Transboundary and Emerging Diseases

Transboundary and Emerging Diseases

REVIEW ARTICLE

A Systematic Review of the Comparative Epidemiology of Avian and Human Influenza A H5N1 and H7N9 – Lessons and Unanswered Questions

C. Bui[1], A. Bethmont[1], A. A. Chughtai[1], L. Gardner[2], S. Sarkar[3], S. Hassan[1], H. Seale[1] and C. R. MacIntyre[1]

[1] School of Public Health and Community Medicine, University of New South Wales, Sydney, NSW, Australia
[2] School of Civil and Environmental Engineering, University of New South Wales, Sydney, NSW, Australia
[3] Section of Integrative Biology, University of Texas at Austin, Austin, TX, USA

Keywords:
avian influenza epidemiology; H5N1; H7N9; exposure; transmission; poultry

Correspondence:
C. Bui. School of Public Health and Community Medicine, University of New South Wales, Sydney, NSW 2052, Australia. Tel.: +61 (2) 9385 3811; Fax: +61 (2) 9313 6185; E-mail: chau.bui@unsw.edu.au

Received for publication September 6, 2014

doi:10.1111/tbed.12327

Summary

The aim of this work was to explore the comparative epidemiology of influenza viruses, H5N1 and H7N9, in both bird and human populations. Specifically, the article examines similarities and differences between the two viruses in their genetic characteristics, distribution patterns in human and bird populations and postulated mechanisms of global spread. In summary, H5N1 is pathogenic in birds, while H7N9 is not. Yet both have caused sporadic human cases, without evidence of sustained, human-to-human spread. The number of H7N9 human cases in the first year following its emergence far exceeded that of H5N1 over the same time frame. Despite the higher incidence of H7N9, the spatial distribution of H5N1 within a comparable time frame is considerably greater than that of H7N9, both within China and globally. The pattern of spread of H5N1 in humans and birds around the world is consistent with spread through wild bird migration and poultry trade activities. In contrast, human cases of H7N9 and isolations of H7N9 in birds and the environment have largely occurred in a number of contiguous provinces in south-eastern China. Although rates of contact with birds appear to be similar in H5N1 and H7N9 cases, there is a predominance of incidental contact reported for H7N9 as opposed to close, high-risk contact for H5N1. Despite the high number of human cases of H7N9 and the assumed transmission being from birds, the corresponding level of H7N9 virus in birds in surveillance studies has been low, particularly in poultry farms. H7N9 viruses are also diversifying at a much greater rate than H5N1 viruses. Analyses of certain H7N9 strains demonstrate similarities with engineered transmissible H5N1 viruses which make it more adaptable to the human respiratory tract. These differences in the human and bird epidemiology of H5N1 and H7N9 raise unanswered questions as to how H7N9 has spread, which should be investigated further.

Introduction

Avian influenza viruses (AIVs) are divided on the basis of their pathogenicity in chickens into highly pathogenic (HPAI) viruses and low pathogenic (LPAI) viruses (To et al., 2013). Most AIVs are LPAI and are asymptomatic in most bird hosts. However, some subtypes, including H5 and H7, undergo antigenic shift and drift, thereby developing into HPAI viruses which may cause high rates of mortality among their hosts (Munster et al., 2005; Duan et al., 2007). There are both HPAI and LPAI types of H5N1, with the majority of reported H5N1 being of the HPAI type, and

only a few sporadic reports of LPAI H5N1 in Korea, Japan and North America (Spackman et al., 2007; Kim et al., 2011). Unlike H5N1, the novel H7N9 is only a LPAI virus, and infections to date have been predominantly asymptomatic (Pantin-Jackwood et al., 2014). Despite these classifications, actual pathogenic potential varies according to the individual host, viral strain and environmental pressures. For instance, HPAI viruses can exist in geese and ducks asymptomatically (Kida et al., 1980; Chen et al., 2004; Hulse-Post et al., 2005; Sturm-Ramirez et al., 2005; Songserm et al., 2006b; Gaidet et al., 2008).

The ability for a virus to transmit from one species to another depends on many factors including viral mutation rate, level of exposure to infected avian species, host susceptibility, social or environmental conditions conducive for virus transmission and sometimes the availability of an intermediate host (most commonly pigs) which acts as a genetic mixing vessel between birds and humans (Chan et al., 2013; To et al., 2013). There are currently approximately 103 AIVs circulating among wild bird and domestic poultry populations, out 144 known AIVs (Lu et al., 2014). Of these, eight have been reported to transmit to humans (To et al., 2013), with only H5N1 and H7N9 having demonstrated high pathogenicity.

The most familiar zoonotic AIV, H5N1, first emerged in humans in 1997 in Hong Kong and then re-emerged in Mainland China in 2003. Of the 21 recorded AIV outbreaks in poultry prior to 2003, two were caused by H5N1 (in Great Britain 1959 and 1991) (Morris and Jackson, 2005). With the exception of H5N1, these outbreaks were largely contained through interventions such as culling and vaccination. Examples include outbreaks of H5N2 in Pennsylvania in 1983–1984 (Bean et al., 1985), H5N2 in Mexico in 1993 (Horimoto et al., 1995) and nine other HPAI outbreaks which occurred in Europe, North America and Australia (Alexander, 2007; Peiris et al., 2007). In contrast, the 1997 H5N1 virus was the first AIV to remain endemic in parts of Asia for over 16 years (Sims and Jeggo, 2014). Since its re-emergence in 2003, H5N1 has remained endemic in birds, with ongoing sporadic human cases. Spread of H5N1 among birds occurs through domestic poultry trading activities, and wild birds are thought to also play a role, due to their mobility across flyways which extend up to 2600 km (Takekawa et al., 2013). Spread of H5N1 to humans mostly occurs through close poultry contact; however, human-to-human transmission is suspected to have occurred in rare cases (Ungchusak et al., 2005; Yang et al., 2007b).

In 2013, a new zoonotic AIV, H7N9, emerged in humans in China, with a small number of cases reported in a few other countries. This article compares the viral and epidemiological characteristics of H5N1 and H7N9 in birds and humans, to understand the emergence of H7N9 in the context of what is known historically about H5N1.

Materials and Methods

We reviewed research investigating the genetic characteristics, epidemiology and mechanisms of global spread of H5N1 and H7N9 in birds and humans. A search was conducted through Google Scholar and OVID BIOSIS using the key terms 'avian influenza', 'H5N1' and 'H7N9'. Articles were limited to those in published in the English language and those that had been published by August 2014. Additional articles were identified by iteratively searching each article's cited reference sections.

The human and bird epidemiology of H5N1 and H7N9 was compared over the same time period of the first year following the occurrence of the first human case of each virus. For H5N1, we included both the year following its emergence (10 May 1997–9 May 1998) and re-emergence (25 November 2003–24 November 2004). For H7N9, we included the year of 19 February 2013–18 February 2014. We compiled data on the frequency of laboratory-confirmed human cases of H5N1 and H7N9 reported to the World Health Organization (WHO) by location and day, month and year of illness onset using the archives of the WHO Global Outbreak and Alert Response Network (World Health Organization, 2014b) and cumulative case numbers reported in monthly risk assessment summaries and data reports released by the World Health Organization (2014a,c).

We compiled data on the frequency of laboratory-confirmed outbreaks of H5N1 and H7N9 in bird species by date, bird type (i.e. domestic poultry or wild bird) and location using the Food and Agriculture Organization's (FAO) EMPRES-i Global Animal Disease Information System (Food and Agriculture Organisation of the United Nations, 2014), the World Animal Health Information Database Interface (World Organisation for Animal Health, 2014) and articles identified using the method outlined above. We compiled these data for human and bird cases into a database in Microsoft Excel® with information on each case's species (human, domestic poultry or wild bird), country, date of illness onset and, in the case of domestic poultry, if available the place of infection (live bird market (LBM) or poultry farm). If information was available, poultry farms were classified as either a commercial farm or a backyard farm. In this review, commercial farms were defined as those that produce birds as egg or meat market products or live products to LBMs (sector 1, 2 or 3 farms as defined by the FAO), and backyard farms were defined as those that hold birds for local consumption (sector 4 farms

as defined by the FAO). A few articles describe households which keep poultry; we classified such households as backyard farms.

Using these data, we created an epidemic curve showing the frequency of laboratory-confirmed human cases of H5N1 and H7N9 in the year following the initial case of each virus using Microsoft Excel® (see Fig. 1). For a small proportion of cases (2.2% of H7N9 cases and 27.9% of H5N1 cases), precise information on the date of illness onset was unavailable. For these cases, we estimated the date of illness onset using the middle date of a known date range for the particular case. Maps were also created to compare the spatial distribution of laboratory-confirmed cases of H5N1 and H7N9 in humans and birds in the year following the initial human case of each virus (see Fig. 2). The maps were created by exporting incidence data categorized by country and Chinese province into ArcGIS® software (ArcGIS®, 2014). Shapefiles used to produce background maps of the relevant countries and Chinese provinces were obtained from publically available sources created by the ArcGIS® community. Maps were visually enhanced using Adobe Photoshop CS5®.

