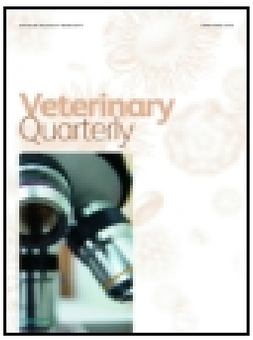

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Review article

Dynamics of avian coronavirus circulation in commercial and non-commercial birds in Asia – a review.

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Abstract
It is essential to understand the latest situation regarding avian coronaviruses (ACoVs), commonly referred to as the well-known avian infectious bronchitis virus (IBV), given that new and diverse types of IBV are continually being identified worldwide, particularly ones that are isolated from commercial poultry and associated with a wide range of disease conditions. The existing IBVs continue to evolve in various geographic areas in Asia, which results in the recombination and co-circulation between IBV types. This makes it increasingly difficult to prevent and control IBV infections, despite routine vaccination. Some ACoVs have also been identified in other avian species and they may pose a threat of cross-transmission to commercial sectors. The present review provides an overview of IBV circulation and the dynamic emergence of new variants found throughout Asia via the recombination of IBV strains. In addition to commercial poultry, backyard poultry and free-ranging birds may serve as a 'hub' for ACoV transmission within a particular area. These birds may be capable of spreading viruses, either to areas of close proximity, or to remote places via migration and trade.

Keywords: avian; poultry; chicken; coronavirus; infectious bronchitis virus; Asia; review

1. Introduction
Coronaviruses (CoVs) are known to be one of the major respiratory pathogens that cause a range of diseases in both human and animal communities. Some have led to concerns for a threat to

global public health in the twenty-first century, such as the CoVs causing severe acute respiratory syndrome (SARS) (Zhong et al. 2003) and those responsible for the recently identified Middle East respiratory syndrome (MERS) (Zaki et al. 2012). For CoVs in avian species, avian coronaviruses (ACoVs) are classified into the genus *Gammacoronavirus*. The infectious bronchitis virus (IBV) is among the most important ACoVs affecting the poultry industry. IBV was first reported as an avian respiratory pathogen in the 1930s in Massachusetts, USA. It exhibits extensive antigenic variation, and the strains present in each country are almost unique. Therefore, many genotypes of IBV have been identified worldwide, and new variants keep emerging despite vaccination (reviewed in de Wit et al. 2011; Jackwood 2012). Vaccines against IBVs are generally effective, but new strains continue to emerge causing clinical diseases and production problems in vaccinated flocks, eventually having an economic impact on the global poultry industry (Gelb et al. 2005; Liu et al. 2006; Han et al. 2011). The pathogenicity of IBV is very complex as it is influenced by many factors, such as the strain of the virus, the breed of chicken, environmental conditions, and concurrent infection from other pathogens. IBV alone may not cause severe and devastating disease, but IBV-infected birds can be susceptible to superinfection by bacteria (for example, *Escherichia coli*), mycoplasma (for example, *Mycoplasma gallisepticum*, *M. synoviae*) and co-infection with other viruses such as the infectious bursal disease virus (IBDV), Newcastle disease virus (NDV), avian influenza virus (AIV), and Marek's disease virus (MDV) (Bradbury 1984; Matthijs et al. 2003; Cavanagh and Gelb 2008; Dwars et al. 2009).

IBV consists of a single-stranded positive-sense RNA genome. Its genome encodes four structural proteins: phosphorylated nucleocapsid protein (N), membrane glycoprotein (M), spike glycoprotein (S), and small envelope protein (E) (Cavanagh 2007). The spike glycoprotein S, in the form of club-shaped projections present on the surface of the virus, is post-translationally cleavable into two subunits: the S1 forming the outer spike portion of the protein; and the S2, the protein anchoring it to the viral envelope. The S1 is responsible for attachment to the host cell receptors, while the S2 subunit mediates fusion of the virus and the host cell membrane, thereby entering into the host cells. Moreover, the S1 subunit contains epitopes and determinants for serotype-specificity, hemagglutinin activity, and for neutralizing antibodies that provide protective immunity (Masters 2006; Cavanagh and Gelb 2008).

All known different IBV genetic types appear to have little or no overlap to cross-protect each other, causing existing recurrent outbreaks. Currently, genotypes based on the sequence of the S1 protein gene, especially in the hypervariable 5' region (HVR), are used for classification of IBVs. This genotyping is very useful in the continuous determination of the epidemic genotype of IBV field strains, and for predicting the effectiveness of vaccines against field isolates. In addition, the production of a new generation of vaccines, genetically related to the circulating IBV local strains, is economically beneficial for control of infectious bronchitis (IB) in global geographic regions.

This review aims to provide an update on the dynamics of avian coronavirus, particularly focusing on the economically important IBV strains that are circulating in commercial farms in

Asian countries. The review also identifies the potential risks of IBV spreading in a traditional backyard poultry farming situation, which usually has links to rural communities and contributes to local consumption. The review goes on to discuss the IB situation occurring in species of birds other than poultry. This information draws attention to how possible diverse IBVs (and also other ACoVs) are persistently circulating around this continent.

The collection of IBV isolates in different Asian geographic regions is listed in Table 1. This includes: country of origin, name and genetic types of the isolates, tissue tropism, common breeds, and age range of IBV-infected birds. GenBank accession numbers are included that can document the reference citation of each representative strain. Figure 1 illustrates the phylogenetic tree indicating the relationship between the S1 amino acid sequences of the selected strains obtained from the Asian IBV isolates listed in Table 1.

2. The contributions of commercial poultry on different geographic area, to the recurrent emergence of new virus strains and their relationship to available vaccines

