years ago; Virus has been present in dog populations living in humane shelters (Crawford *et al.,* 2005). H5N1 influenza viruses are placed in ten distinct HA phylogenetic clades (0–9) and the clade 2 viruses are divided into different subclades. The clade 2.2 viruses, characterized by BHG/QH/3 /05, were isolated from wild birds in China (Abdelghafar *et al.,* 2008). They contain genetic markers amino acid lysine at position (627 of PB2) and the absence of a potential N-linked glycosylation site at HA amino acid (positions 158–160) is responsible for replication and transmission to other mammals (Hatta *et al.,* 2001). BHG/QH/3/05 can replicate more efficiently in dogs than the other strains (Chen *et al.,* 2010). H5N1 avian influenza virus was first identified when an outbreak occurs in Hong Kong in 1997 (Chen *et al.,* 2006) then it was reported from Asia, Europe, and Africa, can infect wide range of species including pigs (Choi *et al.,* 2005) poultry (Mehrabanpour *et al.,* 2007) humans (Maines *et al.,* 2005), cats (Songserm *et al.,* 2006), tigers (Keawcharoen *et al.,* 2004) and ferrets (Zitzow *et al.,* 2002). Dogs are highly susceptible to H5N1 showing clinical signs of fever, anorexia, conjunctivitis, and labored breathing (Chen *et al.,* 2010). A fatal case of dog was reported after ingestion of HPAIV H5N1 positive duck meat in Thailand.

Histopathological examination revealed that the lung was severely affected with pulmonary edema and interstitial pneumonia (Songserm *et al.,* 2006). On genetic analysis, it was similar to the H5N1 viruses isolated in Thailand from a tiger (CU-T3) in 2004 (Keawcharoen *et al.,* 2004). A serological study was carried out in central Thailand to examine 629 village dogs for H5- specific antibodies. It was reported that 160 dogs (25.44%) were positive for H5N1 infection; however, no transmission between dogs was reported (Butler, 2006). Studies have been conducted to know if HP H5N1 influenza virus from dogs can be transmitted to man (Giese *et al.,* 2008; Maas *et al.,* 2007). It was revealed from these studies that after inoculation of HP H5N1 influenza virus in dogs within 2 days p.i, signs such as conjunctivitis and transiently elevated body temperature, shading of virus from nasal cavity for short time were observed (Maas *et al.,* 2007) or no virus has been detected (Giese *et al.,* 2008). It was suggested that dogs may play vital role in the adaptation of H5N1 virus to other animals. Recently outbreak has been reported from China, where H5N1 was isolated from dead raccoon dogs possessing specific genotypes to infect mammals and humans that are not known to infect these hosts (Qi *et al.,* 2009), viral attachment occurs in receptors present in the lower respiratory tract ,trachea and nose (Maas *et al.,* 2007). Experimental infection in dogs showed that beagle dogs are highly susceptible to H5N1 influenza virus by shedding virus through their nose and transmit to humans (Chen *et al.,* 2010). In a mouse model, inoculation of A/Vietnam/1230/04 (H5N1), mortality was observed by 6 days post infection (Kim *et al.,* 2015), more potent inflammatory response was recorded with inoculation of H1N1 influenza virus (Cilloniz *et al.,* 2010). Role of inflammatory response to pathogenesis after induction of H5N1 influenza virus was determined in mice lacking inflammatory signaling receptors i-e

TNFR1, TNF-R2, and IL-1RI, showed low level of cytokine production in lung tissues, less morbidity and a prolonged delay of death (Perrone *et al.,* 2010). Recently, a study was carried out to compare pathogenicity of H5N1 virus in domestic cats and dogs, after infection cat was observed to be highly susceptible, showing severe fibrosis, bronchitis and alveolitis with infiltration of inflammatory cells in lungs, perivascular cuffing in brain and finally death, whereas, no severe lesions were observed in dogs. Higher level of genes related to the inflammatory cytokines, chemokines, Toll-like receptors and apoptotic factors were expressed in cats than dogs (Kim *et al.,* 2015).

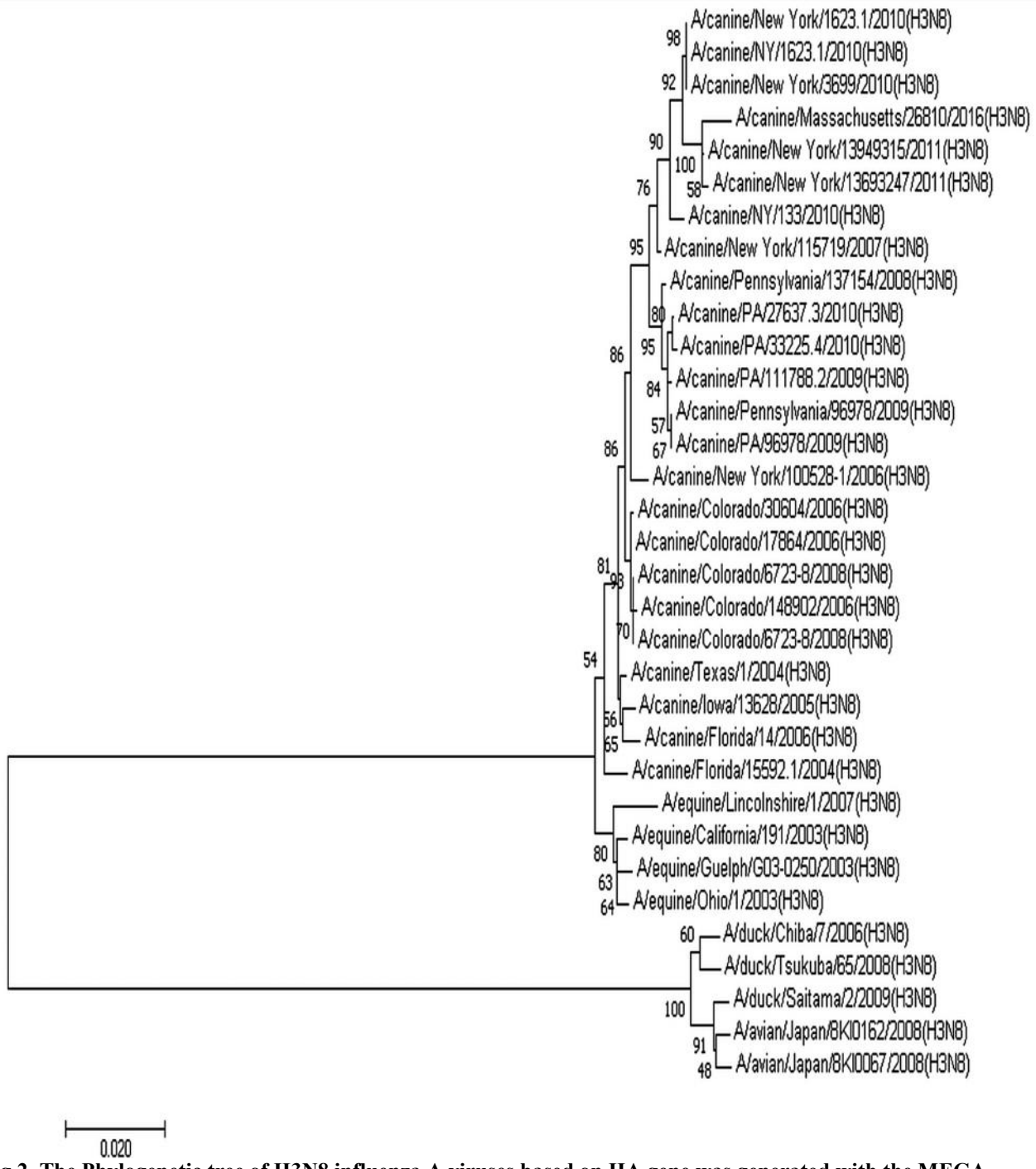

Fig 2. The Phylogenetic tree of H3N8 influenza A viruses based on HA gene was generated with the MEGA program (version 7.0) by using neighbor-joining analysis and bootstrap test (1000 replicates).

Subtype H5N2: Dogs play important part role in interspecies transmission and spread of canine influenza virus (Giese *et al.,* 2008; Song *et al.,* 2008). H5N2 has been mostly isolated from birds but only few viruses are associated with infection in animals (Lee *et al.,* 2009). In 2009, influenza virus H5N2 having low pathogenicity was reported in China from dogs having respiratory signs. H5N2 was emerged due to reassortment of swine influenza virus H5N1 and avian influenza virus H9N2 (Zeng *et al.,* 2013). Experimentally it was clear that influenza virus can be transmitted through direct contact showing respiratory signs of sneezing, nasal discharge and mild coughing, transient elevated body temperature, conjunctivitis (Guang *et al.,* 2012). Six dogs of from experimental groups showed seroconversion and shedding of virus in nasal swabs and finally recovered. Spread of the virus can occur due to the close contact with H5N2 infected and noninfected dogs (Song *et al.,* 2013). H5N2 virus can be transmitted to other animals after direct contact between infected dogs, cats and chickens (Hai-xia *et al.,* 2014). Due to close contact of dogs with each other, H5N2 can infect the other animal species and may have zoonotic potential (Guang *et al.,* 2012).