Results

The key genetic and epidemiological characteristics of H5N1 and H7N9 are summarized in Table 1. A number of important differences are apparent. Regarding human cases, median ages, gender distributions, cumulative number of cases over comparable time periods and case fatality rates differ markedly between the two viruses. Regarding birds, detection rates are lower for H7N9, particularly in farms. Information on the type of farms that were tested was not available in most cases. Genetic analyses show H5N1 and H7N9 have similarly likely emerged through reassortment of AIVs isolated in both domestic and wild birds, although the rate of genetic evolution differs considerably.

Genetic characteristics of H5N1 and H7N9

New AIVs can arise from either point mutation, recombination of partial genes, or genetic reassortment of whole genes. Point mutations are responsible for most AIV evolution (Sims and Jeggo, 2014). The genesis of both H5N1 and

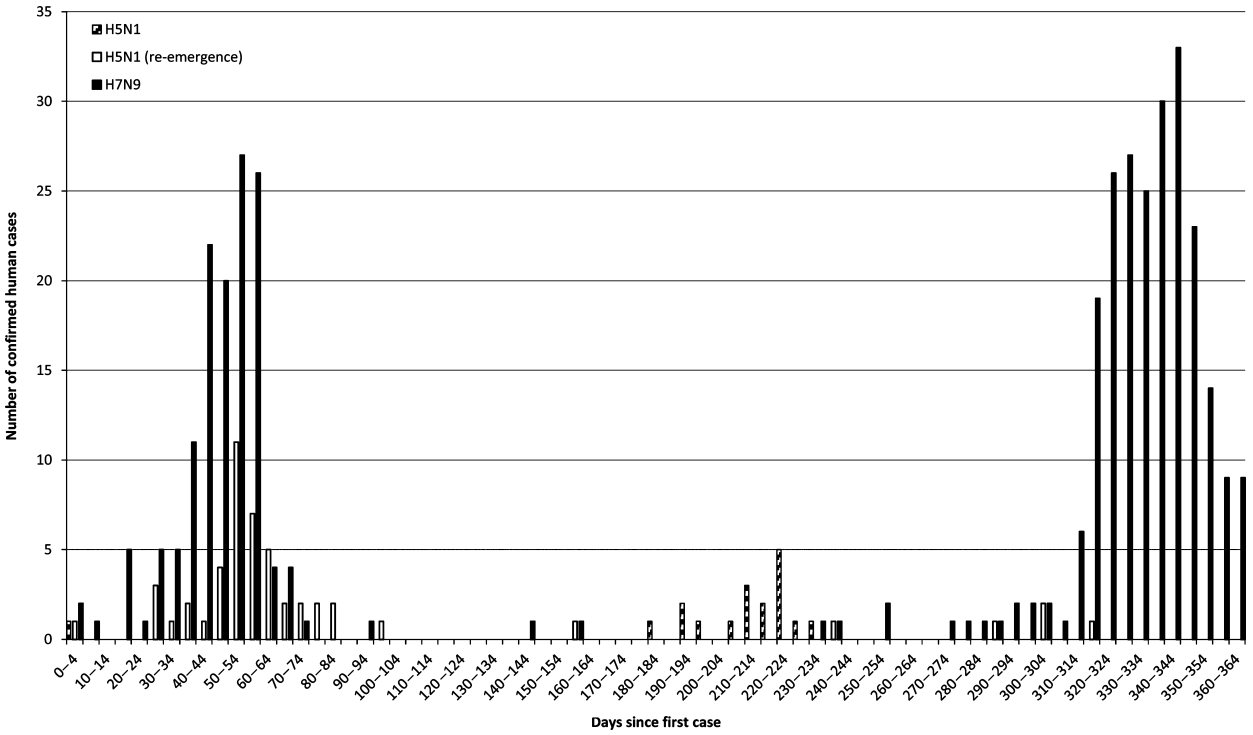

Fig. 1. Frequency of laboratory-confirmed human cases of H5N1 and H7N9 in the year following the initial case of each virus, by number of days since initial case. The initial emergence of H5N1 in 1997 is depicted (day 0 = 10 May 1997), as well as the re-emergence of H5N1 in 2003 (day 0 = 25 November 2003). For H7N9, day 0 = 19 February 2013.

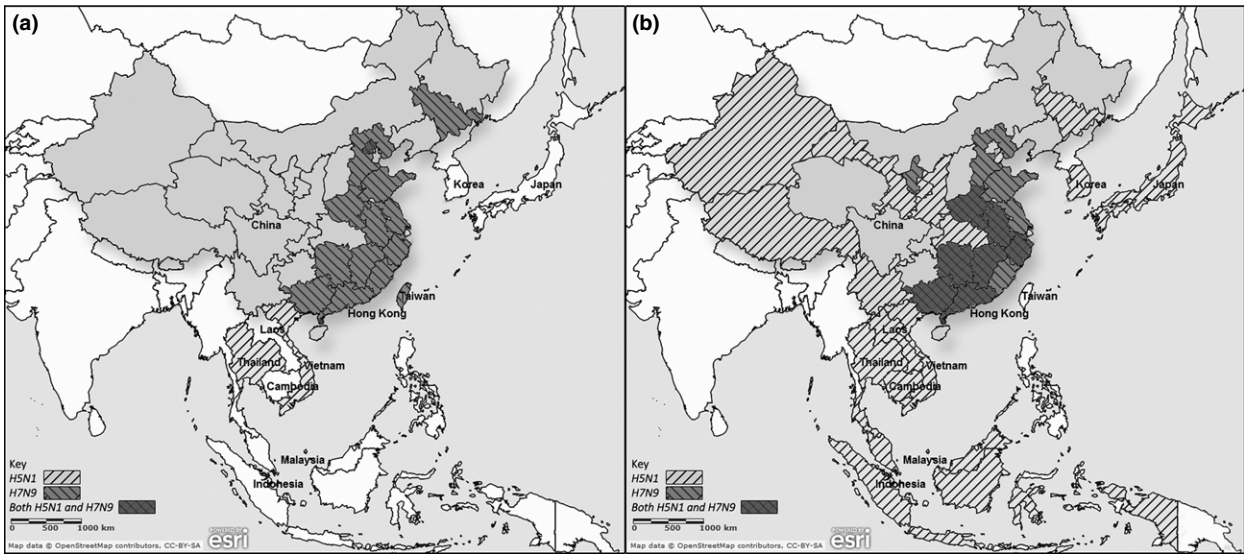

Fig. 2. Distribution of laboratory-confirmed cases of H5N1 and H7N9 in humans (panel a) and birds (panel b) in the year following the initial human case of each virus. For H5N1, both the years following its emergence (10 May 1997–9 May 1998) and re-emergence (25 November 2003–24 November 2004) are shown. For H7N9, 19 February 2013–18 February 2014 is shown.

H7N9 occurred through genetic reassortment (Sims and Jeggo, 2014). Analysis of individual HA, NA and internal genes of the first 1997 Hong Kong H5N1 virus (Xu et al., 1999) and selected 2013 H7N9 viruses (Gao et al., 2013b; Kageyama et al., 2013; Liu et al., 2013) showed similarities to various AIVs that have been previously isolated from both domestic and wild bird species, listed in Table 1. Notably, both viruses have internal genes which are derived from H9N2 viruses.

In the 18 years since the first isolation of H5N1 in 1996, there have only been sporadic reports of new genetic variants, occurring in poultry in Hong Kong in 2000 and 2001 (Guan et al., 2002; Webster et al., 2002), in two humans in 2003 (Sturm-Ramirez et al., 2004), and in wild birds in 2005 (Liu et al., 2005; Chen et al., 2006a). This list excludes the 1998 isolation in humans that was closely related to the original H5N1. From 1996 to 2001, there have been only six reported H5N1 reassorted genotypes in birds (A, B, C, D, E and X_0) (Guan et al., 2002) and, from 2002 to 2004, only eight new H5N1 genotypes (V, W, X_1, X_2, X_3, Y, Z and Z^+) (Macken et al., 2006; Le and Nguyen, 2014). Zhao et al. (2008) reported that there were 21 reassortants of H5N1 by 2007. H5N1 viruses belonging to genotype Z make up the majority of H5N1 viruses isolated, with 60 of the 62 H5N1 isolates from 2003 being of this genotype (Li et al., 2004). In contrast, H7N9 is evolving and diversifying at a faster rate. The genetic reassortment of H7N9 considerably exceeds that of H5N1, with 27 genotypes documented in <4 months (Cui et al., 2014). The 'G0' genotype series are dominant in human H7N9 isolates, and the G0 and G2 genotype series are dominant in poultry H7N9 isolates (Cui et al., 2014). Most H7N9 genotypes were detected around the Yangtze River delta area in China (Wang et al., 2014b).