2.1. The Far East

2.1.1. Mainland China

In China, IBVs were isolated and identified in the early 1980s. Since that time, IB outbreaks have been ongoing in both vaccinated and non-vaccinated flocks, and have had an economic impact. Vaccines, usually based on a Massachusetts (Mass, M41), a Connecticut (Conn), and a 4/91 strain, have been used extensively in poultry farms for many years. However, these vaccines provided very little protection against Chinese isolates. This is because vaccines and field strains belong to different phylogenetic clusters that have larger evolutionary distances, indicating different genotypes (Liu et al. 2006; Han et al. 2011; Li et al. 2012; Ma et al. 2012). The obvious signs of IB in vaccinated commercial broilers were respiratory symptoms. Post mortem findings indicated inflammation of the upper respiratory tract, the kidneys and the proventriculus. There was a broad range of debilitating symptoms while mortality sometimes occurred when co-infection was present. The most prevalent signs in layer hens included decreased egg production, deformed eggs, and increased mortality. A nephropathogenic LX4 type, one among the predominant Chinese variants, was purported to have originated in China in the mid-1980s. Importantly, a predominant QX-IBV, a new IBV variant that was classified within the LX4 group, was reported (Yudong et al. 1998) and spread extensively to other regions in China and also to other countries (reviewed in de Wit et al. 2011; Jackwood 2012; Ma et al. 2012). This type of IBV caused severe nephritis, proventricultis and atrophic oviducts, which resulted in a decrease in egg production (Yudong et al. 1998). In previous years, outbreaks of many IBV strains, such as the Mass-type associated nephropathogenic strains, were reported in China. Nevertheless, other strains with a partial relationship to the Mass-type were also identified (Li and Yang 2001; Yu et al. 2001; Liu and Kong 2004; Bing et al. 2007). In addition, virus isolation between 1995 and 2004 indicated that at least seven genotypes were detected, mainly being nephropathogenic strains. However, a number of genotypes were not only indigenous to China, but some had a genetic relationship to those isolated from neighboring

countries, for example, Korea and Taiwan (Liu et al. 2006). Also the major groups of the more recently isolated IBVs belonged to the Chinese types, which differed from both the vaccine and the non-Chinese strains (Yan et al. 2011). Therefore, different IBV strains have been increasingly co-circulating in the poultry population.

The geographic distribution of IBVs indicated a wide variety of IBV types present in China. For instance, in southern China the dominant signs of IB were associated with respiratory distress and nephritis in chickens of different age groups. Some isolates were classified into Taiwanese-type (TW-I), Mass-type and proventriculitis-type viruses (Li et al. 2010; Zou et al. 2010; Yan et al. 2011; Li et al. 2013). In addition, IBVs isolated from broilers and broiler breeders at various ages from eastern, southern, south-western and central parts of China were classified into different genetic groups. These flocks exhibited typical respiratory and nephropathogenic IB symptoms, and experienced pathological changes. Nephropathogenic IBVs were mainly A2-like (QX-IBV) strains, and they showed evolutionary distance from vaccine strains. Among others, HN08, 4/91, Gray and Mass-types were also identified. Moreover, recombination events were observed between a LX4 and a teal-isolate (tl/CH/LDT3/03I-type), contributing to the emergence of a new variant. Interestingly, a recent Taiwanese-type (TW-II) was also detected in mainland China. Corresponding investigations were presented indicating that the Chinese strains had also been isolated in Taiwan (Han et al. 2011; Ji et al. 2011; Li et al. 2012; Luo et al. 2012; Ma et al. 2012; Li et al. 2013). Predominantly nephropathogenic LX4-type IBVs had apparently replaced the previously prevalent IBVs in China (Li et al. 2013). Recently, the divergence of new IBV variants that could be further classified was also demonstrated. For instance, IBV isolates in Cluster I and Cluster II had dissimilar amino acid sequences at a different position in the S1 subunit (Ma et al. 2012). Moreover, a GX-NN09032 isolate was associated with a recombination found in four IBV strains (He et al. 2012), while YN-type IBV was genetically similar to most of the prevalent Chinese strains but displayed more severe pathogenicity than the previously reported IBVs (Feng et al. 2012). Another example showed that a CK/CH/LSL/99I-type isolate was recently predominant in southern China. The S1 gene of this isolate had the greatest diversity. Positive selections were detected, not only in the S1 gene but also in the M and N genes. Recombination with vaccine strains, in particular a 4/91-type, was also detected (Mo et al. 2013). Therefore, the trend of IBV local strains isolated in different Chinese regions continually changes as novel variants are discovered. Consecutive investigations over a 15-year period have so far identified at least nine genetic types and, according to sequence and phylogenetic analyses of the S1 gene (Table 1), a couple of IBV variants currently found in China.

Thus, it is now clear that various IBV field variants are co-circulating in China and appear to continually evolve. Vaccine strains might have an important role in the appearance of new IBV variants via recombination. In addition, IBV evolution is driven by the generation of both genetic diversity and selection. For the effective control of IB, alternative vaccines rather than common Mass-type vaccines are needed.

2.1.2. Taiwan

The first IBV (TP/64) appeared in Taiwan in 1965, and was isolated from layers that suffered from respiratory distress and a drop in egg production (Tseng et al. 1996). IB outbreaks occurred frequently even though a vaccination program was widely used. The most common vaccine used in Taiwan was based on a Mass-type. The S1 phylogeny of the Taiwanese isolates demonstrated the following groups: a Taiwanese Group I (TW-I), a Taiwanese Group II (TW-II), a Chinese-type, and a Mass-type. For the indigenous groups, the first Taiwanese isolate was classified as TW-II. However, according to the results of recent studies, most of these isolates belonged to TW-I. In addition, some of the remaining isolates appeared to be vaccine strains, including a Mass-type IBV field strain and one belonging to a Chinese J2 strain. The existence of Chinese IBV in Taiwan was unusual because of the prohibited importation of poultry products between Taiwan and mainland China (Huang et al. 2004). Later, Huang and Wang (2006) developed attenuated vaccines derived from Taiwanese IBVs by the passage of the viruses in embryonated eggs. Thereafter, they demonstrated that the attenuation of these IBVs resulted in substitutions between two and six amino acids found in the S1 gene, and a few amino acid substitutions found in the S2 subunit (Huang and Wang 2007). This indicated that the S1 gene had undergone a high degree of mutation. Furthermore, Chen et al. (2009) studied the evidence of an IBV isolated in 2002, which demonstrated that the recombinants of Taiwanese IBVs had chimeric IBV genome arrangements originating from parental strains similar to those of Taiwan and China. Chen et al. (2010) further indicated that one isolate showed evidence of frequent recombination with the China-like strain in the S gene. Another isolate demonstrated the genome organization of the China-like strain in the S2 gene, and the H120-like genome fragments within the M protein gene. This would again suggest that IBVs in Taiwan undergo genetic recombination and evolution.

2.1.3.Japan

IBVs were first isolated in Japan in the 1950s. Since then, outbreaks have been ongoing (Nakamura et al. 1954), although the common vaccines used in Japan were Mass and Conn serotypes. Mase et al. (2004) described five different genetic groups of the Japanese isolates. These included the well-known Mass and Gray types, and a unique Japanese type that was discovered during the outbreaks. The other two emerged groups were closely related to the Chinese and Taiwanese isolates.