Subtype H1N1: Novel strains are being emerged due to the coinfection with different influenza viruses having zoonotic potential (Sun *et al.,* 2014). Dogs are companion animals having close contact with humans, so they carry canine influenza virus and have a great threat to human health (Su *et al.,* 2013b). H1N1/ 2009 mainly infect human population but it can be transmitted to animals including pigs, poultry, dogs and ferrets (Dundon *et al.,* 2010; Sponseller *et al.,* 2010). In 2009 influenza virus H1N1 pandemic occurred worldwide as a result of multiple reassortment events comprising of avian, human and swine influenza A virus strains (Brockwell *et al.,* 2009). In China, pH1N1 was isolated from two pet dogs admitted at the Animal Hospital of the China Agricultural University, Beijing in December 2009 (Mail, 2009a); during same month a case of pH1N1 infection in a 13 year old pet dog was reported from New York, USA after direct contact of dog with its owner who was infected with pH1N1. Dog showed clinical signs of lethargy, coughing, anorexia, pyrexia, and pneumonia. It was concluded that virus can be transmitted from humans to dogs (Mail, 2009b). A total of 1,061 serum samples were collected in Italy and found 7 (0.7%) of the canine serum samples positive to the virus, transmission of the virus occurs by aerosol or close contact of infected pet owners and pets during mid-November 2009 (Dundon *et al.,* 2010).

Similarly serological study to investigate influenza A (H1N1) pdm09 infection was carried out in Germany. A total of 1150 sera were collected in 2010 and 2011 from dogs and cats. ELISA tests have confirmed the prevalence of 0.13% in dogs and 1.93% in cats (Damiani *et al.,* 2012). Studies have shown that H1N1/2009 virus is highly infectious for dogs but with low infection rates (Lin *et al.,* 2012a). Recently, H1N1/2009 virus was isolated from two dogs having few clinical signs of low fever and occasional cough, histopathological examination revealed no apparent lesions in tonsils, interstitial edema and inflammation of inflammatory cells around blood vessels in the lung, immunohistochemistry showed presence of viral antigens in trachea and lung (Lin *et al.,* 2012a). High sero-prevalence of pdm09 (H1N1) virus was observed in dog by using a hemagglutination inhibition (HI) assay (24.7%) and a microneutralization (MN) assay (10.8%) (Dundon *et al.,* 2010; Lin *et al.,* 2012a). Dogs did not showed clinical signs of influenza infection that supports the idea that dogs may play an important role in the human influenza ecology in China (Su *et al.,* 2014).

Subtype H3N1: In 2012, H3N1 a putative reassortant between pandemic H1N1/2009 and H3N2 CIV, was isolated from dogs through the surveillance program of the Korean National Veterinary Research and Quarantine Service. Genetic investigations have shown that the H3N1 was highly similar (99.1–99.9 %) to pandemic H1N1/2009, only HA gene nucleotide sequence was 99.6 % similar to H3N2 isolated in Korea and China. According to the genetic and phylogenetic analyses novel H3N1 Canine influenza virus might be a natural reassortant between the H3N2 canine virus and the pandemic H1N1 virus. Macroscopic and microscopic examination of lung lesions were characterized by mild reddish consolidation with focal lesions and mild to moderate focal interstitial pneumonia so the novel CIV H3N1 was not pathogenic as the CIV H3N2 but could be shed through the respiratory tract and cause moderate lung lesions. Lower shedding of virus was resulted due to the asymptomatic infection or relatively mild pathogenicity (Song *et al.,* 2012). Reassortant viruses can be emerge by co-infection of the seasonal H1N1 virus (A/New Jersey/15/2007) and the pandemic H1N1 virus (A/Tennessee/1-560/2009) (Ilyushina *et al.,* 2010), this is also in the case of H3N1 when coinfection of two strains of influenza virus occurs, most of the dominant progeny viruses were reassortant having the HA gene from the seasonal strain and the remaining genes from the pandemic virus, which was consistent with the genetic characteristics of the novel H3N1 CIV (Song *et al.,* 2012).

Subtype H9N2: H9N2 is a low pathogenic avian influenza (LPAI) virus firstly reported in turkeys in Wisconsin in 1966 (Homme and Easterday, 1970). Historically Southern China is an epicenter of pandemic influenza virus infections (Shortridge and Stuart, 1982). In China first outbreak of the H9N2 influenza virus was reported in chickens from Guangdong province of Southern China during November 1992 to May 1994,

10%–40% mortality in broilers and 14%–75% reduction in egg production was observed, laboratory analysis showed mild flu-like symptoms in specified pathogen free (SPF) chickens (Chen *et al.,* 1994). Influenza virus H9N2 A/Canine/Guangxi/1/2011 was firstly isolated from dogs in southern China. Infection was characterized by elevation of body temperature, vomiting, loss of appetite, coughing, sneezing and nasal discharge. Serological survey from early 2010 to late 2011 by haemagglutination inhibition (HI) test demonstrated positive rate of 20.21% (92/455) in eight pet clinics and 28.98% (273/942) in fourteen counties of Guangxi. Again in 2012, a total of 914 blood serum samples were collected from dogs and high prevalence rate 44.85% (410/914) was confirmed by HI assay, suggesting the circulation of H9N2 virus among dogs (Sun *et al.,* 2013). Novel viral strain H9N2 A/Canine/Guangxi/1/2011 was confirmed by phylogenetic analysis as in agreement with earlier reports (Xu *et al.,* 2007). H9N2 influenza virus can replicate efficiently in dogs and cats via the upper respiratory tract.

Virus can be transmitted between cats but not between dogs (Zhang *et al.,* 2013). The infection animal models include chickens, quails, BALB/c mice (Li *et al.,* 2005), guinea pigs (Sun *et al.,* 2010a) and ferrets (Ku *et al.,* 2014) were used to study pathogenicity of the virus. Virulence and replication of the virus can be enhanced by combination of M147L and E627K on PB2 proteins in mice infected with mouse-adapted H9N2 virus (Wang *et al.,* 2012).Currently, BJ94-like, G1-like, and Y439-like lineages of H9N2 virus are being circulating in China (Sun *et al.,* 2010b). BJ94-like H9N2 virus was inoculated in beagles only few underwent seroconversion and showing mild fever (Zhou *et al.,* 2015).

Transmission of canine influenza virus: Two main and basic mechanisms behind interspecies transmission of influenza virus may be possible (Lipatov *et al.,* 2004). First is the direct transmission of essentially unaltered virus from one species to another e-g human infection with the H5N1 subtype of avian influenza virus (Guan *et al.,* 2004). Second is a consequence of the segmented nature of the influenza virus genome. eg, influenza pandemics in 1957 and 1968 has been reported due to novel viruses generated by gene reassortment between avian and human influenza viruses (Lipatov *et al.,* 2004). Virus ability to enter from one specie to specie depends upon several factors i-e some viruses cannot enter into new host specie because of lack of appropriate receptors, while some virus can get access to enter but they cannot complete virus replication cycle (Morse, 1997). H3 subtype viruses are capable to human, avian and mammalian hosts. H3N8 and H3N2 canine viruses are different from human strains both genetically and antigenically so there is possibility that these or similar viruses can be transmitted from dogs to human population (Harder and Vahlenkamp, 2010). Influenza virus H5N1 of avian origin and human H3N2 and H1N1 are not capable of transmitting to dogs but infection in canines can be caused by two subtypes H3N8 and H3N2 and efficiently circulating in America, Europe, and Asia (Harder and Vahlenkamp, 2010; Nerome *et al.,* 1981).

Influenza virus infection: It is vital to understand the mechanisms involved in the interaction between influenza virus and bacterial organisms for success in fight against viral and secondary bacterial infections (Smith *et al.,* 2013). Infections due to virus-bacteria interaction is the major cause of influenza pneumonia because of synergistic effect during invasion of respiratory tract (Callan *et al.,* 1997). Bacterial infections may be the main cause of death related to influenza virus infection in the absence of preexisting comorbidity (Fowlkes *et al.,* 2011). Interaction of extracellular proteases with the HA may initiate viral infection or can be infectious with uncleaved hemagglutination through the host cell endoprotease (Nagatake, 2003). Expression of influenza virus in the mouse model has been well explained by the use of Enzyme-Linked Immunosorbent Assay (ELISA) that induces the cytokine and chemokine milieu while induction levels are different depending upon the strain of mouse. Higher level of cytokines and chemokines were found in the BAL fluid of DBA/2 as compared to C57BL/6 mice leading to increased lung pathology (Srivastava *et al.,* 2009). During influenza virus infection, high levels of proinflammatory cytokines including IFN-γ, IL-1α, IL-6, MIP-1α, MCP-1, and KC were expressed in lungs leading to severe lung consolidation and destruction of tissue architecture (Perrone *et al.,* 2008).