Analyses of certain H7N9 strains demonstrate similarities with engineered transmissible H5N1 viruses (Herfst et al., 2012; Imai et al., 2012). Examples of the major mutations demonstrating human tropism have been identified by Gao et al. (2013b) and are outlined in Table 1. The T160A mutation decreases affinity to 'avian' α 2,3 sialic acid receptors, the Q226L substitution results in preferential binding to human tracheal epithelia, and the E627K mutation enables easier replication in mammalian cells.

Gao et al. (2013b) additionally noted amino acid deletions in the stalk region of NA that are similar to deletions seen previously in a naturally occurring H5N1 and are associated with a change to respiratory tract tropism in chickens from intestinal tract tropism (Sorrell et al., 2010) and enhanced viral replication (Baigent and McCauley, 2001). As intensive farming and densely housed small spaces are conducive to respiratory transmission, H5N1 viruses which have been circulating among housed gallinaceous (land-based) poultry have adapted to favour oropharyngeal excretion and airborne transmission (Lebarbenchon et al., 2010). For H7N9, an experimental study showed that the virus demonstrates tropism towards the upper respiratory tract particularly in poultry, with viral shedding occurring more at the oropharyngeal region in chickens and quails, compared to ducks and geese (Pantin-Jackwood et al., 2014). The novel H7N9 is therefore better adapted to transmission in land-based poultry rather than wild waterfowl, suggesting that the endemicity of AIVs circulating in

Table 1. Summary of key genetic and epidemiological characteristics of H5N1 and H7N9

	H5N1	H7N9
Genetic characteristics		
Mechanism of emergence	Genetic reassortment	Genetic reassortment
HA similarities	H5N1 isolated from a domestic geese (*Anser anser domesticus*) (Tang et al., 1998)	H7N3 isolated from a domestic Shaoxing pockmark ducks (*Anas platyrhyncha var.domestica*) in Zhejiang, China (Haibo et al., 2012)
NA similarities	H6N1 isolated from a green-winged teal duck (*Anas carolinensis*) found dead in a live bird market (Hoffmann et al., 2000)	H7N9 found during sampling of wild birds of unknown species in South Korea (Kim et al., 2012); H11N9 isolated from a mallard duck (*Anas platyrhynchos*) in Czech Republic in 2010 (Nagy et al., 2014); H7N9 isolated from a common teal (*Anas crecca*), in Spain in 2008 (Busquets et al., 2010)
Internal gene similarities	H9N2 found in a quail (unknown if specifically a Japanese quail, *Coturnix japonica*) (Guan et al., 1999)	H9N2 virus isolated from a brambling (*Fringilla montifringilla*) in Beijing (Xu et al., 2013); multiple H9N2 viruses from domestic chickens (*Gallus domesticus*) isolated from a flock in Shanghai in 2012 and Jiangsu in 2011 (Kageyama et al., 2013)
Number of genetic reassortants found	21 (over 6 years from 1996 to 2003) (Zhao et al., 2008)	27 (over 4 months from March 2013 to May 2013) (Cui et al., 2014)
H7N9 mutations similar to engineered transmissible H5N1 viruses	n/a	T160A mutation at the 150-loop, substitution Q226L at the 210-loop, E627K mutation in the PB2 gene (Gao et al., 2013b)
Avian epidemiology		
Spatial distribution	Asia, Europe, America, Africa (Food and Agriculture Organisation of the United Nations, 2014)	China, Hong-Kong (Food and Agriculture Organisation of the United Nations, 2014)
Virus detection rates % (positive samples/total samples)[a]		
In poultry farms	0.1 (23/22024) commercial farms, 10.5 (151/1435) backyard farms (El-Zoghby et al., 2013)	0 (0/690) (Shi et al., 2013), 24 (20/84) (Fan et al., 2014), 0 (0/37) (Wang et al., 2014a)[b]
In live bird markets	11.4 (108/944) (El-Zoghby et al., 2013); 18 (90/502) (Horm et al., 2013); 0.01 (2/189) (Nguyen et al., 2005); ranges from 0 to 0.06 (0/445–33/533) in waterfowl and 0 to 0.02 (0/1891–323/14 691 in terrestrial species (Li et al., 2004)	0.07 (20/280) (Shi et al., 2013); 4–22.2 (Han et al., 2014), 66 (41/62) (Wang et al., 2014a)
In wild birds	<0.01 (3/10 761) (Gilbert et al., 2012); <0.01 (24/2414) (Happold et al., 2008); 0.02 (14/728) (Lee et al., 2011); 0 (0/5460) (Wee et al., 2006)	<0.01 (1/2198) (Zhao et al., 2014)[c]
Incubation period (minimum number of days from inoculation to shedding)	1 (Spekreijse et al., 2011)	2 (Pantin-Jackwood et al., 2014) (however, shedding was not measured at day 1 post-inoculation)
Estimated R0	2.26 (95% CI, 2.01–2.55) to 2.64 (95% CI, 2.02–3.47) (Tiensin et al., 2007)	Not yet quantifiable (Pinsent et al., 2014)
Human epidemiology		
Emergence	Emerged in February 1997 in Hong Kong, re-emerged in 2003 in Beijing, China (World Health Organization, 2014a)	Emerged in March 2013 in Shanghai, China (World Health Organization, 2014a)
Spatial distribution	Reported from 17 countries, predominantly Indonesia, Egypt, Vietnam, Cambodia and China (World Health Organization, 2014a)	Reported from 4 countries, predominantly China, cases reported by other countries were likely infected in China (World Health Organization, 2014a).
Cumulative number of cases (as of 31 July 2014)	683	450
Median age	18–26 years(Sedyaningsih et al., 2007; Liem et al., 2009; Cowling et al., 2013)	Approximately 62 years (Cowling et al., 2013)
Gender differences	Gender differences vary between countries (Abdel-Ghafar et al., 2008), no gender difference in China (Cowling et al., 2013)	67% of cases in China are male. More males in urban areas and no gender difference in rural areas (Cowling et al., 2013)

(continued)

Table 1. (continued)

	H5N1	H7N9
Case fatality rate	60%, higher in younger age groups (Abdel-Ghafar et al., 2008)	22%, higher in older age groups (Skowronski et al., 2013)
Incubation period (days)	Median: 4 (range 2–8) (Beigel et al., 2005); median: 5 (range 2–9.5) (Huai et al., 2008); mean: 3.3 (Cowling et al., 2013); mean: 5 (Oner et al., 2006)	Median: 6 (range 1–10) (Li et al., 2014), mean: 3.1 (Cowling et al., 2013), mean: 3.3 (Yu et al., 2014a)
Estimated R0	1.14 (95% CI, 0.61–2.14) (Yang et al., 2007a), 0.06 (95% CI, 0.01–0.2) (Ferguson et al., 2004)	0.10 (Chowell et al., 2013), 0.47 (Tang et al., 1998)
Proportion of cases exposed to poultry	58–84% (Chotpitayasunondh et al., 2005) (Rabinowitz et al., 2012)	56–75% (Cowling et al., 2013; Gao et al., 2013a; Li et al., 2014)

[a]Sampling techniques differ considerably between studies.
[b]A pigeon farm (World Organisation for Animal Health, 2014), one commercial farm (World Organisation for Animal Health, 2014) and a backyard farm also reported positive H7N9 (Han et al., 2013).
[c]Additional sources also report H7N9 from one wild pigeon (World Organisation for Animal Health, 2014) and four wild waterfowl (Ling et al., 2014).

poultry may now play a dominant role in the genesis of new viruses, surpassing that of wild waterfowl.

Distribution of H5N1 and H7N9

In 1997, outbreaks of HPAI H5N1 were reported in three commercial chicken farms in Hong Kong (Shortridge et al., 1998). In the same year, 18 human cases of H5N1 were reported in Hong Kong. An H5N1 virus isolated from a human case in Hong Kong showed similarities to an H5N1 virus previously isolated from a sick goose in Guangdong Province, China, in 1996 (Xu et al., 1999). From 1997 to 2003, limited bird outbreaks were detected in Hong Kong and China (Cauthen et al., 2000; Guan et al., 2002; Chen et al., 2004; Ellis et al., 2004; Li et al., 2004) but no human cases. In February 2003, the virus re-emerged among humans in China, and from 2003 to 2005, poultry outbreaks were detected in multiple countries in Asia (World Health Organization, 2011). Human cases occurred sporadically in these countries, predominantly Thailand, Vietnam, Cambodia, Indonesia and China, with cases typically coinciding with or following poultry outbreaks (World Health Organization, 2011).

In April 2005, the first mass outbreak of HPAI H5N1 in wild birds was reported in Qinghai Lake, China – a significant stopover site within the Central Asian Flyway (Chen et al., 2006a). In July 2005, the same H5N1 virus isolated in Qinghai was reported in dead migratory birds in Russia, the first country to report H5N1 outside Asia (World Health Organization, 2011). Thereafter, H5N1 began to be reported in poultry and wild birds in Europe, Africa and the Middle East, as well as continuing in Asia (World Health Organization, 2011). Similarly, human cases began to be reported in Africa and the Middle East, predominantly in Egypt, as well as continuing to be reported in Asia (World Health Organization, 2011).