Major clinical signs caused by Japanese-type IBVs in poultry were associated particularly with respiratory and kidney form of IB. These types included a Mass-type (respiratory form), a JP-I (respiratory, kidney and reproductive form), a JP-II (kidney form), and a JP-III (respiratory and kidney form). Later, Shieh et al. (2004) demonstrated a new Japanese IBV subtype, which had a S1 sequence most similar to those of Australian strains, while the N sequence was closely related to those of North American strains. This new Japanese variant might have recombined with Australian-related and North American-related IBVs. Shimazaki et al. (2008) subsequently described a new virulent 4/91 variant. These viruses caused severe respiratory symptoms and weight loss in young chicks. The S1 analysis indicated that the isolates were closely related to

Spanish and French isolates, suggesting that the 4/91 variants were derived from a foreign field isolate. In addition, some IBV strains had high sequence similarity with that of a 4/91 vaccine strain commonly used in Japan, suggesting that vaccine-like viruses were derived from a vaccine (Shimazaki et al. 2009). Earlier, in 2002, Japan had introduced the 4/91 IBV vaccine, and was trading a large amount of poultry products from European countries. The introduction of the vaccine, and the trading of poultry products, might have provided the transmission routes for those strains (Mase et al. 2008). Subsequently, Mase et al. (2010) reported a novel genotype isolated in 2009, designated as JP-IV. This variant was isolated from commercial layers unable to start laying eggs. Neither respiratory form of IB nor increased mortality were observed. The sequence analysis indicated that the isolate shared an ancestor with an IBV isolated in the south of China, namely the TC07-2 strain. So far, overall investigations of circulating IBVs in Japan indicate cross-transmission from foreign isolates as well as continual evolution.

2.1.4. Korea

Outbreaks caused by IBVs were first reported in Korea in1986 from a laying flock that exhibited decreased egg production (Rhee et al. 1986). A nephropathogenic strain was then identified in 1990. Following this, a wide variety of IBV strains were classified. Three clusters were differentiated into non-Korean strains, including Arkansas (Ark), Conn and Mass types, whereas the rest of the IBV strains, such as a KM91, were unique to Korea (Lee et al. 2004). In the beginning, a Mass-type IBV was the only vaccine strain used in Korea (King 1988). But, at a later date, vaccine strains based on a Mass, a H120 and a KM91 were also implemented to control IB. The common Korean IBV, isolated between 2001 and 2003 from broilers and broiler breeders, was classified as KM91 and Ark-type isolates (Jang et al. 2007). Later, Lee et al. (2008) studied the genetic groups of IBVs obtained from 2003 to 2006, which indicated that the unique Korean (K-I) group could be further divided into the respiratory subgroups K-Ia and K-Ib. Furthermore, the K-II group was closely related to nephropathogenic variants isolated from China and Japan, while the K-III group was closely related to the enteric IBV isolated from China that caused proventriculitis. From these results, K-Ia and K-II were the most prevalent strains. Recently, it was shown that the new clusters of Korean IBVs had recombination events of the S1 gene with putative parental strains originating from KM91-like or QX-like subgroups (Lim et al. 2011). More recently, Mo et al. (2013) identified an IBV circulation in Korea from the isolates from 1990 to 2011. These findings indicated that New Cluster 1 was prevalent between 2009 and 2010, and was then replaced by the predominant QX-like virus in 2011. Another recent study by Song et al. (2013) also declared the recombination of Korean IBV to be between an indigenous Korean-type and Mass-type vaccines currently used in Korea (such as Ma5, H52 and H120 vaccines). Likewise, a recombination was also predicted between the following: (1) New Cluster 1 and QX-like, (2) K-I and H120, and (3) KM91 and QX-like. In conclusion, the currently circulating Korean IBVs appear to be a respiratory strain K-I, a nephropathogenic strain K-II with subgroups KM91-like and QX-like, an enteric strain, and some other recent strains (for example K-III, New Cluster 1, and New Cluster 2). Natural

recombinations occur frequently between these heterologous strains and vaccines that were classified into different genetic groups, and may cause the continuous evolution of new IBV variants in Korea.

2.2. The Southeast Asia

Extensive poultry farming in Thailand and Malaysia is industrialized to accommodate the export of poultry products. Repeated outbreaks were reported despite the use of vaccines to control IB in commercial poultry. The molecular evolution of IBV strains in Malaysia is not evidently known. Two Malaysian IBV isolates were studied. One, with a history of high mortality and severe kidney lesions, was isolated in 1994 from a broiler farm in Perak in the northern part of the Malaysian peninsular. Ten years later, an isolated virus, which exhibited tracheal and pulmonary congestion, was detected from a layer farm in Selangor bordered by Perak to the north. The S1 phylogenetic analysis of these two isolates indicated non-M41 strains, but one of them shared about 90% identity with the Chinese QX-like IBV. Another isolate belonged to a variant strain with lower identity to the known reference IBVs. However, these two isolates shared a common origin based on the spike S2 and N protein genes (Zulperi et al. 2009).

In Thailand, the first reported IB outbreak occurred between 1953 and 1954 (Chindavanig 1962). Later, IB was shown to be a disease with important economic consequences for the Thai poultry industry. Although vaccines, such as Conn, H120, Ma5, Mass, and Armidale A3, appeared to be very commonly used in commercial farms, IBV spread all over the country. The most common IBV strains in Thailand belonged to a Mass-type, but a 4/91-type IBV was also reported (Cook et al. 1996). Genetically, the recently isolated Thai IBVs were characterized and found to be similar to the QX-like strain, and the indigenous strain was identified according to the HVR of the S1 gene (Pohuang et al. 2009). Most of the isolates were from H120-vaccinated commercial broiler flocks raised in central Thailand. These flocks suffered from airway problems. Pohuang et al. (2011) isolated and identified the viruses based on a full-length S1 gene analysis. The viruses were, therefore, classified into the following groups: a group unique to Thailand Group I, a QX-like Group II, and a Mass-type Group III. This study also showed the recombination events of the local isolates. The viruses in Group I had 5´-terminus of the THA001 origin isolated in Thailand in the late 1990s, while the 3´-terminus belonged to the QX-like Group II. In addition, the viruses in Group II shared the S1 sequence of the Chinese QX-IBV, but the rest of the sequence belonged to the Chinese strain JX/99/01. Further studies are required to determine the circulation and recombination of IBV variants in other parts of the country. In fact, the vaccination program needs to be revised.