Coinfection of influenza a virus with staphylococcal species: *Staphylococcus aureus* is considered as major pathogen with commonly circulating influenza virus causing fatal pneumonia (Finelli *et al.,* 2008; Morens *et al.,* 2008). Now a day they are major cause of bacterial pneumonia, mainly in children with influenza infection (Finelli *et al.,* 2008). Secondary bacterial pneumonia during epidemic influenza seasons in 1957 and 1968 was a major cause of mortality (Simonsen *et al.,* 2000) while *S. aureus* was mostly associated with these infections (Finelli *et al.,* 2008). *S. aureus* mouse model can increase bacterial titers in secondary organs, lungs and blood along with inflammatory lung damage which cause high morbidity as well as mortality in combined infection with influenza virus than was evident with either pathogen alone. Higher viral and bacterial lung titers were observed during coinfection when it was compared with single infections. Staphylococcal super infection results in fulminant illness, pneumonia and high level of mortality in mice coinfected with influenza virus and *S. aureus* due to altered cellular response to infection, higher degree of damage to lung parenchyma and

increased bacterial load in the liver, kidney and spleen. At 72 hours of infection high level of Panton-Valentine leukocidin and α-hemolysin were expressed in mice infected with *S. aureus* (Iverson *et al.,* 2011). *S. pseudintermedius* in BALB/c mouse model can be particularly important due to its ability of inducing brain damage by crossing the blood–brain barrier and subsequent long term colonization (Kalhoro, *et al.,* 2017). Coinfection of CIV H3N2 and *Staphylococcus pseudintermedius* caused severe clinical picture and body weight loss in BALB/C mice with increased Histopathological lesions in brain, spleen and lung as compared to infection given by either pathogen alone (Kalhoro *et al.,* 2016). Influenza virus and PVL-producing *S. aureus* are responsible for inflammation, lung damage, lysis of neutrophil and massive release of granule proteases (Mahalingam and Karupiah, 1999). Cytokine IFN-γ and Polymorphonuclear (PMN) leukocytes expression was reported higher in coinfected group as compared with bacteria-infected mice (Lee *et al.,* 2010c). Innate immune response during influenza virus infection was impaired due to activation of IFN signaling protein Stat1 (Shornick *et al.,* 2008). A study by Lee (Lee *et al.,* 2010c) showed higher IFN- γ expression and increased PMN cellular response in murine model infected with influenza virus and *Staphylococcus aureus* with those infected with *Staphylococcus aureus* alone. Mice infected with influenza virus are highly susceptible to the *Staphylococcus aureus* infection due to suppression of Th17 responses by reduced cytokine IL-1β expression. Colonization of *Staphylococcus aureus* is stimulated by suppressed Th17 responses by reduced antimicrobial peptide (neutrophil gelatinase-associated lipocalin) concentration that limits bacterial growth (Robinson *et al.,* 2015). Levels of proinflammatory cytokines IFN-γ, TNF-α and IL-6 are elevated in mice inoculated with influenza virus and staphylococcal enterotoxin B or LPS, demonstrating that before influenza, infection primed influenza infected cells for rapid cytokine production upon secondary challenge with bacterial components (Zhang *et al.,* 1996). Increased IFNg levels and decreased low IL-13 levels after 7d.p.i, with influenza virus mice were more susceptible to the *S. aureus* super infection (Rynda Apple *et al.,* 2014). An animal model was used to study these associations and found that coinfection have enhanced the bacterial dissemination and inflammatory reactions (Braun *et al.,* 2007), bacteria-supportive functions by influenza virus facilitates the bacterial colonization and impairing bacterial clearance (Peltola and Mccullers, 2004), inflammatory responses as well as recruitment of immune cells are altered (Iverson *et al.,* 2011).

Histopathological analysis of coinfection in animal models has shown tracheobronchitis and bronchiolitis (Lu *et al.,* 1999). *S. aureus* strains have gained evolved virulence as well as antibacterial resistance traits (Navarro *et al.,* 2008). During coinfection *S. aureus* is responsible for blocking defense against influenza virus by firstly stimulation of IFN-beta upon super-infection, following IFN signaling and impairment of gene expression due block of STAT1-STAT2 dimerization leading towards increased viral growth and severity of disease during co-infection (Warnking *et al.,* 2015). Bacterial proteases play an important role in the influenza virus infection because they are necessary to cleave the viral HA into its active form. In a mouse model coinfected with influenza virus A and *S. aureus,* significantly less morbidity and mortality was observed in *S. aureus* strain deficient of the HA activating protease as compared to coinfected mice with *S. aureus* strain positive for the protease (Tashiro *et al.,* 1987). In humans patients coinfected with influenza virus and *Staphylococcus aureus* develop more severe pneumonia when compared with patients infected with *Staphylococcus aureus* alone (Takayama *et al.,* 2014).

Coinfection of influenza a virus with streptococcal species: Influenza pandemics annually cause high level of morbidity as well as mortality worldwide (Madhi *et al.,* 2004). During pandemics, secondary bacterial pneumonia is the main cause of the fatalities. It was hypothesized from 1890 to 1950 that the influenza infection is a poly microbial infection in which a low pathogenicity inciting agent (virus) acted synergistically with a known pneumopathogenic bacteria (Morens *et al.,* 2008). Bacterial pathogens can cause respiratory infections by invading mucosal surface of the respiratory tract (Kalhoro *et al.,* 2015). Combined infection leads to worse conditions and more severe results as compared with infection caused by either pathogen alone (Madhi *et al.,* 2004). Attention towards this synergism came when first pandemic of influenza virus in1918 caused 40 to 50 million deaths (Short *et al.,* 2012). Infection with the virus alone could be fatal but majority of deaths occurred due to secondary bacterial pneumonia. Combined infection of influenza and pneumonia is lethal and ranked as 6th major cause of death worldwide. As compared to other types of influenza virus typical influenzal illness, the incidence of excess hospitalizations and mortalities were disproportionately higher during H3N2 epidemics than other subtypes (H1N1) or B viruses (Simonsen, 1999). Influenza virus infection has also been involved in the transmission of *S. pneumoniae* directly *via* inhalation of aerosols or indirectly *via* contact with contaminated material (Kadioglu *et al.,* 2008). There is an association of increased incidence of IPD due to viral infection in the respiratory tract, particularly influenza A virus causing pneumococcal meningitis and pneumonia (O'Brien *et al.,* 2000). Combined influenza and *S. pneumoniae* infection contribute significantly to the deaths all around the world (Simonsen, 1999). Exposure to pneumococcal seven days

after influenza infection in mice leads to severe pathological lesions in lungs and can cause 100% mortality, if pneumococcal inculcation leads influenza infection survival rate will be increased, so it was presumed that influenza virus infection primes for an increase of lethal pneumococcal pneumonia with a dose dependent mechanism (McCullers and Rehg, 2002). Mice showed inflammatory responses and bacterial load after inoculation of influenza virus following *S. pneumoniae.* Following exposure to *S. pneumoniae* bacterial load in lung of influenza-exposed mice was higher at 24 and 48 h compared to control mice. Neutrophilic count was increased in coinfected sequentially-infected group; level of cytokines IL-1 beta and TNF-α was increased in virus inoculated group following bacterial exposure (LeVine *et al.,* 2001). Otitis media, sepsis and meningitis were observed in influenza A exposed animals before or association with bacterial pathogen (Abraham *et al.,* 2007). Gradual weight loss and mortality were observed in mice coinfected with influenza virus (H1N1) and *S. pneumoniae*, while mice exposed to *S. pneumoniae* 7 days after infection with influenza virus, becomes highly bacteremic and died within 24 h. The trachea is responsible for the entry of the S. *pneumoniae* from the nasal mucosa to colonize in the lungs causing pneumonia (Takase *et al.,* 1999). Influenza virus causes alteration in tracheal epithelium to enhance susceptibility to the S. *pneumoniae* infection resulting in lung damage (Nugent and Pesanti, 1983). On 7th day, susceptibility to S. *pneumoniae* was witnessed after an influenza infection in the lungs of mice due to infection in tracheal respiratory epithelium (LeVine *et al.,* 2001; McCullers and Rehg, 2002; McNamee and Harmsen, 2006).