H7N9 was first reported among humans in Shanghai, China, in February 2013, and first detected in poultry and wild birds in Mainland China in April 2013. To date, the virus has been detected in domestic poultry in 13 provinces in eastern Mainland China as well as once in Hong Kong (Food and Agriculture Organisation of the United Nations, 2014), and it has been reported in humans in 13 contiguous provinces in eastern Mainland China, as well as non-contiguous Jilin in northern Mainland China (World Health Organization, 2014c). Less than 5% of human cases have been reported in countries other than China, including Hong Kong, Taiwan and Malaysia, and these cases travelled to affected areas of China prior to illness onset (World Health Organization, 2014c). From 2004 to 2005, H5N1 human cases were reported in a far larger number of Chinese municipalities, provinces and autonomous regions (26/31 regions) than H7N9 human cases to date (15/31 regions) (Fang et al., 2008; Wan et al., 2011).

Table S1 and S2 in the Supporting Information show the number of human cases and domestic bird outbreaks for H5N1 (Table S1) and H7N9 (Table S2) over time for each country which has reported H5N1 in humans. For H5N1, countries reporting high numbers of human cases generally report substantially higher numbers of H5N1 outbreaks in poultry. However, the reverse is true for H7N9, where the number of human cases tends to be substantially larger than the number of poultry outbreaks.

H5N1 and H7N9 in bird populations

Reported signs of H5N1 infection in chickens include cyanosis of the comb and wattles, haemorrhaging on the shanks, coughing, conjunctivitis, nasal and ocular discharge, depression and inappetence (Dubey et al., 2012; El-Zoghby et al., 2013). On a flock level, reports have ranged from mild decreases in egg production to acute

mortalities of up to 50% within a 24-h period (Dubey et al., 2012; El-Zoghby et al., 2013). Waterfowl species, particularly ducks, have been reported to be infected with H5N1 asymptomatically (Chen et al., 2004; Hulse-Post et al., 2005; Sturm-Ramirez et al., 2005; Songserm et al., 2006b). In outbreaks in Korea, domesticated ducks infected with H5N1 resulted in no mortality, while the same virus strain was reported to have caused acute, severe disease and mortality in chickens (Lee et al., 2008). In contrast, H5N1 has also been reported to cause severe disease and mass mortality in wild and resident waterfowl species, demonstrating the wide spectrum of clinical signs seen in these species (Ellis et al., 2004; Chen et al., 2005).

There are no reported clinical signs in H7N9-infected birds in experimental studies of chickens, pigeons, Japanese quails, mallard ducks, Pekin ducks, Muscovy ducks and Embden geese (Pantin-Jackwood et al., 2014) or in surveillance reports, with the exception of a recent report in which poultry co-infected with H9N2 showed clinical signs and mortality (Fan et al., 2014). Genetic analysis of the HA cleavage site also shows lack of multibasic amino acids at the HA cleavage sites, indicative of high pathogenicity (Senne et al., 1996; Subbarao et al., 2003; Shi et al., 2013).

The primary reservoirs of AIVs are considered to be wild bird species with an affinity to freshwater bodies and coastal regions, mainly from the Anseriformes and Charadriiformes families (Stallknecht and Shane, 1988; Alexander, 2007). These species are thought to introduce AIVs (mainly LPAI types), either directly or indirectly (e.g. through shared water sources or via contaminated feed), into domestic poultry populations (Alexander, 2007). Secondary spread by human activities is thought to be the main mechanism by which AIVs spread among poultry networks (Alexander, 2007). Within poultry networks, LBMs in particular can play an important role in the maintenance and spread of AIV as these places typically hold many susceptible birds together in close proximity. The level of AIV circulation within a LBM, however, depends largely on its size and level of biosecurity, factors which are often not conveyed in LBM surveillance reports.

Table 1 provides detection rates of H5N1 and H7N9 in birds from a range of studies, with targeted surveillance studies showing much higher detection rates than national surveillance data (Fan et al., 2014; Han et al., 2014; Wang et al., 2014a). Detection rates of H5N1 in different bird populations (wild birds, domestic poultry) and premises (poultry farms, LBMs) vary according to country, year and sampling methods used. However, surveillance studies generally show low detection rates among wild bird populations. Among domestic poultry, surveillance studies in Egypt and China indicate that H5N1 is more prevalent in LBMs and backyard farms as opposed to commercial poultry farms (Jiang et al., 2010; El-Zoghby et al., 2013). In LBMs, surveillance has indicated H5N1 is more prevalent where waterfowl species are the predominant species, and in farms, H5N1 is more prevalent where chickens and waterfowl species are kept together (Abdelwhab et al., 2010; El-Zoghby et al., 2013). In a surveillance report in Nigeria, H5N1 was reported to have been largely found in backyard, small-scale and free-range farms; however, the proportion of H5N1 found across the different settings was not reported – it is not known whether the study included commercial farms as part of the surveillance (Joannis et al., 2008). It is hence important to note that surveillance studies may be inadvertently targeting well-managed (sector 1) farms, or backyard (sector 4) farms, and may exclude farms from sectors 2 or 3 (commercial farms which sell to LBMs).

In contrast to H5N1, H7N9 has largely been isolated only from LBMs, and at low rates of 0.07% (20/280) (Shi et al., 2013). However, targeted surveillance shows higher rates from 4% to 66% (Han et al., 2014; Wang et al., 2014a). To date, the only isolations in poultry farms were in a pigeon farm, two commercial farms, and one backyard farm (Han et al., 2013; Fan et al., 2014; World Organisation for Animal Health, 2014). Table 2 provides a summary of the first 12 months of emergence for both viruses, and also the re-emergence of H5N1. In the time period between 1997 and 1998, H5N1 was only reported in Hong Kong, in only at least three markets and three commercial chicken farms. However, from 2003 to 2004, the available data suggest that H5N1 was prevalent in multiple, mainly commercial, farms and LBMs and had also spread across wider area of nine countries. Over a comparable time period, H7N9 was detected in just one pigeon farm and multiple LBMs.

In contrast to outbreaks of H5N1, where hundreds to thousands of wild or domestic birds have been reported to be affected per outbreak (Sims et al., 2003; Chen et al., 2005; Kwon et al., 2005), detection of H7N9 in wild or domestic birds is low. Detection rates in poultry range from 0.16% to 0.02% (Shi et al., 2013; Ling et al., 2014) or 0% to 0.61% according to the national animal H7N9-monitoring reports of China's Ministry of Agriculture (see Table S3 in Supporting Information). To date, the only isolations of H7N9 in wild bird populations are from four wild waterfowl (unknown species, unspecified sampling methods) (Ling et al., 2014), one tree sparrow (unknown species name) (Zhao et al., 2014) and one wild pigeon (possibly *Streptopelia* spp.) (World Organisation for Animal Health, 2014).

H5N1 and H7N9 in human populations

The human epidemiology of H5N1 and H7N9 differs significantly. The incidence per year of H7N9 is far greater than that of H5N1. There were almost 10 times more cases of H7N9 compared to H5N1 in the first year after

Table 2. Number of laboratory-confirmed human cases and avian outbreaks due to H5N1 and H7N9 and number of affected countries in 12 months following emergence of the virus in humans

			Number of avian outbreaks[a]			Number of countries in which the virus was detected	
Virus	Time period	Number of human cases	Farms	Live bird markets	Wild birds	Birds	Humans
H5N1	10 May 1997 to 9 May 1998	18	3[b]	>3c	0	1	1
	25 November 2003 to 24 November 2004	50	21[d]	?[d,e]	?[e]	9	3
H7N9	19 February 2013 to 18 February 2014	373	1	33	3	2	3[f]

[a]FAO EMPRESi does not break outbreak data into farms and LBM.
[b]Outbreaks occurred Mar–May 1997 (Shortridge et al., 1998; Sims et al., 2003).
[c]More than three market stalls were infected (Sims et al., 2003).
[d]Data only available for Korea and Japan (Mase et al., 2005; Wee et al., 2006).
[e]An unspecified number of LBMs in China and Hong Kong were found to be H5N1 positive during surveillance from 2000 to 2004, and from 2002 to 2004, H5N1 was isolated sporadically from various wild birds in Hong Kong (Li et al., 2004).
[f]H7N9 detected in Mainland China, Hong Kong and Taiwan.

emergence. There have been 450 laboratory-confirmed cases of H7N9 reported since its emergence in 2013, a period of <18 months, compared to only 50 human cases of H5N1 the first year of re-emergence. A total of 683 laboratory-confirmed cases reported of H5N1 have been reported over 18 years since 1997. Figure 1 illustrates this difference in magnitude by showing the epidemic curve of laboratory-confirmed cases of H5N1 and H7N9 in the 12 months after the initial case of each virus. In this period, 18, 50 and 373 cases were reported for H5N1 (initial emergence in 1997), H5N1 (re-emergence in 2003) and H7N9, respectively. Despite the greater incidence of H7N9, the spatial distribution of H5N1 within a comparable time frame is considerably greater than that of H7N9, both within China and globally, as shown in Fig. 2.