2.3. The South Asia

IBV was reported to be prevalent in India. The most prevalent form was primarily the respiratory form correlated to a Mass-type. It is important to note that India used to be free from IBV variant forms. A novel genotype was reported only recently with the emergence of an Indian nephropathogenic form of IB (Bayry et al. 2005). This IBV was isolated from the outbreak that

caused diseases in one to two week old commercial broilers. Diseases resulted in visceral gout and nephritis. Clinical signs showed respiratory disorders. Grossly, distended ureters filled with uric acid, interstitial nephritis, granular degeneration, vacuolation and desquamation of tubular epithelium were observed. Eventually, by virus isolation and sequencing, Sumi et al. (2012) confirmed a novel nephropathogenic IBV that belonged to a 4/91 genotype. For genotyping, this was the first occurrence of a novel IBV isolated in India.

In Pakistan, M41-type IBV antigens were commonly detected in the lungs and tracheas of broilers and layer hens of various ages. Several IBV genotypes from commercial chickens were also tested serologically, confirming the presence of seropositive M41, D274, D1466 and 4/91 strains (Ahmed et al. 2007). To date, no IBV classification based on genetic analysis has been performed in Pakistan.

2.4. The Middle East

2.4.1. Iran

In Iran, IB is one of the most important respiratory diseases of broilers. The first isolation of an IBV in Iranian poultry was reported in 1994 (Aghakhan et al. 1994). Several Iranian isolates were identified at a later date, and a 4/91-type appeared to be one of the predominant types (Shoushtari et al. 2008). Mass-type vaccines are the only officially authorized vaccines. In vaccinated flocks, failure of the Mass-type vaccination often occurred, either due to the use of unrelated vaccine strains, or due to there being no partial cross protection of vaccines against field isolates (Seyfi Abad Shapouri et al. 2004). Boroomand et al. (2012) studied the Iranian 4/91-IBV infection in one-day old commercial broilers, demonstrating that this particular strain was widely distributed in tissue of the respiratory, urogenital and digestive tracts. However, they observed only mild clinical respiratory signs and depression. The Iranian 4/91 isolates were thus unlikely to cause mortality, severe clinical signs or gross lesions in infected poultry. Instead, they replicated virus in some tissues that made birds susceptible to other pathogens because of the failure of the immune system. In addition, Asasi et al. (2013) studied acute phase factors, pro-inflammatory cytokines and serum sialic acids, indicating that these variables increased after inoculation with an Iranian IBV. Moreover, they did not find many other IBV strains, such as the common Mass-type virus (Jahantigh et al. 2013). In summary, at present, IBV isolates in Iran belong predominantly to the 4/91 type, and ultimately, improvements to the vaccination program will be required.

2.4.2. Iraq

IBV 4/91-type is commonly detected in Iraq. Three different IBV vaccines (H120, Ma5, and attenuated 4/91 strains) were commonly used on poultry farms (Mahmood et al. 2011). However, outbreaks have continued to occur repeatedly, which has resulted in high mortality in broiler farms, associated with renal lesions in both vaccinated and non-vaccinated flocks. Recently, a new genotype in Iraq, designated as the nephropathogenic Sul/01/09 genotype, was discovered by sequencing the S1 gene, and was compared with the other known IBVs (Mahmood et al.

2011). This new genotype was isolated from commercial poultry that suffered from kidney disease, despite regular immunization with 4/91 and Ma5 vaccines. This kidney-type IBV was closely related to viruses isolated in Israel and Egypt. Furthermore, Amin et al. (2012) demonstrated a QX-like IBV in Iraq, isolated from vaccinated broiler breeders that suffered from several clinical signs related to respiratory disease. Post-mortem examination revealed purulent inflammation in the bronchi and oedema in subcutaneous tissue. All of the animals were immunized with Mass-type, H120 and Ma5 vaccines. The S1 phylogeny revealed that the viruses showed a high nucleotide identity with those of QX-like Chinese strains isolated between 2009 and 2010. However, some isolates had a nucleotide identity that correlated with the unique QX-type virus sequence from the Middle East-type isolated in Israel in 2004. This indicates co-circulation of two QX-like types in Iraq.

2.4.3. Israel

In Israel, the only permitted vaccines are the live attenuated H120, or an inactivated Mass-type serotype. Since 1995, four IBV genotypes have been identified as follows: a Mass-type field isolate, which differed slightly from the vaccine strain H120; two novel variants, Variant I and Variant II; and a variant IS/720/99 (Meir et al. 1998). Later, in 2000, severe outbreaks of a novel IBV variant caused acute renal disease, high mortality, and poor weight gain in vaccinated broilers. The outbreaks resulted in huge economic losses to the Israeli broiler industry. This isolated IBV was then identified as a new nephropathogenic variant. The virus shared approximately 70% similarity with the vaccine strain H120. With the H120 protection test, 91% protection to the trachea and only 25% protection to the kidney were observed. In addition to the H120 relationship, this virus was also closely related to the Egyptian isolates (Meir et al. 2004). More recently, Gelb et al. (2005) studied the Israeli IBV strains, mainly associated with respiratory and renal diseases, isolated between 1996 and 2000 from broilers and layers. Four genetic groups were clustered by a restriction fragment length polymorphism (RFLP) fragment pattern of the S1 gene as follows: a Mass-type, a Variant I, a Variant II and a novel group. These isolated IBVs had a poor level of protection by the H120 vaccine. Thus, using homologous viruses as vaccines would ensure the efficacy of IB control.

2.4.4 .Jordan

In the past, a Mass-type IBV was the only field strain present in Jordan, and all commercial flocks were vaccinated against it using the corresponding vaccine. Further investigations indicated the presence of IBV field serotypes other than the Mass-type. By hemagglutination inhibition (HI) titers, Ark, DE-075-like, JMK and Mass-like serotypes were shown to be present. Similarly, the Mass and other serotypes were also classified in other Middle-Eastern countries (Gharaibeh 2007; Roussan et al. 2008a). Moreover, Roussan et al. (2008b) studied genotyping of IBV in Jordanian broiler flocks suffering from respiratory disease. They detected specific groups of a Mass-type, a 4/91-type and a D274-type IBV. Roussan et al. (2009) subsequently studied commercial broilers, broiler breeders and layers that were free from respiratory disease,

indicating seropositivity for Mass, 4/91 and D274 serotypes. Ababneh et al. (2012) subsequently reported the IB outbreaks investigated in Iraq, Jordan, and Saudi Arabia in which diseases were associated with respiratory signs accompanied by nephritis, watery cysts in the ovary, and swollen oviducts resulting in egg production problems. Phylogenetics based on the HVR of the S1 gene referred to a Chinese CK/CH/LDL/97I isolate indicating its Far Eastern origins. All of these flocks were vaccinated based on Mass and H120 strains, suggesting vaccination failure since less than 80% nucleotides were found to be identical to the vaccine strains. An IBV strain CK/CH/LDL/97I that caused proventriculitis in poultry was first reported in China in 1995 (Liu et al. 2009). In recent years, this strain has been isolated from other organs of infected birds, such as the trachea. Amino acid homology of the S1 gene of this strain was less than 79% compared with those vaccine strains used in Jordan (Ababneh et al. 2012). Therefore, only homologous protection should be considered to accomplish immunity against this strain. Ultimately, the Far Eastern IBV variants detected in the Middle East illustrate that the active spreading of IBVs within and between geographic areas in this region continues to evolve.