In vivo coinfection studies in mice have shown that after 90 minutes, number of S. *pneumoniae* increased in influenza-infected than non–influenza-infected tracheas (Plotkowski *et al.,* 1986). Several mechanisms are possible for synergistic interaction among influenza virus and *Streptococcus pneumococcus*. It is supposed that influenza virus initiates alterations of the host that predisposes to the secondary bacterial infections. Alteration due to regeneration of the ciliated respiratory epithelium (Plotkowski *et al.,* 1993), influenza mediated phagocytic dysfunction; cytokine expression in influenza virus infection causes bacterial adherence as well as invasion due to alteration in lung receptors (McCullers and Rehg, 2002). Ferrets can be used as a model to assess synergism among influenza virus and *Streptococcus pneumoniae*. Coinfected ferrets showed high level of pneumococcal nasal wash titers, increased WBC count and segmented cells, alveolar epithelial hyperplasia and interstitial hyper cellularity in lungs than those infected with pneumococcus alone (Peltola and Mccullers, 2004), while significantly lower level of viral titers in the nasopharynx was witnessed in mice coinfected with pneumococcus and influenza virus than mice infected with influenza virus alone (Diavatopoulos *et al.,* 2010). Pneumococcus can inhibit influenza virus A infection, reduce normal flora of mice by antibiotic treatment resulting in significantly increased pulmonary viral titers and decrease adaptive immune response to influenza virus (Ichinohe *et al.,* 2011). Cytokines play an important role in the innate immunity response. Natural killer cells kill infected cells and produce cytokines during early stages in viral infection (Short *et al.,* 2012). Higher levels of IFN γ and TNF α cytokines was observed in lungs coinfected with Flu/Strep (Damjanovic *et al.,* 2013).

Influenza virus if given alone is not lethal but it can stimulate secondary bacterial infection that can be lethal (Layne *et al.,* 2001). Viral infections may leads to secondary bacterial infections by damaging respiratory epithelium, impairing mucociliary function, activation of host inflammatory responses, increase regulation or exposure of different receptors (McCullers, 2006). Experimental results revealed that mice infected with influenza virus increases susceptibility to secondary *S. pneumoniae* infection by increasing cytokine level in the lungs. Mice infected with influenza virus followed by *S. pneumoniae* on 6 day can elevate pro inflammatory cytokines in lungs after 24 hours (McNamee and Harmsen, 2006). Mice infected with S. *pneumoniae* and subsequently with influenza virus results in the synergistic stimulation of interferons (type I) that reduces the number of macrophages by reduced production of CC-chemokine ligand 2 (CCL2), resulting in increased bacterial colonization (Nakamura *et al.,* 2011). Influenza virus can increase susceptibility to *S. pneumoniae* during replication of virus altering platelet activating factor receptor (PAF) expressed on the epithelial cells (Cundell *et al.,* 1995).

Coinfection of influenza a virus with other bacterial species: Several studies has been done in animal models after recognition that bacterial super infection usually accompanied fatal influenza during Spanish influenza epidemic in 1918, *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus,* and *Branhamella catarrhalis* were frequently isolated (Abraham *et al.,* 2007). Animal models including mice, macaques, ferrets, chinchillas, guinea pigs, cotton rats, chickens and pigs were being used to study influenza virus infection, among these animals mice was usually used to study host response due to presence of gene knock-out strains (Shahangian *et al.,* 2009). Mouse adopted strains were used for these studies because mice is not a natural host to influenza virus, lung alveoli of mice is different from lungs of humans and pigs, (Winkler and Cheville, 1984), non expression of an ortholog to human IL-8 (Guillot *et al.,* 2005). There are several mechanisms through which flu infection leads to secondary bacterial infection that includes respiratory epithelial barrier as well as expression of receptors

(Peltola and Mccullers, 2004), changing the host immune responses (Didierlaurent *et al.,* 2008) and impairment of alveolar macrophage phagocytic function that interferes in the bacteria uptake and killing (Astry and Jakab, 1984). During influenza infection alone and co-infection with Hib, IL-6 was up-regulated in the lungs having pro and anti-inflammatory characteristics and responsible for induction of fever and the acute phase proteins in response to inflammation (Kaiser *et al.,* 2001). Proinflammatory cytokine TNF can be produced by single infections with influenza virus or Hib, while excessive production of TNF leads to immunopathology (Zhang *et al.,* 1996)**.** Severe lung inflammation by pandemic strain during Spanish flu in 1918 was observed (Tumpey *et al.,* 2005a) due to elevated proinflammatory cytokines and increased number of neutrophils into the lung (Tumpey *et al.,* 2005b).

Bordetella pertussis BPZE1 strain were used as highly effective prophylactic agent due to induced H3N2 and H1N1 influenza viruses against lethal pneumonitis by reducing lung immunopathology and proinflammatory cytokines and chemokines production, without altering viral load (Li *et al.,* 2010a). Experiments have explored the association between influenza virus and *H. influenzae* in pigs and mice (Francis and De Torregrosa, 1945). Sub lethal infection of mice after inhalation of aerosolized pneumococci with influenza virus could prime for fatal pneumonia (Harford *et al.,* 1946). Influenza virus and the *H. influenzae* respiratory tract pathogens when coinfected in mice interact synergistically to cause more severe disease, finally resulted in mortality (Lee *et al.,* 2010b).

Conclusions: Influenza A virus may more easily acquire the ability to infect human through adaption in dogs and other mammals. Coinfection with influenza virus and bacteria species can be noticed in most of the hosts. Although IAV subtypes in dogs may not cause a serious pandemic influenza in dogs, and there are not any reports of viruses transmitted from dogs to humans, whether humans will be co-infected with bacteria and Influenza A virus in dogs is still unknown. In addition to the above, there are some key problems that should be solved. For instance, what factor led to the interspecies transmission of influenza virus? What are the reasons for continuous transmission of influenza virus between dogs? Only by solving these problems completely influenza virus infection could be effectively controlled. In order to reinforce the prevention and control of IAV, researches on vaccine should also be promoted.

Acknowledgements: This work was supported by the National Key R & D Program of China (2017YFD0501101), International S & amp; T Cooperation Program of China (2014DFG32770) and Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

REFERENCES

Abdelghafar, A. N., T. Chotpitayasunondh, Z. Gao, F.G. Hayden, N.D. Hien, M.D. De Jong, A. Naghdaliyev, J.S.M. Peiris, N. Shindo, S. Soeroso, and T.M. Uyeki (2008). Update on avian influenza A (H5N1) virus infection in humans. N. Engl. J. Med. 358, 3:261-273.

Abraham, J.L., D.O. Morris, G.C. Griffeth, F.S. Shofer, and S.C. Rankin (2007). Surveillance of healthy cats and cats with inflammatory skin disease for colonization of the skin by methicillin resistant coagulase positive staphylococci and *Staphylococcus schleiferi ssp. schleiferi*. Vet. Dermatol. 18:252-259.

Astry, C.L. and G. J. Jakab (1984). Influenza virus-induced immune complexes suppress alveolar macrophage phagocytosis. J.Virol. 50:287-292.

Braun, L.E., D. E. Sutter, M.C. Eichelberger, L. Pletneva, J.F. Kokai-Kun, J.C. Blanco, A. G. Prince, and M.G. Ottolini (2007). Co-infection of the cotton rat (Sigmodon hispidus) with *Staphylococcus aureus* and influenza A virus results in synergistic disease. Microb. Pathog. 43: 208-216.

Brockwell Staats, C., R.G. Webster, and R.J. Webby. (2009). Diversity of influenza viruses in swine and the emergence of a novel human pandemic influenza A (H1N1). Influenza Other Respir. Viruses 3:207-213.

Bunpapong, N., N. Nonthabenjawan, S. Chaiwong, R. Tangwangvivat, S. Boonyapisitsopa, W. Jairak, R. Tuanudom, D. Prakairungnamthip, S. Suradhat, R. Thanawongnuwech and A. Amonsin (2014). Genetic characterization of canine influenza A virus (H3N2) in Thailand. Virus genes 48: 56-63.

Butler, D. (2006). Thai dogs carry bird-flu virus, but will they spread it? Nature 439: 773.

Callan, R.J., F.A. Hartmann, S. West, and V. S. Hinshaw (1997). Cleavage of influenza A virus H1 hemagglutinin by swine respiratory bacterial proteases. J. Virol. 71:7579-7585.

Chen, B., Z. Zhang, and W. Chen (1994). Isolation and preliminary serological characterization of type A influenza viruses from chickens. Chin. J. Vet. Med.(Chinese) 22:3-5.

Chen, H., Y. Li, Z. Li, J. Shi, K. Shinya, G. Deng, Q. Qi, G. Tian, S. Fan, H. Zhao, and Y. Sun (2006). Properties and dissemination of H5N1 viruses isolated during an influenza outbreak in migratory waterfowl in western China. J. Virol. 80 :5976-5983.