The viruses also show a very different age-specific epidemiology, with the median age of H5N1 cases ranging from 18 to 26 years, depending on the country of report (Sedyaningsih et al., 2007; Liem et al., 2009; Cowling et al., 2013), and the median age of H7N9 cases approximately 62 years (Cowling et al., 2013). In terms of gender differences in case frequency, H7N9 shows a clear male predominance (67% of cases) (Cowling et al., 2013). For H5N1, gender differences are not large and appear to be dependent on the country of report (Abdel-Ghafar et al., 2008). Interestingly, no gender differences in human H5N1 cases are evident in China, where they are evident for H7N9 (Cowling et al., 2013). The case fatality rate (CFR) is also substantially higher for H5N1 (60%) (Abdel-Ghafar et al., 2008), than for H7N9 (22%) (Skowronski et al., 2013).

There are some similarities between the two viruses. For both viruses, the majority of cases report some contact with poultry prior to illness onset: 58% to 84% for H5N1 (Chotpitayasunondh et al., 2005; Rabinowitz et al., 2012) and 56% to 75% for H7N9 (Cowling et al., 2013; Gao et al., 2013a; Li et al., 2014). However, the level of close, high-risk contact appears to be much higher for H5N1, with a large proportion of assumed contact among H7N9 cases being incidental (Cowling et al., 2013). Cowling et al. (2013) reported that of those cases reporting poultry exposure, contact was defined in the majority of H7N9 cases as visiting live poultry markets (43 of 84), whereas the degree of contact for the majority of H5N1 cases was exposure to sick or dead poultry (16 of 41) or backyard poultry (21 of 41).

Non-sustained human-to-human transmission is suspected to have also occurred for both viruses at similar rates (Hien et al., 2004; Olsen et al., 2005; Ungchusak et al., 2005; Yang et al., 2007a; To et al., 2013; Li et al., 2014; Qiu et al., 2014). The viruses also appear to cause similar types of influenza-like illness, along with diarrhoea, vomiting, and abdominal pain and bleeding in rare cases (Beigel et al., 2005; Kandeel et al., 2010). Complications include acute respiratory distress syndrome, septic shock, pneumonia and multiorgan failure (Li et al., 2014).

Mechanisms of spread of H5N1 and H7N9

The spread of AIVs globally is thought to be the result of transmission through wild bird migratory flyways and poultry trade routes. The seasonal migration of certain waterfowl and shorebird species, such as the ruddy shelduck (*Tadorna ferruginea*) and bar-headed geese (*Anser indicus*), is thought to facilitate the maintenance and spread of AIVs because these species travel long distances across continents and also congregate in massive numbers at stopover sites in communal water bodies, providing conducive conditions for viral transmission (Alexander, 2007).

Introduction of H5N1 into poultry populations can occur through wild bird migration (Ducatez et al., 2006; Liang et al., 2010; Prosser et al., 2011) or poultry movement and trade (Chen et al., 2006b; Kilpatrick et al., 2006; Farnsworth and Ward, 2009). Gilbert et al. (2006) were the first to find close spatial and temporal relations between H5N1 bird outbreak locations and the autumn waterfowl migration route from central Asia to the Caspian Sea and Black Sea basins. The HPAI H5N1 strains found near the Black Sea were the same as those from the 2005 Qinghai Lake outbreak in China (L'Vov D et al., 2006). A global, spatial-temporal analysis of H5N1 outbreaks in birds from 2004 to 2006 has shown that routes of spread coincide spatially with major migration flyways (East Asia flyway, East Africa–West Asia flyway, Black Sea–Mediterranean Sea flyway and Central Asia flyway) and that timing of outbreaks coincides temporally with respective seasonality of bird migrations (Liang et al., 2010). Kilpatrick et al. (2006) collated data on phylogenetic relationships, global bird trade and wild bird migration patterns to predict how H5N1 was introduced into a particular country. The authors found that introductions of H5N1 into European countries were largely due to wild bird migrations, whereas for Asian countries, introductions were mainly or equally due to poultry trading activities. In Bangladesh and Indonesia, countries where H5N1 is endemic in poultry, H5N1 poultry outbreaks were found to be strongly associated with factors such as human population density and the number of commercial poultry per region (Loth et al., 2010; Farnsworth et al., 2011), with Farnsworth et al. (2011) noting that movement of virus between commercial and backyard poultry likely contributed to maintenance and spread of H5N1 in Indonesia. In southern Cambodia, poultry trade consists predominantly of rural backyard farms (sector 4), with poultry movement mainly occurring uni-directionally towards only a few markets in urban regions (Van Kerkhove et al., 2009). Studies in southern China, Cambodia and Vietnam show H5N1 introduction to markets is also largely dependent on the behaviours of live poultry traders (Martin et al., 2011; Fournie et al., 2012). It is clear then that poultry trade routes and wild bird migration have both played a role in the spread of H5N1 globally.

Mechanisms of spread of H7N9 are less well understood. Only one study has explored the mechanism by which H7N9 is spreading within China. Ling et al. (2014) investigated 131 human patients of H7N9 up to May 2013 and suggested that H7N9 dissemination may occur in three ways: migratory birds; large farmers and wholesale distribution by logistics; and fragmented transportation. However, the limited detection of H7N9 in wild birds, LBMs and particularly poultry farms in bird surveillance studies, as discussed earlier, does not support a major role of wild bird migration and poultry trade in the spread of H7N9. Fang et al. (2013) and Gilbert et al. (2014) accurately modelled H7N9 spread using the density of LBMs as the key predictor variable. However, neither model factored in the low levels of H7N9 virus detected in LBMs. Notably, poultry trade has already played a role in introducing H7N9 to countries, as seen in Hong Kong in 2014, where a consignment of silky chickens was found to be H7N9 positive and was traced back to a commercial poultry farm in Guangdong Province, China (World Organisation for Animal Health, 2014).

Discussion

There are important differences in the patterns of spread of H5N1 and H7N9 which remain unexplained. The spread of H5N1 is clearly associated with wild bird migration pathways and poultry trade routes and shows a corresponding diverse pattern of spread, whereas for H7N9, the association with wild bird flyways or poultry trade routes is less clear, with H7N9 spread largely restricted to a number of geographically contiguous areas. H5N1 human cases have had a higher rate of exposure to sick and dead birds than those of H7N9, for which higher rates of incidental bird contact have been reported. Furthermore, the incidence and genetic diversity of H7N9 have been higher than that of H5N1, without corresponding high levels of the virus in birds and notably absent or low levels in poultry farms (farm types were not specified). Genetic analysis of H7N9 also demonstrates that the virus is better adapted to land-based poultry, yet it is not found widely in poultry. The finding of genetic sequences similar to engineered AIVs and conferring adaptation to humans is also puzzling. How H7N9 is spreading, therefore, remains uncertain.

Gilbert et al. (2014) and Lam et al. (2013) have explained the large diversity of H7N9 genotypes as evidence that H7N9 may have been circulating extensively among birds prior to its emergence in humans. However, there is no evidence of extensive circulation of H7N9 in poultry prior to human infection in February 2013. Cui et al. (2014) and Yu et al. (2014b) suggest that the H9N2 virus, another AIV which is widespread in poultry in China, contributed significantly to the diversification of the H7N9 viruses through continuous reassortment events. Wang et al. (2014b) propose that the diversification of H7N9 and the ability for H7N9 to transmit between species were brought about by a genetic tuning mechanism. The authors describe the process as involving progressive amino acid substitutions and H9N2 reassortment events, with constant inter-species transmission involving species such as quails and pigeons that have mammalian-like receptors. However, the internal genes of H5N1 also resemble internal genes of H9N2 viruses, and yet, H5N1 has not diversified at the rate of H7N9.

The presence of human adaptation markers in the genetic make-up of H7N9 viruses suggests H7N9 may have been circulating and adapting in humans before the first known cases emerged in February 2013. While there is no evidence of H7N9 previously circulating in humans, the occurrence of asymptomatic human infections suggests that such cases may have occurred and gone undetected. Prior to the emergence of H7N9 in 2013, N9 influenza subtypes were not known to infect humans, and hence, all humans should have been equally susceptible to disease. However, most children who have been infected with H7N9 have presented asymptomatically, suggesting that they may have had previous exposure to H7N9 or other similar viruses (Zeng et al., 2014). A retrospective serological study of 1544 people with occupational exposure to poultry and wild birds from eastern provinces of Mainland China indicated none had previous H7N9 infection (Bai et al., 2013). If the virus was not circulating prior to 2013 and yet appears to have adapted to humans, it is important to understand how this adaptation occurred and whether it could have occurred by natural random genetic mutation alone.