Taken overall, the published data on IBV isolation and characterization in Asia, suggests that the circulation of IBV strains is not only limited within each particular area, but some strains appear to spread between regions. Moreover, major IBV types found in the Far Eastern countries consist of the following: QX-type and QX-like viruses; new IBV variants derived from recombination events between local, foreign, and vaccine strains; and some indigenous local-type viruses. However, particular QX variants seem to be the predominant Asian IBV strains that may well play a crucial role in their spreading throughout Asia. In addition, they have also spread to European countries (Beato et al. 2005; Bochkov et al. 2006; Valastro et al. 2010). In the Middle East, a 4/91-type is the prevalent type. Some others (for example Iraq/IS720/Sul/01/09 and Egypt/IS720/Beni-Seuf/01 isolates) are circulating in northern African countries. In addition, co-circulation of the existing IBV strains as well as the currently used live vaccines, may also play a major role in the potential recombination of IBVs, making the incidence of new evolving IBV variants highly likely (reviewed in de Wit et al. 2011; Jackwood 2012). Most of the newly emerged IBVs were not significantly genetically identical to vaccine strains used in a particular area, resulting in low protection or even vaccination failure.

3. The contributions of backyard poultry on the small-scale and non-commercial poultry operations, to the transmission of avian coronaviruses

During the 2004 outbreaks of the highly pathogenic avian influenza subtype H5N1 (HPAI H5N1) in Southeast Asia, disease control measures that covered most of the poultry operations, except for small-holder native poultry farming, were officially implemented by the governments. Studies on risk analysis indicated that good sanitization in farming areas provided a lower risk of HPAI, whereas backyard farms where owners traded live poultry experienced a higher risk of infections (Paul et al. 2011).

In Asia, the backyard poultry system is often correlated with the rural community, and greatly contributes to local consumption and agricultural activities. The purpose of backyard

poultry farming in rural areas is either small-scale production or a non-commercial operation (free-ranging domesticated birds). Traditional poultry trading is often conducted daily or weekly. Therefore, flocks may get infected by vehicles or equipment and tools shared between farms. Egg collection, transport and trading activities among poultry farms can spread the disease to other flocks (Figure 2). For instance, in Cambodia, poultry being moved to live bird markets via poultry traders was a potential 'hub' for the spread of HPAI H5N1 (van Kerkhove et al. 2009). In Vietnam, the route from poultry traders to live bird markets was the key to HPAI H5N1 transmission (Soares-Magalhaes 2010). Furthermore, study on poultry market chains in China demonstrated that H5N1-infected live poultry markets presented a more significant problem than non-infected markets (Martin 2011). In Thailand, although the number of poultry traded in traditional networks is small compared with other production systems, poultry trading continues all year round, and may thus surreptitiously contribute to the spread of any disease. Live backyard poultry trading is usually based on the activities of traders who buy chickens from villages and supply urban markets with poultry meat products. In addition, trade always flows from live poultry to slaughterhouses (Choprakarn et al. 2006). Poolkhet et al. (2013a) studied the movement and trading patterns of backyard poultry in Thailand. With regard to the spread of H5N1 to the backyard farming area, they found that the pattern of disease transmission was local spreading outwardly. They also indicated a close relationship between owners' houses and fresh food markets. This relationship needs the attention of authorities to prevent future outbreaks. At the same time, Poolkhet et al. (2013b) specified that the important factors in the spread of avian flu in backyard farming systems are: the farmers themselves, neighbors with backyard poultry, and visitors to sport arenas or training fields of fighting poultry. Moreover, Wiratsudakul et al. (2014) studied the dynamics of backyard poultry flows in traditional trade networks. Flows of backyard poultry trade indicated that traders ran businesses only near their villages. The average distance of poultry movement ranged from four to 25 kilometers, determining a spatial scale for the risk of H5N1 transmission to be spread through the traditional poultry market. As a result, overlapping poultry supply zones might also enable disease transmission over extensive distances through combined expansion and the relocation process. In addition, an increased number of poultry being traded occurred during special Asian festivals such as the Chinese New Year (February), the Thai New Year (April), and the international New Year (January). Live poultry movements and activities precede these festivals by about 15 days, which might lead to a higher risk of disease transmission compared to the other months of the year.

Although the above studies were particularly focused on HPAI H5N1 transmission in backyard poultry, this information might be of use to serve as a model for other respiratory infectious disease surveillance and control programs. It is applicable for the control and prevention of avian coronavirus-associated diseases in backyard poultry due to the same mode and route of transmission (OIE 2012). Movement activities and poultry trading between farms can cause the spread of diseases throughout the neighbourhood and into other areas. Thus, the spread of disease could be limited by removing infected individuals, and hence breaking down the bionetwork.

Consequently, poor backyard farming conditions most likely play an important role in the spread of respiratory diseases. Backyard poultry usually show subclinical symptoms rather than obvious clinical presentations. Most of them are not vaccinated. Promkuntod et al. (2014) reported IBV infection in unvaccinated backyard poultry, showing a range of clinical conditions (Table 2). Poor backyard husbandry, therefore, poses a potential risk because farmers pay little attention to biosecurity, thereby generating an unconcern for disease prevention and control. Therefore, backyard poultry may potentially play a role in the epidemiology of ACoV-associated diseases.

4. The contribution of avian species other than poultry to the transmission of avian coronaviruses

ACoVs that cause diseases in poultry are mainly based on IBVs, especially those producing a range of symptoms in commercial and village poultry (Cavanagh 2007; Cavanagh and Gelb 2008). In recent years, CoVs have been isolated in other birds, for example, in pheasants and turkeys. However, the ACoVs found in these birds were genetically distinct from IBVs. Furthermore, birds other than galliformes were also shown to be susceptible to ACoVs, that is, IBVs and IBV-like types (reviewed in Cavanagh 2005; Chu et al. 2011).