Chen, Y., Y.N. Mo, H. B. Zhou, Z. Z. Wei, G.J. Wang, Q.X. Yu, X. Xiao, W.J. Yang, and W.J. Huang (2015). Emergence of human-like H3N2

influenza viruses in pet dogs in Guangxi, China. Virol. J.12:10.

Chen, Y., G. Zhong, G. Wang, G. Deng, Y. Li, J. Shi, Z. Zhang, Y. Guan, Y. Jiang, Z. Bu, and Y. Kawaoka (2010). Dogs are highly susceptible to H5N1 avian influenza virus. Virology 405:15-19.

Choi, Y.K., T.D. Nguyen, H. Ozaki, R.J. Webby, P. Puthavathana, C. Buranathal, A. Chaisingh, P. Auewarakul, N.T.H Hanh, S.K. Ma, and P.Y. Hui (2005). Studies of H5N1 influenza virus infection of pigs by using viruses isolated in Vietnam and Thailand in 2004. J. Virol. 79:10821-10825.

Cilloniz, C., M.J. Pantin-Jackwood, C. Ni, A.G. Goodman, X. Peng, S.C. Proll, V.S. Carter, E.R. Rosenzweig, K.J. Szretter, J.M. Katz, and M.J. Korth (2010). Lethal dissemination of H5N1 influenza virus is associated with dysregulation of inflammation and lipoxin signaling in a mouse model of infection. J. Virol. 84:7613-7624.

Crawford, P., E.J. Dubovi, W.L. Castleman, I. Stephenson, E.P.J. Gibbs, L. Chen, C. Smith, R.C. Hill, P. Ferro, J. Pompey, and R.A. Bright (2005). Transmission of equine influenza virus to dogs. Science 310:482-485.

Cundell, D., H.R. Masnre, and E.I.Tuomanen (1995). The molecular basis of pneumococcal infection: a hypothesis. Clin. Infect. Dis. 21:S204-S12.

Daly, J.M., A.S. Blunden, S. Macrae, J. Miller, S.J. Bowman, J. Kolodziejek, N. Nowotny, and K.C (Smith). 2008. Transmission of equine influenza virus to English foxhounds. Emerg. Infect. Dis.14:461.

Damiani, A., D. Kalthoff, M. Beer, E. Müller, and N. Osterrieder (2012). Serological survey in dogs and cats for influenza A (H1N1) pdm09 in Germany. Zoonoses Public health 59:549-552.

Damjanovic, D., R. Lai, M. Jeyanathan, C.M. Hogaboam, and Z. Xing (2013). Marked improvement of severe lung immunopathology by influenza-associated pneumococcal superinfection requires the control of both bacterial replication and host immune responses. Am. J. Pathol. 183:868-8680.

Dangi, T, and A. Jain (2012). Influenza virus: A brief overview. Proc. Nat. Acad. Sci, Ind. Sec. B: Biol. Sci. 82:111-121.

Diavatopoulos, D.A., K.R. Short, J.T Price, J.J. Wilksch, L.E. Brown, D.E. Briles, R.A. Strugnell, and O.L. Wijburg (2010). Influenza A virus facilitates S*treptococcus pneumoniae* transmission and disease. FASEB J. 24:1789-1798.

Didierlaurent, A., J. Goulding, S. Patel, R. Snelgrove, L. Low, M. Bebien, T. Lawrence, L.S. van Rijt, B.N. Lambrecht, J.C. Sirard, and T. Hussell (2008). Sustained desensitization to bacterial Toll-like receptor ligands after resolutionof respiratory influenza infection. J. Exp. Med. 205:323-329.

Dubovi, E. J, and B. L. Njaa (2008). Canine influenza. Vet. Clin. North. Am. Small Anim. Pract. 38:827-8235.

Dundon, W.G., P. De Benedictis, E. Viale, and I. Capua (2010). Serologic evidence of pandemic (H1N1) 2009 infection in dogs, Italy. Emerg. Infect. Dis. 16:2019.

Finelli, L., A. Fiore, R. Dhara, L. Brammer, D.K. Shay, L. Kamimoto, A. Fry, J. Hageman, R. Gorwitz, J. Bresee, and T. Uyeki (2008). Influenza-associated pediatric mortality in the United States: increase of *Staphylococcus aureus* coinfection. Pediatrics 122:805-811.

Fowlkes, A.L., P. Arguin, M.S. Biggerstaff, J. Gindler, D. Blau, S. Jain, R. Dhara, J. McLaughlin, E. Turnipseed, J.J. Meyer, and J.K. Louie, J.K (2011). Epidemiology of 2009 pandemic influenza A (H1N1) deaths in the United States, April–July 2009. Clin. Infect. Dis. 52:S60-8.

Francis, T, and M.V. De Torregrosa (1945). Combined infection of mice with H. influenzae and influenza virus by the intranasal route. J. Infect. Dis. 76:70-77.

Gibbs, E.P.J, and T.C. Anderson (2010). Equine and canine influenza: a review of current events. Anim. Health Res. Rev. 11:43-51.

Giese, M., T. Harder, J. Teifke, R. Klopfleisch, A. Breithaupt, T. Mettenleiter, and T.W. Vahlenkamp (2008). Experimental infection and natural contact exposure of dogs with avian influenza virus (H5N1). Emerg. Infect. Dis. 14:308-310.

Guan, Y., L. L. M. Poon, C.Y. Cheung, T.M. Ellis, W. Lim, A.S. Lipatov, K.H. Chan, K.M. Sturm-Ramirez, C.L. Cheung, Y.H.C. Leung, and K.Y. Yuen (2004). H5N1 influenza: a protean pandemic threat. Proc. Natt. Acad. Sci. USA 101:8156-8161.

Guang-Jian, Z, L. Zong-Shuai, Z. Yan-Li, J. Shi-Jin, and X. Zhi-Jing (2012). Genetic characterization of a novel influenza A virus H5N2 isolated from a dog in China. Vet. Microbiol. 155:409-416.

Guillot, L., R. Le-Goffic, S. Bloch, N. Escriou, S. Akira, M. Chignard, and M. Si-Tahar (2005). Involvement of toll-like receptor 3 in the immune response of lung epithelial cells to double-stranded RNA and influenza A virus. J. Biol. Chem. 280:5571-5580.

Hai-Xia, F., L. Yuan-Yuan, S. Qian-Qian, L. Z. Shuai, Z. F. Xia, Z. Y.Li, J. S. Jin, and X. Z. Jing (2014). Interspecies transmission of canine influenza virus H5N2 to cats and chickens by close contact with experimentally infected dogs. Vet. Microbiol. 170: 414-417.

Harder, T.C, and T.W. Vahlenkamp (2010). Influenza virus infections in dogs and cats. Vet. Immunol. Immunopathol. 134:54-60.

Harford, C.G., M.R. Smith, and W.B. Wood Jr (1946). Sulfonamide chemotherapy of combined infection with influenza virus and bacteria. J. Exp. Med. 83:505.

Hatta, M., P. Gao, P. Halfmann, and Y. Kawaoka (2001). Molecular basis for high virulence of Hong Kong H5N1 influenza A viruses. Science 293:1840-1842.

Homme, P, and B. Easterday (1970). Avian influenza virus infections. IV. Response of pheasants, ducks, and geese to Influenza A/Turkey/Wisconsin/1966 virus. Avian Dis. 285-290.

Ichinohe, T., I.K. Pang, Y. Kumamoto, D.R. Peaper, J.H. Ho, T.S. Murray, and A. Iwasaki (2011). Microbiota regulates immune defense against respiratory tract influenza A virus infection. Proc. Natt. Acad. Sci. USA 108: 5354-5359.

Ilyushina, N. A., M.F. Ducatez, J.E. Rehg, B.M. Marathe, H. Marjuki, N.V. Bovin, R.G. Webster, and R.J. Webby (2010). Does pandemic A/H1N1 virus have the potential to become more pathogenic? MBio 1:e00249-10.

Iverson, A.R., K.L. Boyd, J.L. Mcauley, L.R. Plano, M. E. Hart, and J.A. Mccullers (2011). Influenza virus primes mice for pneumonia from *Staphylococcus aureus*. J. Infect. Dis. 203:880-888.

Jeoung, H.Y., S.I. Lim, B.H. Shin, J.A. Lim, Y.J. Song, D.S. Song, B.K. Kang, H.J. Moon, and D.J. An. (2013). A novel canine influenza H3N2 virus isolated from cats in an animal shelter. Vet. Microbiol. 165:281-286**.**

Jirjis, F.F., M.S. Deshpande, A.L. Tubbs, H. Jayappa, N. Lakshmanan, and T.L. Wasmoen (2010). Transmission of canine influenza virus (H3N8) among susceptible dogs. Vet. Microbiol. 144:303-309.