The gender distributions of H7N9 and H5N1 cases are very different. Biases in the age and sex distribution of human cases of H7N9 towards older males have been hypothesized to at least partially reflect differences in live poultry exposure, with some speculating that elderly males tend to visit LBMs more frequently than younger males and females (Cowling et al., 2013; Zhuang et al., 2013). Yet in Huzhou city, a female bias (with approximately 60% of cases female) was seen, consistent with anecdotal evidence of greater female exposure to LBMs in that city (Han et al., 2013). Biases in age and sex distribution of H5N1 are more difficult to attribute to live poultry exposure. Sex biases vary considerably between countries with some countries showing no biases, some male biases and other female biases (Abdel-Ghafar et al., 2008). Some of these biases have been attributed to local poultry practices, such as a female bias in cases in Azerbaijan (Gilsdorf et al., 2006). Importantly, examination of this issue has typically been based on anecdotal evidence of poultry practices. Systematic study is required before conclusions can be drawn. Interestingly, in urban areas of China, H7N9 cases are biased towards males, while H5N1 cases are not sex biased (Cowling et al., 2013). This suggests that factors other than poultry exposure play major roles in the transmission of the viruses to humans.

H7N9 infection in birds appears to have spread over contiguous provinces in south-eastern Mainland China, whereas the 2003–2004 outbreaks of H5N1 in birds occurred in over 10 Asian countries and affected a wider area of Mainland China. The concentration of H7N9 in south-eastern Mainland China may be explained by differences in poultry production in this region. Provinces in south-eastern Mainland China have greater small-holder poultry production systems, whereas north-eastern regions have greater commercial, intensive poultry production systems. The latter systems, while containing higher poultry density, generally have higher biosecurity standards. It is therefore consistent that H7N9 emerged and spread in provinces in south-eastern China. H5N1 was also predominantly isolated in humans and birds in the south-eastern provinces, consistent with poultry production practices.

To date, the low levels of H7N9 detection in poultry farms have not been investigated. These low levels and the limited spread of H7N9 outside Mainland China may be explained by reductions in poultry exports, as well as the strict poultry trade regulations and border control polices implemented in China following outbreaks of H5N1. Greater emerging disease preparedness by Chinese officials and the implementation of large-scale culling of birds and closure of live poultry trading activities immediately following H7N9 detection may have also contributed to the limited spread of H7N9 (Murhekar et al., 2013). Additionally, the asymptomatic presentation of H7N9 in birds creates difficulties in detecting the virus.

The role of wild bird migration in the spread of H7N9 has not yet been elucidated. There have been scarce isolations of the virus in migratory wild birds, and genetically, H7N9 is better adapted to spread in domestic poultry. Additionally, naturally occurring H7N9 has yet to be found outside of China, although it may be too early to look, considering H5N1 was first reported in Europe and Africa in 2005, nearly a decade after its first emergence in 1997. An outbreak of H7N9 reported in Jilin in 2014 is highly unusual in that it is only the second time that H7N9 has been reported in a commercial poultry farm and the first time that co-infection with two LPAI viruses (H7N9 and H9N2) caused clinical illness in birds (Fan et al., 2014).

A similar proportion of H5N1 and H7N9 human cases report any exposure to poultry prior to illness onset. However, it is important to note that the intensity of exposure associated with each virus has not been well delineated. Poultry exposure among H7N9 cases appears to largely be low level and incidental – such as walking through an LBM – while poultry exposure among H5N1 cases appears to largely be high level – such as slaughtering sick or dead birds (Cowling et al., 2013). Incidental exposure as a transmission mechanism is biologically tenuous, especially in the context of LBMs where H7N9 prevalence has been reported to be very low. This raises questions as to the exact role of poultry exposure in the transmission of H7N9 to humans and the need to better quantify levels of exposure to understand transmission mechanisms.

The reasons for a much higher incidence of H7N9 – 10 times the incidence of H5N1 in a similar time frame,

despite little evidence of H7N9 in birds and the environment – are yet to be elucidated. It is possible that the reported prevalence of H7N9 in birds underestimates true prevalence due to the difficulty of detecting asymptomatic infections. However, active surveillance of poultry has also failed to detect the virus in high proportions (Ministry of Agriculture, 2014).

It is possible that indirect contact may play a larger role in the transmission of H7N9 from birds to humans, especially considering that AIV transmission between wild birds occurs through indirect contact via contaminated water sources (Alexander, 2007). Two strains of H7N9 were tested for their infectivity after being exposed to different environments or chemical treatments; while most other orthomyxoviridae viruses are generally sensitive to acidic conditions, H7N9 was found to be tolerant to moderately acidic and alkali conditions (Zou et al., 2013). It is unknown what treatments were used in the LBM stalls where H7N9 virus had been found.

It is also possible that other animal hosts, such as terrestrial non-migratory wild birds or even non-avian species, play a role in the spread of H7N9 and transmission to humans. Experimental studies of a 2013 H7N9 strain among chickens showed the virus had poor infectivity and low transmission potential, as well as inefficient ability to transmit to ferrets (mammalian models for human influenzas) (Ku et al., 2014), demonstrating that there should be consideration of factors other than poultry exposure involved in human infection of H7N9. Analysis of genetic sequences of H7N9 from bird and humans hosts suggests potential for possible involvement of a bridge species which transmits the virus from poultry to humans (Pantin-Jackwood et al., 2014). Some researchers have suggested that other non-migratory wild bird species such as finches and pigeons may play a role in the spread of H7N9 among birds and humans (Jones et al., 2014).

The discovery of genetic similarities between human isolates of H7N9 and those isolated from bramblings (finch-like birds from the Passeriformes order) (Kageyama et al., 2013; Zhang et al., 2013) prompted Jones et al. (2014) to investigate the role of small, terrestrial birds in H7N9 transmission, species which have been generally considered to be unlikely carriers of AIV. Experimental inoculation and transmission studies showed finches and sparrows have biological potential to serve as intermediaries for transmission among poultry and humans. Jones et al. (2014) also noted that small terrestrial birds such as these are common household pets among elderly Chinese men.

It is also possible that other non-avian species may play a role. H5N1 has been isolated in dogs (Songserm et al., 2006a; Su et al., 2014), felines (Keawcharoen et al., 2004; Rimmelzwaan et al., 2006; Songserm et al., 2006a; Leschnik et al., 2007), pigs (Choi et al., 2005; Zhu et al., 2008; Nidom et al., 2010) and a stone marten (Klopfleisch et al., 2007). Evidence of H7N9 in feral dogs has been investigated, although findings did not show any H7N9 in these animals (Su et al., 2014). Shriner et al. (2012) found that various AIV subtypes had the ability to replicate efficiently in wild mice without adaptation. To date, the role of rodents in spreading H7N9 has not been investigated.

There are some limitations of this review. This review relies significantly on available bird surveillance reports from published articles and online databases. Many of these sources lack information on sampling methods used; hence, sampling biases may be unaccounted for. Many sources also provide unspecific information regarding species and location of events, resulting in a scarcity of useful data. The data obtained from the OIE and FAO EMPRES-i do not contain information on the type of farm affected or type of LBM affected. With regard to human cases, available information regarding exposure to poultry is often reported ambiguously. In future, surveillance reports for bird events should contain information on specific species and place of isolation (e.g. LBM, farm and type of farm), and for humans, specific information on the level of poultry exposure should be reported.

Another limitation is that there are unquantifiable differences in the diagnosis and reporting systems across the three comparable 12-month time periods following first human occurrence of each virus. For example, a review by Ferguson et al. (2004) stated that there was no actual systematic surveillance system in place for the detection of H5N1 in animals prior to 2004 – rather, the detection of virus largely occurred following large numbers of bird morbidities or mortalities. Countries reporting H5N1 during the virus's second emergence were largely those with under-developed veterinary services infrastructures (such as Vietnam, Thailand, Indonesia), and national surveillance relied predominantly on passive reporting systems. In contrast, following the emergence of H7N9, an up-scaled national surveillance system was established, with active testing of many animal and environmental samples (Ministry of Agriculture, 2014). The absence of rigorous sampling and reporting of bird surveillance activities during both 12-month time periods for H5N1 is important to note as this weakens comparability of the two viruses, in relation to virus detection rates in birds. Some under-reporting of human cases is suspected; however, it is likely to not be extensive considering the global importance and rarity of the disease.

To conclude, for H5N1, the mechanisms of spread clearly correspond to bird migration patterns and poultry trade routes, and close contact with infected poultry plays a clear role in human infection. For H7N9, however, mechanisms of spread and transmission are far less clear. The distribution of H7N9 is unusually concentrated in a

number of contiguous provinces in south-eastern Mainland China. Virological and epidemiological findings suggest there is insufficient evidence to support exposure to infected poultry as the sole risk factor for human H7N9 infection. The vastly higher rate of H7N9 human infection than H5N1 human infection in a comparable time frame is also inexplicable without a corresponding high level of H7N9 infection apparent in birds. Higher levels of infection in birds were, however, observed for H5N1 despite a much lower incidence of human cases. The high proportion of incidental bird exposure in histories of human H7N9 cases further highlights the need to quantify the level of poultry exposure as high or low level when investigating human cases. In summary, H7N9 has a very different epidemiological pattern to H5N1, in birds and humans, as well as inconsistencies in the observed pattern, with no clear explanation as to how or why this virus has affected humans at such a high rate. Further epidemiological and modelling studies may help understand the spread of this infection.