In Asia, particularly in China, CoVs that were antigenically related to IBV (IBV-like) in terms of their genome incorporation and the sequences of the encoded genes, were discovered in other galliform bird species such as peafowl, partridges, guinea fowl and teals. Ito et al. (1991) reported CoVs isolated from the guinea fowl. Field observations and infection under laboratory conditions indicated that the virus from guinea fowl had a host range of more than one bird species. Besides, it was shown that the viral protein of peafowl CoVs had more than 99% identity with the commercial IBV H120 vaccines (Liu et al. 2005). This indicated that the viruses recovered from peafowl had originated from vaccinated chickens in the same neighborhood. Another ACoV isolated from peafowl was a Mass-type IBV that was experimentally pathogenic to domestic chickens. This suggested that the peafowl might have acted as a natural reservoir for this IBV (Sun et al. 2007) (Table 2).

Among non-galliform birds, the ACoV isolates from teal in China that were kept near domesticated chickens had a spike protein with 90% identity to a nephropathogenic IBV (Liu et al. 2005). This isolated virus could also experimentally infect kidneys of domestic chickens, indicating that the teal virus was certainly a nephropathogenic IBV that had cross-transmitted to birds from neighbouring farms. Moreover, Qian et al. (2006) isolated and characterized an ACoV from pigeons that had pancreatitis. Hypothetically, this virus was identified as a novel *gammacoronavirus* that had a closer genetic relationship to IBV strains (Table 2).

Overall, these avian species would evidently act as a natural reservoir or carrier of IBV. When birds migrate, these IBV strains could be transported for long distances. In line with this, it was already shown that pathogenic avian influenza viruses could be transmitted via a variety of bird species, including wild birds, domestic captive birds and free-range village birds (Tiensin 2011) (Figure 2). In summary, IBVs can replicate in galliform species other than chickens and in

some non-galliform birds. The viruses isolated from these birds, however, are genetically related, whether they are of IBV origin or they are the common viruses found in these birds. Thus, different bird species may potentially transmit viruses to other free-living birds, or to susceptible poultry populations, when they are in contact with each other under any given circumstance.

5. Conclusion

IBVs still provide a major pathogen for the poultry industry in spite of routine vaccination. Moreover, IBV circulation in backyard chickens and free-living birds seems to be silently endemic. The widespread distribution of IBVs in Asia is either due to intra-regional or inter-regional dynamics. Therefore, it is necessary to know which IBV types are circulating in particular farms and in their neighbourhoods. Finally, it is essential to determine whether available vaccines are expected to be protective; otherwise new vaccines need to be developed.

It is well-known that two major forces drive RNA virus evolution: mutations due to the high error rates of the viral RNA polymerase, and the recombination of the S1 sequences in CoVs. This generates new IBV strains or genotypes worldwide. In line with this, it has been shown that the re-assortment and adaptation of RNA viruses to the hosts that generate the diversity of viruses, for example, has led to various subtypes of pathogenic avian influenza virus (Nichol et al. 2000; Yu et al. 2001; Jackwood et al. 2012). In addition to genetic variation, a complex interplay of factors influencing IBV emergence may also play an important role. These include environmental factors such as ecological change, social movement, and behavioural influences. Moreover, global expansion of agriculture, rapid population growth, advances of transportation, illegal trading, inefficient biosecurity and traditional farming systems that are unaware of IB, can be associated with factors playing a role in IBV emergence (Nichol et al. 2000; Bayry 2013).

In Asia, three major poultry production systems exist, comprising mass-produced poultry operations, small-scale poultry production, and backyard poultry farming. Strict farming management provides a well-established biosecurity, and an adequate vaccination program for commercial poultry. In contrast, if poor husbandry continues to take place among small-holder and backyard poultry producers living in areas of geographic concentration and high housing density, dispersed throughout rural areas, this will greatly augment the spread of IB. Traditional poultry farming may also facilitate continuous spreading of IBV within the area, and perhaps to flocks in the surrounding regions. Thus, compartmentalization of backyard poultry farming is one of the most successful management procedures to reduce the transmission of diseases to commercial and non-commercial poultry. Moreover, resident and migratory free-living birds may harbor IBVs and transmit them to other birds, or they may carry common ACoVs in nature that can spread to poultry and other bird populations. These birds may also play a critical role in the epidemiology of IB.

In summary, this review highlights the overall dynamic emergence of IBVs in commercial and non-commercial poultry, as well as in other avian species living in the villages. Factors contributing to co-circulation and generation of new emerging IBV strains are as

follows: 1) genetic variation of the IBV as a result of mutations, insertions and deletions, especially in the S1 genes; 2) recombination between local IBV strains circulating in the poultry flocks; 3) recombination between local strains and vaccine strains used in the field; and 4) interaction of environmental and social factors. Therefore, future multidisciplinary approaches require further useful information, focusing on the ongoing genotype evolution, monitoring ACoV circulation in avian species, and providing risk analyses of small-scale native poultry production. This information could be variously obtained by means of virology, bioinformatics and epidemiology of ACoV-associated diseases.