Jung, K., C. Lee, B. Kang, B. Park, J. Oh, and D. Song. (2010). Pathology in dogs with experimental canine H3N2 influenza virus infection. Res. Vet. Sci. 88:523-527.

Kadioglu, A., J. N. Weiser, J.C. Paton, and P.W. Andrew (2008). The role of *Streptococcus pneumoniae* virulence factors in host respiratory colonization and disease. Nat. Rev. Microbiol. 6:288-301.

Kaiser, L., R.S. Fritz, S.E. Straus, L. Gubareva, and F.G. Hayden (2001). Symptom pathogenesis during acute influenza: Interleukin 6 and Other cytokine responses. J. Med. Virol. 64:262-268.

Kalhoro, D.H., S. Luo, X. Xie, Y.B. Zhao, C.P. Lu, and Y.J. Liu (2015). *Streptococcus pluranimalium* isolated from a canine respiratory case: identification and experimental infection in mice. Pak Vet J, 35:388-390.

Kalhoro, D.H., S. Gao, M. S. Kalhoro, F. Parveen, M. Tariq, S. A. Pirzado, and Y. J. Liu (2017). *Staphylococcus pseudintermedius* isolation from canine, bacterial colonization and clinical picture in balb/c mouse model. The J. Anim. Plant Sci. 27:422-429.

Kalhoro, D.H., S. Gao, X. Xie, S. Liang, S. Luo, Y. Zhao, and Y. Liu (2016). Canine influenza virus coinfection with *Staphylococcus pseudintermedius* enhances bacterial colonization, virus load and clinical presentation in mice. BMC Vet. Res. 12:87.

Kalhoro, D.H., S. Liang, M.S. Kalhoro, S.A. Pirzado, N. Rajput, M. Naeem, F. Parveen, and Y. Liu (2018). Identification and Genetic Evolution Analysis of One Strain of H3N2 Canine Influenza Virus Isolated from Nanjing, China. P.J. Zool. 50:817-824

Kang, Y.M., H.M. Kim, K.B. Ku, E.H. Park, J. Yum, and S. H. Seo (2013). H3N2 canine influenza virus causes severe morbidity in dogs with induction of genes related to inflammation and apoptosis. Vet. Res. 44:92.

Kasel, J.A., R.H. Alford, V. Knight, G.H. Waddell, and M.M. Sigel (1965). Experimental infection of human volunteers with equine influenza virus. Nature 206: 41-43.

Keawcharoen, J., K. Oraveerakul, T. Kuiken, R.A. Fouchier, A. Amonsin, S. Payungporn, S. Noppornpanth, S. Wattanodorn, A. Theambooniers, R. Tantilertcharoen, and R. Pattanarangsan (2004). Avian influenza H5N1 in tigers and leopards. Emerg. Infect. Dis. 10:2189-2191.

Kim, H.M., E.H. Park, J. Yum, H.S. Kim, and S. H. Seo. (2015). Greater virulence of highly pathogenic H5N1 influenza virus in cats than in dogs. Arch. Virol. 160:305-313.

Kirkland, P.D., D.S. Finlaison, E. Crispe, and A.C. Hurt. (2010). Influenza virus transmission from horses to dogs, Australia. Emerg. Infect. Dis. 16:699.

Kruth, S.A., S. Carman, and J. S. Weese (2008). Seroprevalence of antibodies to canine influenza virus in dogs in Ontario. Can. Vet. J. 49:800.

Ku, K.B., E.H. Park, J. Yum, H.M. Kim, Y.M. Kang, J.C. Kim, J.A. Kim, H.S. Kim, and S.H. Seo (2014). Transmissibility of novel H7N9 and H9N2 avian

influenza viruses between chickens and ferrets. Virology 450:316-323.

Layne, S.P., T. J. Beugelsdijk, C.K.N. Patel, J.K. Taubenberger, N.J. Cox, I.D. Gust, A.J. Hay, M. Tashiro, and D. Lavanchy (2001). A global lab against influenza. Science 293:1729.

Lee, C., K. Jung, J. Oh, T. Oh, S. Han, J. Hwang, M. Yeom, D. Son, J. Kim, B. Park, and H. Moon (2010a). Protective efficacy and immunogenicity of an inactivated avian-origin H3N2 canine influenza vaccine in dogs challenged with the virulent virus. Vet. Microbiol. 143:184-188.

Lee, J.H., P.N.Q. Pascua, M.S. Song, Y.H. Baek, C.J. Kim, H.W. Choi, M.H. Sung, R.J. Webby, R.G. Webster, H. Poo, and Y.K. Choi (2009). Isolation and genetic characterization of H5N2 influenza viruses from pigs in Korea. J .Virol. 83:4205-4215.

Lee, L.N., P. Dias, D. Han, S. Yoon, A. Shea, V. Zakharov, D. Parham, and S.R. Sarawar (2010b). A Mouse Model of Lethal Synergism Between Influenza Virus and *Haemophilus influenzae*. Am. J. Pathol. 176:800-811.

Lee, M.H., C. Arrecubieta, F.J. Martin, A. Prince, A.C. Borczuk, and F.D. Lowy 2010c). A postinfluenza model of *Staphylococcus aureus* pneumonia. J. Infect. Dis. 201:508-515.

Levine, A.M., V. Koeningsknecht, and J.M. Stark (2001). Decreased pulmonary clearance of *S. pneumoniae* following influenza A infection in mice. J. Virol. Meth. 94:173-186.

Li, C., K. Yu, G. Tian, D. Yu, L. Liu, B. Jing, J. Ping, and H. Chen (2005). Evolution of H9N2 influenza viruses from domestic poultry in Mainland China. Virology 340:70-83.

Li, R., A. Lim, M.C. Phoon, T. Narasaraju, J.K. Ng, W.P. Poh, M.K. Sim, V.T.Chow, C. Locht, and S. Alonso (2010a). Attenuated Bordetella pertussis protects against highly pathogenic influenza A viruses by dampening the cytokine storm. J. Virol. 84:7105-7113.

Li, S., Z. Shi, P. OJiao, G. Zhang, Z. Zhong, W. Tian, L.P. Long, Z. Cai, X. Zhu, M. Liao, and X.F. Wan (2010b). Avian-origin H3N2 canine influenza A viruses in Southern China. Infect. Genet. Evol. 10:1286-1288.

Lin, D., S. Sun, L. Du, J. Ma, L. Fan, J. Pu, Y. Sun, J. Zhao, H. Sun, and J. Liu (2012a). Natural and experimental infection of dogs with pandemic H1N1/2009 influenza virus. J. Gen. Virol. 93:119-123.

Lin, Y., Y. Zhao, X. Zeng, C. Lu, and Y. Liu (2012b). Genetic and pathobiologic characterization of H3N2 canine influenza viruses isolated in the Jiangsu Province of China in 2009–2010. Vet. Microb. 158:247-258.

Lin, Y., X. Xie, Y. Zhao, D.H. Kalhoro, C. Lu, and Y. Liu (2016). Enhanced replication of avian-origin H3N2 canine influenza virus in eggs, cell cultures and mice by a two-amino acid insertion in neuraminidase stalk. Vet. Res. 47: 53.

Lipatov, A.S., E.A. Govorkova, R. J. Webby, H. Ozaki, M. Peiris, Y. Guan, L. Poon, and R.G. Webster (2004). Influenza: emergence and control. J. Virol. 78 :8951-8959.

Lu, X., T.M. Tumpey,T. Morken, S.R. Zaki, N.J. Cox and J.M. Katz (1999). A mouse model for the evaluation of pathogenesis and immunity to influenza A (H5N1) viruses isolated from humans. J. Virol. 73:5903-59011.

Maas, R., M. Tacken, L. Ruuls, G. Koch, E. Van Rooij, and N. Stockhofe-Zurwieden (2007). Avian influenza (H5N1) susceptibility and receptors in dogs. Emerg. Infect. Dis. 13:1219.

Madhi, S.A., K.P. Klugman, and T.V.T. Group (2004). A role for *Streptococcus pneumoniae* in virus-associated pneumonia. Nat. Med. 10:811-813.

Mahalingam, S, and G. Karupiah (1999). Chemokines and chemokine receptors in infectious diseases. Immunol. Cell Biol. 77:469-475.

Mail, P (2009a). PRO/AH/ED Influenza pandemic (H1N1) 2009, animal (30): China, canine. Nov 28, 2009. Archive Number 20091128.4079.

Mail, P (2009b). PRO/AH/EDR Influenza pandemic (H1N1) 2009, animal (40): USA (NY), canine. Dec 22, 2009. Archive Number 20091222.

Maines, T. R., X.H. Lu, S.M. Erb, L. Edwards, J. Guarner, P.W. Greer, D.C. Nguyen, K.J. Szretter, L.M. Chen, P. Thawatsupha, and M. Chittaganpitch (2005). Avian influenza (H5N1) viruses isolated from humans in Asia in 2004 exhibit increased virulence in mammals. J. Virol. 79:11788-800.