References

Abdel-Ghafar, A. N., T. Chotpitayasunondh, Z. Gao, F. G. Hayden, D. H. Nguyen, M. D. de Jong, A. Naghdaliyev, J. S. 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, 261–273.

Abdelwhab, E. M., A. A. Selim, A. Arafa, S. Galal, W. H. Kilany, M. K. Hassan, M. M. Aly, and M. H. Hafez, 2010: Circulation of avian influenza H5N1 in live bird markets in Egypt. *Avian Dis.* 54, 911–914.

Alexander, D. J., 2007: An overview of the epidemiology of avian influenza. *Vaccine* 25, 5637–5644.

ArcGIS®, 2014: ArcGIS® and ArcMap™ are the intellectual property of Esri and are used herein under license. Copyright © Esri. All rights reserved. For more information about Esri® software, Available at www.esri.com (accessed August 28, 2014).

Bai, T., J. Zhou, and Y. Shu, 2013: Serologic study for influenza A (H7N9) among high-risk groups in China. *N. Engl. J. Med.* 368, 2339–2340.

Baigent, S. J., and J. W. McCauley, 2001: Glycosylation of haemagglutinin and stalk-length of neuraminidase combine to regulate the growth of avian influenza viruses in tissue culture. *Virus Res.* 79, 177–185.

Bean, W. J., Y. Kawaoka, J. M. Wood, J. E. Pearson, and R. G. Webster, 1985: Characterization of virulent and avirulent A/chicken/Pennsylvania/83 influenza A viruses: potential role of defective interfering RNAs in nature. *J. Virol.* 54, 151–160.

Beigel, J. H., J. Farrar, A. M. Han, F. G. Hayden, R. Hyer, M. D. de Jong, S. Lochindarat, T. K. Nguyen, T. H. Nguyen, T. H. Tran, A. Nicoll, S. Touch, and K. Y. Yuen, 2005: Avian influenza A (H5N1) infection in humans. *N. Engl. J. Med.* 353, 1374–1385.

Busquets, N., A. Alba, S. Napp, A. Sanchez, E. Serrano, R. Rivas, J. I. Nunez, and N. Majo, 2010: Influenza A virus subtypes in wild birds in North-Eastern Spain (Catalonia). *Virus Res.* 149, 10–18.

Cauthen, A. N., D. E. Swayne, S. Schultz-Cherry, M. L. Perdue, and D. L. Suarez, 2000: Continued circulation in China of highly pathogenic avian influenza viruses encoding the hemagglutinin gene associated with the 1997 H5N1 outbreak in poultry and humans. *J. Virol.* 74, 6592–6599.

Chan, J. F., K. K. To, H. Tse, D. Y. Jin, and K. Y. Yuen, 2013: Interspecies transmission and emergence of novel viruses: lessons from bats and birds. *Trends Microbiol.* 21, 544–555.

Chen, H., G. Deng, Z. Li, G. Tian, Y. Li, P. Jiao, L. Zhang, Z. Liu, R. G. Webster, K. Yu, H. Chen, G. Deng, Z. Li, G. Tian, Y. Li, P. Jiao, L. Zhang, Z. Liu, R. G. Webster, and K. Yu, 2004: The evolution of H5N1 influenza viruses in Ducks in Southern China. *Proc. Natl Acad. Sci. USA* 101, 10452–10457.

Chen, H., G. J. Smith, S. Y. Zhang, K. Qin, J. Wang, K. S. Li, R. G. Webster, J. S. Peiris, and Y. Guan, 2005: Avian flu: H5N1 virus outbreak in migratory waterfowl. *Nature* 436, 191–192.

Chen, H., Y. Li, Z. Li, J. Shi, K. Shinya, G. Deng, A. Q. Qi, G. Tian, S. F. fan, H. Zhao, Y. Sun, and Y. Kawaoka, 2006a: Properties and dissemination of H5N1 viruses isolated during an influenza outbreak in migratory waterfowl in western China. *J. Virol.* 80, 5976–5983.

Chen, H., G. J. Smith, K. S. Li, J. Wang, X. H. Fan, J. M. Rayner, D. Vijaykrishna, J. X. Zhang, L. J. Zhang, C. T. Guo, C. L. Cheung, K. M. Xu, L. Duan, K. Huang, K. Qin, Y. H. Leung, W. L. Wu, H. R. Lu, Y. Chen, N. S. Xia, T. S. Naipospos, K. Y. Yuen, S. S. Hassan, S. Bahri, T. D. Nguyen, R. G. Webster, J. S. Peiris, and Y. Guan, 2006b: Establishment of multiple sublineages of H5N1 influenza virus in Asia: implications for pandemic control. *Proc. Natl Acad. Sci. USA* 103, 2845–2850.

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

Chotpitayasunondh, T., K. Ungchusak, W. Hanshaoworakul, S. Chunsuthiwat, P. Sawanpanyalert, R. Kijphati, S. Lochindarat, P. Srisan, P. Suwan, Y. Osotthanakorn, T. Anantasetagoon, S. Kanjanawasri, S. Tanupattarachai, J. Weerakul, R. Chaiwirattana, M. Maneerattanaporn, R. Poolsavatkitikool, K. Chokephaibulkit, A. Apisarnthanarak, and S. F. Dowell, 2005: Human Disease from Influenza A (H5N1), Thailand, 2004. *Emerg. Infect. Dis.* 11, 201–209.

Chowell, G., L. Simonsen, S. Towers, M. A. Miller, C. Viboud, G. Chowell, L. Simonsen, S. Towers, M. A. Miller, and C. Viboud, 2013: Transmission potential of influenza A/H7N9, February to May 2013, China. (Research article)(Report). *BMC Med.* 11, 214.

Cowling, B. J., L. Jin, E. H. Y. Lau, Q. Liao, P. Wu, H. Jiang, T. K. Tsang, J. Zheng, V. J. Fang, Z. Chang, M. Y. Ni, Q. Zhang, D. K. M. Ip, J. Yu, Y. Li, L. Wang, W. Tu, L. Meng, J. T. Wu, H. Luo, Q. Li, Y. Shu, Z. Li, Z. Feng, W. Yang, Y. Wang, G. M. Leung, and H. Yu, 2013: Comparative epidemiology of human infections with avian influenza A H7N9 and H5N1 viruses in China: a population-based study of laboratory-confirmed cases. *Lancet* 382, 129–137.

Cui, L., D. Liu, W. Shi, J. Pan, X. Qi, X. Li, X. Guo, M. Zhou, W. Li, J. Li, J. Haywood, H. Xiao, X. Yu, X. Pu, Y. Wu, H. Yu, K. Zhao, Y. Zhu, B. Wu, T. Jin, Z. Shi, F. Tang, F. Zhu, Q. Sun, L. Wu, R. Yang, J. Yan, F. Lei, B. Zhu, W. Liu, J. Ma, H. Wang, and G. F. Gao, 2014: Dynamic reassortments and genetic heterogeneity of the human-infecting influenza A (H7N9) virus. *Nat. Commun.* 5, 3142.

Duan, L., E. Foni, C. Chiapponi, W. L. Wu, H. Kai, R. G. Webster, K. F. Shortridge, J. S. M. Peiris, G. J. D. Smith, H. Chen, Y. Guan, L. Campitelli, X. H. Fan, Y. H. C. Leung, D. Vijaykrishna, J. X. Zhang, I. Donatelli, M. Delogu, and K. S. Li, 2007: Characterization of low-pathogenic H5 subtype influenza viruses from Eurasia: implications for the origin of highly pathogenic H5N1 viruses. *J. Virol.* 81, 7529–7539.

Dubey, S. C., N. Dahal, S. Nagarajan, C. Tosh, H. V. Murugkar, K. Rinzin, B. Sharma, R. Jain, M. Katare, S. Patil, R. Khandia, Z. Syed, S. Tripathi, P. Behera, M. Kumar, D. D. Kulkarni, and L. Krishna, 2012: Isolation and characterization of influenza A virus (subtype H5N1) that caused the first highly pathogenic avian influenza outbreak in chicken in Bhutan. *Vet. Microbiol.* 155, 100–105.

Ducatez, M. F., C. M. Olinger, A. A. Owoade, S. De Landtsheer, W. Ammerlaan, H. G. Niesters, A. D. Osterhaus, R. A. Fouchier, and C. P. Muller, 2006: Avian flu: multiple introductions of H5N1 in Nigeria. *Nature* 442, 37.

Ellis, T. M., R. Barry Bousfield, L. A. Bissett, K. C. Dyrting, G. S. M. Luk, S. T. Tsim, K. Sturm-ramirez, R. G. Webster, Y. Guan, J. S. M. Peiris, T. M. Ellis, R. Barry Bousfield, L. A. Bissett, K. C. Dyrting, G. S. M. Luk, S. T. Tsim, K. Sturm-ramirez, R. G. Webster, Y. Guan, and J. S. M. Peiris, 2004: Investigation of outbreaks of highly pathogenic H5N1 avian influenza in waterfowl and wild birds in Hong Kong in late 2002. *Avian Pathol.* 33, 492–505.