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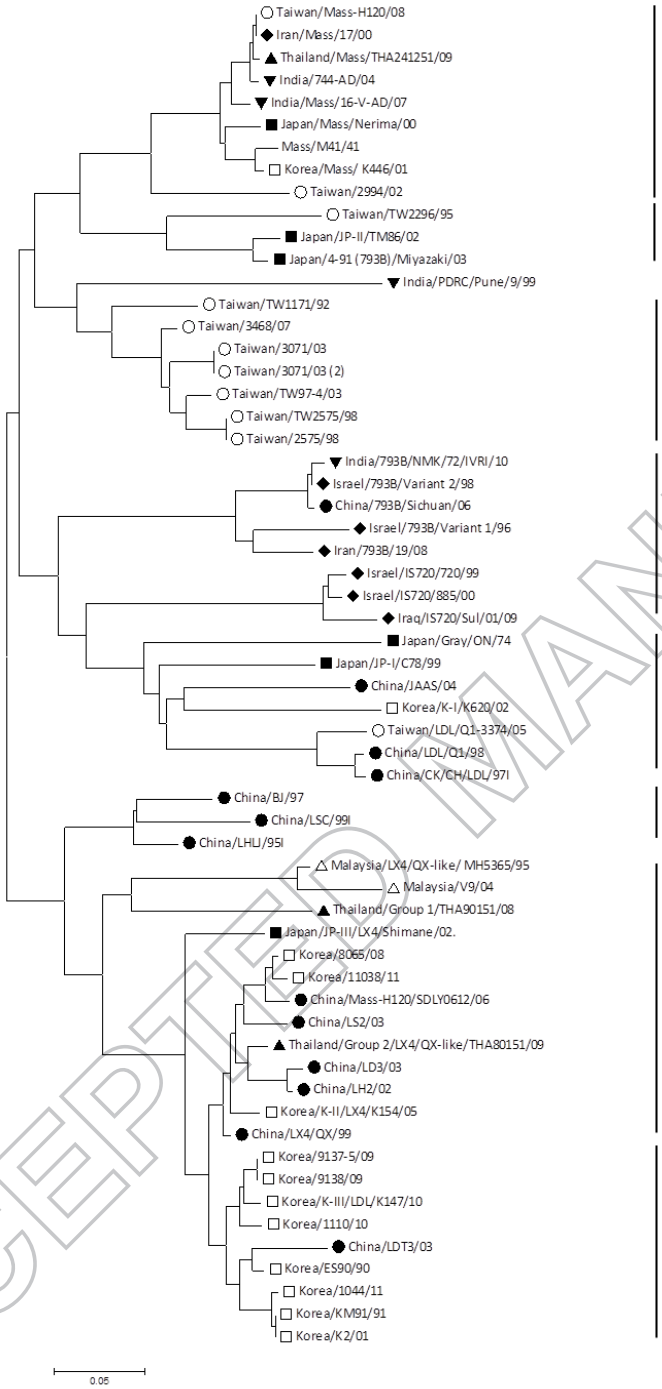

Figure 1. Phylogenetic tree of amino acid sequence of the S1 protein showing diversity of the Asian IBV isolates. The tree was constructed by the maximum-likelihood method with bootstrap values calculated from 1000 replications. The amino acid sequences were aligned with ClustalW in the Mega 6.06 software.

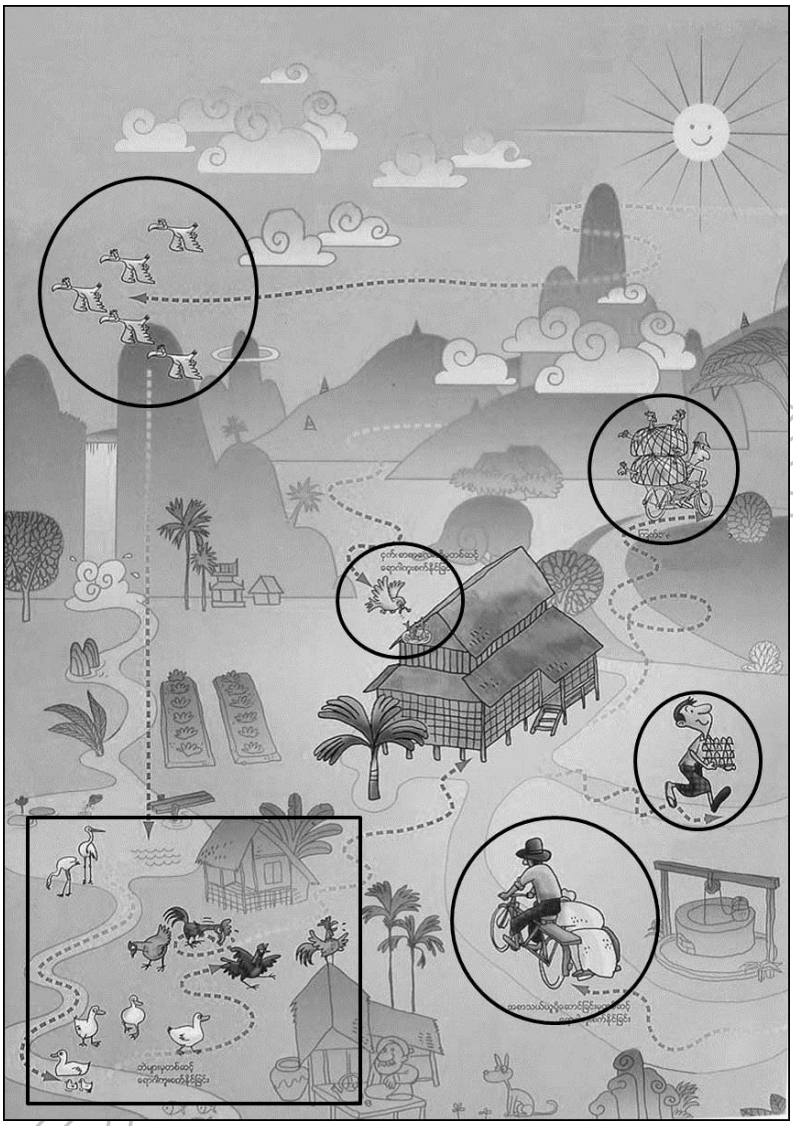

Figure 2. A multiple potential pathway for respiratory disease transmission within the environment, wild birds and backyard poultry of small-scale poultry operations in rural area [adapted from Tiensin (2011), with permission].

Table 1. Infectious bronchitis virus genotypes reported in Asia.