Mccullers, J.A (2006). Insights into the interaction between influenza virus and *pneumococcus*. Clin. Microbiol. Rev. 19:571-582.

Mccullers, J. A, and J.E. Rehg (2002). Lethal synergism between influenza virus and *Streptococcus pneumoniae*: characterization of a mouse model and the role of platelet-activating factor receptor. J. Infect. Dis. 186:341-350.

Mcnamee, L.A, and A.G. Harmsen (2006). Both influenza-induced neutrophil dysfunction and neutrophil-independent mechanisms contribute to increased susceptibility to a secondary *Streptococcus pneumoniae* infection. Infect. Immunol. 74:6707-6721.

Mehrabanpour, M. H., Dadras, A. Khodakaram-Tafti, A. Rahimian, and A. Toffan (2007). Pathological findings of highly pathogenic avian influenza

virus A/Duck/Vietnam/12/2005 (H5N1) in Turkeys. Int. J. Poult. Sci. 6:679-683.

Morens, D.M., J.K Taubenberger, and A.S. Fauci (2008). Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J. Infect. Dis. 198:962-970.

Morse, S.S (1997). The public health threat of emerging viral disease. J. Nutr. 127: 951S-7S.

Nagatake, T (2003). [Potentiation of infectivity and pathogenesis of influenza virus by host and bacterial proteases]. Nihon. Rinsho. 61:1892-1896.

Nakamura, S., K.M. Davis, and J. N. Weiser (2011). Synergistic stimulation of type I interferons during influenza virus coinfection promotes *Streptococcus pneumoniae* colonization in mice. J. Clin. Inves. 121:3657.

Navarro, M. B., B. Huttner, and S. Harbarth (2008). Methicillin-resistant *Staphylococcus aureus* control in the 21st century: beyond the acute care hospital. Curr. Opin. Infect. Dis. 21:372-379.

Nerome, K., M. Ishida, M. Nakayama, A. Oya, C. Kanai, and K. Suwicha (1981). Antigenic and genetic analysis of A/Hong Kong (H3N2) influenza viruses isolated from swine and man. J. Gen. Virol. 56:441-445.

Newton, R., A. Cooke, D. Elton, N. Bryant, A. Rash, S. Bowman, T. Blunden, J. Miller, T.A. Hammond, I. Camm, and M. Day (2007). Canine influenza virus: cross-species transmission from horses. Vet. Rec. 161:142-143.

Nugent, K.M and E.L. Pesanti (1983). Tracheal function during influenza infections. Infect. Immunity 42:1102-1108.

O'brien, K.L., M. I. Walters, J. Sellman, P. Quinlisk, H. Regnery, B. Schwartz, and S.F. Dowell (2000). Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. Clin. Infect. Dis. 30:784-789.

Payungporn, S., P.C. Crawford, T.S. Kouo, L.M. Chen, J. Pompey, W.L. Castleman, E.J. Dubovi, J. M. Katz, and R.O. Donis (2008). Influenza A virus (H3N8) in dogs with respiratory disease, Florida. Emerg. Infect. Dis 14:902.

Peltola, V.T, and J.A. Mccullers (2004). Respiratory viruses predisposing to bacterial infections: rol.e of neuraminidase. Pediatr. Infect. Dis. J. 23:S87-S97.

Perrone, L.A., J.K. Plowden, A. García-Sastre, J.M. Katz, and T. M. Tumpey (2008). H5N1 and 1918 pandemic influenza virus infection results in early and excessive infiltration of macrophages and neutrophils in the lungs of mice. PLoS Pathog. 4:e1000115.

Perrone, L.A., K. J. Szretter, J.M. Katz, J.P. Mizgerd, and T.M. Tumpey (2010). Mice lacking both TNF and IL-1 receptors exhibit reduced lung inflammation and delay in onset of death following infection with a highly virulent H5N1 virus. J. Infect. Dis. 202:1161-1170.

Plotkowski, M., O. Bajolet-Laudinat, and E. Puchelle (1993). Cellular and molecular mechanisms of bacterial adhesion to respiratory mucosa. Eur. Resp. J. 6:903-916.

Plotkowski, M., E. Puchelle, G. Beck, J. Jacquot, and C. Hannoun (1986). Adherence of type I *Streptococcus pneumoniae* to tracheal epithelium of mice infected with influenza A/PR8 virus. Am. Rev. Respir. Dis. 134:1040-1144.

Qi, X., X. Li, P. Rider, W. Fan, H. Gu, L. Xu, Y. Yang, S. Lu, H. Wang, and F. Liu (2009). Molecular characterization of highly pathogenic H5N1 avian influenza A viruses isolated from raccoon dogs in China. PloS one 4:e4682.

Robinson, K.M., J.K. Kolls, and J.F. Alcorn (2015). The immunology of influenza virus-associated bacterial pneumonia. Curr. Opin. Immunol. 34:59-67.

Rynda Apple, A., A. Harmsen, A. S. Erickson, K. Larson, R.V. Morton, L.E. Richert, and A.G. Harmsen (2014). Regulation of IFN γ by IL 13 dictates susceptibility to secondary postinfluenza MRSA pneumonia. Eur. J. Immunol. 44:3263-3272.

Schulz, B., C. Klinkenberg, R. Fux, T. Anderson, P. De Benedictis, and K. Hartmann (2014). Prevalence of canine influenza virus A (H3N8) in dogs in Germany. Vet. J. 202:184-185.

Shahangian, A., E.K. Chow, X. Tian, J.R. Kang, A. Ghaffari, S.Y. Liu, J.A. Belperio, G. Cheng, and J.C. Deng (2009). Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice. J. Clin. Invest. 119:1910-1920.

Shornick, L.P., A.G. Wells, Y. Zhang, A.C. Patel, G. Huang, K. Takami, M. Sosa, N.A. Shukla, E. Agapov, and M.J. Holtzman (2008). Airway epithelial versus immune cell Stat1 function for innate defense against respiratory viral infection. J. Immunol. 180:3319-3328.

Short, K.R., M.N. Habets, P.W. Hermans, and D. A. Diavatopoulos (2012). Interactions between *Streptococcus pneumoniae* and influenza virus: a mutually beneficial relationship? Future Microbiol. 7:609-624.

Shortridge, K.T, and C.Stuart-Harris (1982). An influenza epicentre? Lancet 320, 812-813.

Shu, L. L., Y.P. Lin, S.M. Wright, K.F. Shortridge, and R.G. Webster (1994). Evidence for interspecies transmission and reassortment of influenza A viruses in pigs in southern China. Virology, 202:825-833

Simonsen, L (1999). The global impact of influenza on morbidity and mortality. Vaccine 17:S3-S10.

Simonsen, L., K. Fukuda, L.B. Schonberger, and N.J. Cox (2000). The impact of influenza epidemics on hospitalizations. J. Infect. Dis. 181:831-837.

Smith, A.M., F. R. Adler, R.M. Ribeiro, R.N. Gutenkunst, J.L. McAuley, J.A. McCullers, and A.S. Perelson (2013). Kinetics of coinfection with influenza A virus and *Streptococcus pneumoniae*. PLoS Pathog. 9:e1003238.

Song, D., D. An, H. J Moon, M. J. Yeom, H.Y. Jeong, W.S. Jeong, S.J. Park, H.K. Kim, S.Y. Han, J.S. Oh, and B.K. Park (2011). Interspecies transmission of the canine influenza H3N2 virus to domestic cats in South Korea, 2010. J. Gen. Virol. 92:2350-2355.

Song, D., B. Kang, C. Lee, K. Jung, G. Ha, D. Kang, S. Park, B. Park, and J.Oh (2008). Transmission of avian influenza virus (H3N2) to dogs. Emerg. Infect. Dis. 14:741.

Song, D., C. Lee, B. Kang, K. Jung, T. Oh, H. Kim, B. Park, and J. Oh (2009). Experimental infection of dogs with avian-origin canine influenza A virus (H3N2). Emerg. Infect. Dis. 15:56.

Song, Q.Q., F.X. Zhang, J.J. Liu, Z.S. Ling, Y. L. Zhu, S.J. Jiang, and Z.J. Xie (2013). Dog to dog transmission of a novel influenza virus (H5N2) isolated from a canine. Vet. Microbiol. 161:331-333.

Song, D., H.J. Moon, D.J. An, H.Y. Jeoung, H. Kim, M.J. Yeom, M. Hong, J.H. Nam, S.J. Park, B.K. Park, and J.S. Oh (2012). A novel reassortant canine H3N1 influenza virus between pandemic H1N1 and canine H3N2 influenza viruses in Korea. J. Gen. Virol. 93:551-554.

Songserm, T., A. Amonsin, R. Jam-On, S.H. Namdee, P. Nuananong, P. Sunchai, T. Apiradee, C. Salin, T. Roongroj, and P. Yong (2006). Fatal avian influenza A H5N1 in a dog. Emerg. Infect. Dis. 12:1744.

Sponseller, B.A., E. Strait, A. Jergens, J. Trujillo, K. Harmon, L. Koster, M. Jenkins-Moore, M. Killian, S. Swenson, H. Bender, and K. Waller (2010). Influenza A pandemic (H1N1) 2009 virus infection in domestic cat. Emerg. Infect. Dis. 16:534.

Srivastava, B., P. Błażejewska, M. Heßmann, D. Bruder, R. Geffers, S. Mauel, A.D. Gruber, and K. Schughart (2009). Host genetic background strongly influences the response to influenza a virus infections. PloS one 4:e4857.

Su, S., J. Chen, K. Jia, S.U. Khan, S. He, X. Fu, M. Hong, L. Sun, W. Qi, G.C. Gray, and S. Li (2014). Evidence for Subclinical Influenza A (H1N1) pdm09 Virus Infection among Dogs in Guangdong Province, China. J. Clin. Microbiol. 52:1762-1765.

Su, S., H.T. Li, F.R. Zhao, J.D. Chen, J.X. Xie, Z.M. Chen, Z. Huang, Y.M. Hu, M.Z. Zhang, L.K. Tan, and G.H. Zhang (2013a). Avian-origin H3N2 canine influenza virus circulating in farmed dogs in Guangdong, China. Infect. Genet. Evol. 14:444-449.

Su, S., Z. Yuan, J. Chen, J. Xie, H. Li, Z. Huang, M. Zhang, G. Du, Z. Chen, L. Tu, and Y. Zou (2013b). Short communication: isolation and phylogenetic analysis of an avian-origin H3N2 canine influenza virus in dog shelter, China. Virus Genes 46:554-557.

Sun, X., X. Xu, Q. Liu, D. Liang, C. Li, Q. He, J. Jiang, Y. Cui, J. Li, L. Zheng, and J. Guo (2013). Evidence of avian-like H9N2 influenza A virus among dogs in Guangxi, China. Infect. Genet. Evol. 20:471-475.

Sun, Y., Y. Bi, J. Pu, Y. Hu, J. Wang, H. Gao, L. Liu, Q. Xu, Y. Tan, M. Liu, and X. Guo (2010a). Guinea pig model for evaluating the potential public health risk of swine and avian influenza viruses. PloS One 5:e15537.

Sun, Y., J. Pu, Z. Jiang, T. Guan, Y. Xia, Q. Xu, L. Liu, B. Ma, F. Tian, E.G. Brown, and J. Liu (2010b). Genotypic evolution and antigenic drift of H9N2 influenza viruses in China from 1994 to 2008. Vet. Microbiol. 146: 215-225.

Sun, Y., Y. Shen, X. Zhang, Q. Wang, L. Liu, X. Han, B. Jiang, R. Wang, H. Sun, J. Pu, and D. Lin (2014). A serological survey of canine H3N2, pandemic H1N1/09 and human seasonal H3N2 influenza viruses in dogs in China. Vet. Microbiol. 168:193-196.

Takase, H., H. Nitanai, E. Yamamura, and T. Otani (1999). Facilitated expansion of pneumococcal colonization from the nose to the lower respiratory tract in mice preinfected with influenza virus. Microbiol. Immunol. 43:905-907.

Takayama, Y., H. Yano, Y. Nojima, R. Nakano, R. Okamoto, Y. Hirakata, K. Sunakawa, T. Akahoshi, and M. Kaku (2014). Influence of prior pandemic A (H1N1) 2009 virus infection on invasion of MDCK cells by community-associated methicillin-resistant *Staphylococcus aureus*. J.Infect. Chemother. 20:71-73.

Tashiro, M., P. Ciborowski, H.D. Klenk, G. Pulverer, and R. Rott (1987). Role of *Staphylococcus* protease in the development of influenza pneumonia. Nature 325:536-537.

Tumpey, T.M., C.F. Basler, P.V. Aguilar, H. Zeng, A. Solórzano, D.E. Swayne, N.J. Cox, J.M.Katz, J.K. Taubenberger, P. Palese, and A. Garcia-Sastre (2005a). Characterization of the reconstructed 1918 Spanish influenza pandemic virus. Science 310:77-80.

Tumpey, T.M., A. García-Sastre, J.K. Taubenberger, P. Palese, D.E. Swayne, M.J. Pantin-Jackwood, S. Schultz-Cherry, A. Solórzano, N. Van Rooijen, J. M. Katz, and C.F. Basler (2005b). Pathogenicity of influenza viruses with genes from the 1918 pandemic virus: functional roles of alveolar macrophages and neutrophils in limiting virus replication and mortality in mice. J. Virol. 79:14933-14944.

Wang, J., Y. Sun, Q. Xu, Y. Tan, J. Pu, H. Yang, E.G. Brown, and J. Liu (2012). Mouse-adapted H9N2 influenza A virus PB2 protein M147L and E627K mutations are critical for high virulence. PloS One 7:e40752.

Warnking, K., C. Klemm, B. Löffler, S. Niemann, A. van Krüchten, G. Peters, S. Ludwig, and C. Ehrhardt (2015). Super infection with *Staphylococcus aureus* inhibits influenza virus induced type I IFN signalling through impaired STAT1 STAT2 dimerization. Cell. Microbiol.17:303-317.

Wiley, C., M. Ottoson, M. Garcia, L. Wiley, and C. Otto (2013). The Seroprevalence of Canine Influenza Virus H3N8 in Dogs Participating in a Flyball Tournament in Pennsylvania in 2010: A Follow Up Study. J. Vet. Intern. Med 27:367-370.

Winkler, G.C, and N.F. Cheville (1984). The neonatal porcine lung: ultrastructural morphology and postnatal development of the terminal airways and alveolar region. Anat. Rec. 210:303-313.

Wise, H. M., A. Foeglein, J. Sun, R.M. Dalton, S. Patel, W. Howard, E.C. Anderson, W.S. Barclay, and P. Digard (2009). A complicated message: Identification of a novel PB1-related protein translated from influenza A virus segment 2 mRNA. J. Virol. 83:8021-8031.

Xu, K., G. Smith, J. Bahl, L. Duan, H. Tai, D. Vijaykrishna, J. Wang, J.X. Zhang, K.S. Li, X.H. Fan, and R.G. Webster (2007). The genesis and evolution of H9N2 influenza viruses in poultry from southern China, 2000 to 2005. J. Virol 81:10389-10401.

Yang, X., C. Liu, F. Liu, D. Liu, Y. Chen, H. Zhang, L. Qu, Y. Li, D. Xia, and M. Liu (2014). Identification and genetic characterization of avian-origin H3N2 canine influenza viruses isolated from the Liaoning province of China in 2012. Virus Genes 49:342-347.

Yoon, K.J., V. L. Cooper, K. J. Schwartz, K.M. Harmon, W.I. Kim, B.H. Janke, J. Strohbehn, D. Butts, and J. Troutman (2005). Influenza virus infection in racing greyhounds. Emerg. Infect. Dis 11:1974-1976.

Zeng, X., Y. Lin, Y. Zhao, C. Lu, and Y. Liu (2013). Experimental infection of dogs with H3N2 canine influenza virus from China. Epidemiol. Infect. 141:2595-2603.

Zhang, K., Z. Zhang, Z. Yu, L. Li, K. Cheng, T. Wang, G. Huang, S. Yang, Y. Zhao, N. Feng, and J. Fu (2013). Domestic cats and dogs are susceptible to H9N2 avian influenza virus. Virus Res. 175: 52-57.

Zhang, W.J., S. Sarawar, P. Nguyen, K. Daly, J.E. Rehg, P.C. Doherty, D.L. Woodland, and M. A. Blackman (1996). Lethal synergism between influenza infection and staphylococcal enterotoxin B in mice. J. Immunol. 157:5049-5060.

Zhou, P., S. Huang, W. Zeng, X. Zhang, L. Wang, X. Fu, and S. Li (2016). Seroepidemiological Evidence of Subtype H3N8 Influenza Virus Infection among Pet Dogs in China. PLoS One 11: e0159106.

Zhou, P., L. Wang, S. Huang, C. Fu, H. He, M. Hong, S. Su, and S. Li (2015). Beagle dogs have low susceptibility to BJ94-like H9N2 avian influenza virus. Infect. Genet. Evol. 31:216-220.

Zitzow, L.A., T. Rowe, T. Morken, W.J. Shieh, S. Zaki, and J.M. Katz (2002). Pathogenesis of avian influenza A (H5N1) viruses in ferrets. J. Virol. 76: 4420-4429.