Country	Strain [1]	Type/Group	Tropism [2]	Breed [3]	Age	GenBank no.[4]
China	China/LX4/QX/99	LX4 (QXIBV): China-I	E	B	-	AF193423
	China/LDT3/03	LDT3: China-II	K	B	15 d	AY702975
	China/CK/CH/LHLJ/95I	LHLJ: China-III	K	L	-	DQ167141
	China/BJ/97	BJ: China-IV	K	-	-	AY319651
	China/LDL/Q1/98	LDL: China-V	R, E	L	25-70 d	AF286302
	China/Q1	N1/62: China-VI	-	-	-	AF286302
	China/CK/CH/LSC/95I	LSC: China-VII	K	L	-	DQ167146
	China/Mass/GX-YL1/05	Mass	K	B	51 d	DQ859273
	China/GX-NN7/06	4/91 (793B)	R	B	27 d	EF382349
	China/GX-LZ1/06	HN08	-	-	-	JQ764817
	China/ GX-NN1014/10	TW (Taiwan)	-	-	-	JX292004
	China/GX-G/88	JP type (Japan)	K	B	40 d	EF547363
	China/ GX-NN09032/09	New type	-	-	-	JX292013
Taiwan	Taiwan/3071/03	TW-I	K	B	50 d	EU822339
	Taiwan/2296/95	TW-II	K	B	14 d	AY606321
	Taiwan/2992/02	Variant (China-VII)	K	B	28 d	EU822340
	Taiwan/TW97-4	Variant	R, K	N	28 d	AY296742
	Taiwan/Mass/H120/08	Mass	-	-	-	EU822341
Japan	Japan/JP-I/C78/99	JP-I (vaccine)				AB120653
	Japan/JP/Shizuoka/71	JP-I	R	-	-	AB120631
	Japan/JP-II/TM86/02	JP-II (vaccine)				AB120655
	Japan/JP/Yamanashi/93	JP-II	K	-	-	AB120638
	Japan/JP-III/LX4/Shimane/02	JP-III (LX4)	K	B, L	-	AB120651
	Japan/JP-IV/Ibaraki/168-1/09	JP-IV	-	-	-	-
	Japan/4-91/Miyazaki/03	4/91 (vaccine)	-	-	-	AB120654
	Japan/Gray/ON/74	Gray (vaccine)	-	-	-	AB120658
	Japan/Mass/Nerima/00	Mass (vaccine)	-	-	-	AB363962
	Japan/JP8127/93	Variant	R, RP	L	154 d	AY296744
Korea	Korea/KM91/91	KM91	K	B	-	FJ807946
	Korea/KI/K620/02	K-I	R	B	-	FJ807944
	Korea/8067/08	K-I	K	L	-	JQ920388
	Korea/8065/08	K-II (QX-like)	K, E	L	-	JQ920387
	Korea/11044/11	K-II (KM91-like)	R, K	R, K	-	JQ920402
	Korea/KIII/K147/10	K-III (LDL)	R, K	B	28 d	HM486961
	Korea/Mass/K446/01	Mass	R	B	21 d	AY257063
	Korea/1110/10	Mass	R	BB	-	JQ920397
	Korea/ES90/90	ES90	K	B	-	JQ920406
	Korea/9137-5/09	New Cluster 1	R	B	-	JQ920391
Thailand	Thailand/Group 1/THA90151/08	Group I	R	B	16-30 d	GQ503617
	Thailand/QX-like/THA80151/09	Group II (QX-like)	R	B	-	GQ503616
	Thailand/Mass/THA320352	Group III (Mass)	R	B	-	GQ885131
Malaysia	Malaysia/QX-like MH5365/95	LX4 (QX-like)	K	B	-	EU086600
	Malaysia/V9/04	Variant	R	L	-	FJ518779
India	India/793B/NMK/72/IVRI/10	4/91	R, K	B	7-14 d	HM748585
	India/PDRC/Pune/9/99	Variant	R, K	B	7-14 d	AY091551
	India/Mass/16-V-AD/07	Mass	-	-	-	HM179146
Iran	Iran/793B/19/08	4/91	-	B	-	HQ842714
	Iran/Mass/17/00	Mass	-	L	-	HQ842709
Iraq	Iraq/IS720/Sul/01/09	IS720	R, K	B	-	GQ281656
	Iraq/Iraq/LDL/11	LDL (China)	R, K	BB	25 wk	-
Jordan	Jordan/LDL/JOA2/11	LDL (China)	R, K, RP	L	22 wk	-
	Jordan/Mass	Mass	R	B, L, BB	Vary*	-
	Jordan/4-91	4/91	R	B, L, BB	Vary*	-
	Jordan/D274	D274	R	B, L, BB	Vary *	-
	Jordan/Ark	Ark	R	B, L, BB	Vary **	-
	Jordan/DE-072	DE-072	R	B, L, BB	Vary **	-
Saudi Arabia	Saudi/LDL/Saudi-2/11	LDL (China)	R	B	24 d	-
Israel	Israel/IS720/885/00	IS720	K	B	21-43 d	AY279533
	Israel/793B/Variant 1/96	4/91 Variant 1	K	B	-	AF093795
	Israel/Variant 2/98	Variant 2	K	B	-	AF093794
	Israel/IS720/720/99	IS720	R	B	-	AY091552

[1] country/isolated i.d./year of isolation
[2] R: repiratory, K: kidney, E: enteric, RP: reproductive
[3] B: broiler, L: layer, BB: broiler breeder, N: native
[4] References of IBV isolates can be accessed via to the accession number unless some of them are not available
- Data not available
* IBV typing by RT-PCR
** IBV typing by serology

Table 2. Avian coronaviruses isolated from other galliform birds, non-galliform birds and village/backyard chickens

Bird origin of the isolates	Age	Natural		Experimental		References
		Clinical signs	Lesions	Clinical signs	Lesions	
Guinea fowl : Galliformes 	5-10 days	High mortality, Low feed consumption	Enteritis	*In guinea fowl and chicken,* intranasally: Respiratory distress, Watery diarrhea	-[2]	Ito et. al. 1991.
Domestic peafowl : Galliformes (Pf/CK/LKQ3/03)[1] 	-	Healthy	-	*In 15-d White Leghorn:* No clinical sign observed	-	Liu et al. 2005.
Wild peafowl, (Mass-type like) 	Vary	Healthy	-	*In peafowl:* No clinical signs observed (Specific antibody detected P.I.)	*In peafowl:* No obvious lesions	Sun et al. 2007.
				In 7-d White Leghorn: Listlessness, Huddling, Dark combs, Ruffled feathers	*In white Leghorn:* Hemorrhagic lung and kidney	
Partridge : Galliformes (LX4 isolate) 	-	-	-	-	-	Ma et al., 2012.
Teal : Anseriformes (tl/CH/LDT3/03) 	-	Healthy	-	*In 15-d White Leghorn:* Listlessness, Huddling, Ruffled feathers, Shrunken combs	Swollen and pale kidney, Distended urethra	Liu et al. 2005.
Pigeon :Columbiformes (PCoV:PSH050513) 	-	Upper airway infection, Depression, Wheezing, Watery eyes, Tracheal rale	Swollen pancreas & severe congestion	*In 30-d pigeon, Intranasally & intramuscularly:* Resp. distress, Ruffled feathers, Depression, Excess mucous in trachea	*In 30-d pigeon:* Hemorrhagic & swollen pancreas, Pulmonary lesions	Qian et al. 2006.
				In 15-d White Leghorn, intranasally: Gasping, Nasal discharge, Depression, Lethargy Huddling	*In White Leghorn:* Swollen & hemorrhagic pancreas	
Village/backyard chicken : Galliformes; bantam rooster & fighting chicken (QX-like & indigenous strains) 	30 days to over one year	Subclinical, Depression, Respiratory distress, Kidney disease	Tracheal congestion, Swollen kidney, Enteritis	-	-	Promkuntod et al. 2014.

[1] Parentheses indicate the virus isolate(s)
[2] data not available