El-Zoghby, E. F., M. M. Aly, S. A. Nasef, M. K. Hassan, A. S. Arafa, A. A. Selim, S. G. Kholousy, W. H. Kilany, M. Safwat, E. M. Abdelwhab, and H. M. Hafez, 2013: Surveillance on A/H5N1 virus in domestic poultry and wild birds in Egypt. *Virol. J.* 10, 203.

Fan, M., B. Huang, A. Wang, L. Deng, D. Wu, X. Lu, Q. Zhao, S. Xu, F. Havers, Y. Wang, J. Wu, Y. Yin, B. Sun, J. Yao, and N. Xiang, 2014: Human Influenza A(H7N9) Virus Infection Associated with Poultry Farm, Northeastern China. *Emerg. Infect. Dis.* 20, 1902–1905.

Fang, L. Q., S. J. de Vlas, S. Liang, C. W. Looman, P. Gong, B. Xu, L. Yan, H. Yang, J. H. Richardus, and W. C. Cao, 2008: Environmental factors contributing to the spread of H5N1 avian influenza in mainland China. *PLoS One* 3, e2268.

Fang, L.-Q., X.-L. Li, K. Liu, Y.-J. Li, H.-W. Yao, S. Liang, Y. Yang, Z.-J. Feng, G. C. Gray, and W.-C. Cao, 2013: Mapping Spread and Risk of Avian Influenza A (H7N9) in China. *Sci. Rep.* 3, Article No. 2722.

Farnsworth, M. L., and M. P. Ward, 2009: Identifying spatio-temporal patterns of transboundary disease spread: examples using avian influenza H5N1 outbreaks. *Vet. Res.* 40, 20.

Farnsworth, M. L., S. Fitchett, M. M. Hidayat, C. Lockhart, C. Hamilton-West, E. Brum, S. Angus, B. Poermadjaja, and J. Pinto, 2011: Metapopulation dynamics and determinants of H5N1 highly pathogenic avian influenza outbreaks in Indonesian poultry. *Prev. Vet. Med.* 102, 206–217.

Ferguson, N. M., C. Fraser, C. A. Donnelly, A. C. Ghani, R. M. Anderson, N. M. Ferguson, C. Fraser, C. A. Donnelly, A. C. Ghani, and R. M. Anderson, 2004: Public Health Risk from the Avian H5N1 Influenza Epidemic. *Science* 304, 968–969.

Food and Agriculture Organisation of the United Nations, 2014: EMPRES-i Global Animal Disease Information System. 02/04/2014 edn.

Fournie, G., J. Guitian, S. Desvaux, P. Mangtani, S. Ly, V. C. Cong, S. San, H. Dung do, D. Holl, D. U. Pfeiffer, S. Vong, and A. C. Ghani, 2012: Identifying live bird markets with the potential to act as reservoirs of avian influenza A (H5N1) virus: a survey in northern Viet Nam and Cambodia. *PLoS One* 7, e37986.

Gaidet, N., P. Gil, I. Monne, A. Fusaro, I. Capua, S. Manu, P. Micheloni, U. Ottosson, J. H. Mshelbwala, J. Lubroth, J. Domenech, G. Cattoli, F. Monicat, S. Hammoumi, S. H. Newman, W. Hagemeijer, J. Y. Takekawa, J. Cappelle, T. Dodman, and T. Joannis, 2008: Evidence of infection by H5N2 highly pathogenic avian influenza viruses in healthy wild waterfowl. *PLoS Pathog.* 4, e1000127.

Gao, H. N., H. Z. Lu, B. Cao, B. Du, H. Shang, J. H. Gan, S. H. Lu, Y. D. Yang, Q. Fang, Y. Z. Shen, X. M. Xi, Q. Gu, X. M. Zhou, H. P. Qu, Z. Yan, F. M. Li, W. Zhao, Z. C. Gao, G. F. Wang, L. X. Ruan, W. H. Wang, J. Ye, H. F. Cao, X. W. Li, W. H. Zhang, X. C. Fang, J. He, W. F. Liang, J. Xie, M. Zeng, X. Z. Wu, J. Li, Q. Xia, Z. C. Jin, Q. Chen, C. Tang, Z. Y. Zhang, B. M. Hou, Z. X. Feng, J. F. Sheng, N. S. Zhong, and L. J. Li, 2013a: Clinical findings in 111 cases of influenza A (H7N9) virus infection. *N. Engl. J. Med.* 368, 2277–2285.

Gao, R., B. Cao, Y. Hu, Z. Feng, D. Wang, W. Hu, J. Chen, Z. Jie, H. Qiu, K. Xu, X. Xu, H. Lu, W. Zhu, Z. Gao, N. Xiang, Y. Shen, Z. He, Y. Gu, Z. Zhang, Y. Yang, X. Zhao, L. Zhou, X. Li, S. Zou, Y. Zhang, X. Li, L. Yang, J. Guo, J. Dong, Q. Li, L. Dong, Y. Zhu, T. Bai, S. Wang, P. Hao, W. Yang, Y. Zhang, J. Han, H. Yu, D. Li, G. F. Gao, G. Wu, Y. Wang, Z. Yuan, and Y. Shu, 2013b: Human infection with a novel avian-origin influenza A (H7N9) virus. *N. Engl. J. Med.* 368, 1888–1897.

Gilbert, M., X. Xiao, J. Domenech, J. Lubroth, V. Martin, and J. Slingenbergh, 2006: Anatidae migration in the western palearctic and spread of highly pathogenic avian influenza H5N1 virus. *Emerg. Infect. Dis.* 12, 1650–1656.

Gilbert, M., L. Jambal, W. B. Karesh, A. Fine, E. Shiilegdamba, P. Dulam, R. Sodnomdarjaa, K. Ganzorig, D. Batchuluun, N.

Tseveenmyadag, P. Bolortuya, C. J. Cardona, C. Y. Leung, J. S. Peiris, E. Spackman, D. E. Swayne, and D. O. Joly, 2012: Highly pathogenic avian influenza virus among wild birds in Mongolia. *PLoS One* 7, e44097.

Gilbert, M., N. Golding, H. Zhou, G. R. Wint, T. P. Robinson, A. J. Tatem, S. Lai, S. Zhou, H. Jiang, D. Guo, Z. Huang, J. P. Messina, X. Xiao, C. Linard, T. P. Van Boeckel, V. Martin, S. Bhatt, P. W. Gething, J. J. Farrar, S. I. Hay, and H. Yu, 2014: Predicting the risk of avian influenza A H7N9 infection in live-poultry markets across Asia. *Nat. Commun.* 5, 4116.

Gilsdorf, A., N. Boxall, V. Gasimov, I. Agayev, F. Mammadzade, P. Ursu, E. Gasimov, C. Brown, S. Mardel, D. Jankovic, G. Pimentel, I. A. Ayoub, E. M. Elassal, C. Salvi, D. Legros, C. Pessoa da Silva, A. Hay, R. Andraghetti, G. Rodier, and B. Ganter, 2006: Two clusters of human infection with influenza A/H5N1 virus in the Republic of Azerbaijan, February–March 2006. *Euro. Surveill.* 11, 122–126.

Guan, Y., K. F. Shortridge, S. Krauss, and R. G. Webster, 1999: Molecular characterization of H9N2 influenza viruses: were they the donors of the "internal" genes of H5N1 viruses in Hong Kong? *Proc. Natl Acad. Sci. USA* 96, 9363–9367.

Guan, Y., J. S. Peiris, A. S. Lipatov, T. M. Ellis, K. C. Dyrting, S. Krauss, L. J. Zhang, R. G. Webster, and K. F. Shortridge, 2002: Emergence of multiple genotypes of H5N1 avian influenza viruses in Hong Kong SAR. *Proc. Natl Acad. Sci. USA* 99, 8950–8955.

Hai-bo, W., L. Ru-feng, W. En-kang, Y. Jin-biao, W. Yi-ting, W. Qiao-gang, X. Li-hua, W. Nan-ping, and G. Chao-tan, 2012: Sequence and phylogenetic analysis of H7N3 avian influenza viruses isolated from poultry in China in 2011. *Arch. Virol.* 157, 2017–2021.

Han, J., M. Jin, P. Zhang, J. Liu, L. Wang, D. Wen, X. Wu, G. Liu, Y. Zou, Y. Lv, X. Dong, B. Shao, S. Gu, D. Zhou, Q. Leng, C. Zhang, and K. Lan, 2013: Epidemiological link between exposure to poultry and all influenza A(H7N9) confirmed cases in Huzhou city, China, March to May 2013. *Euro. Surveill.* 18, 32–37.

Han, J., J. Liu, L. Wang, P. Zhang, G. Liu, K. Lan, and C. Zhang, 2014: Persistent detection of avian influenza A/H7N9 virus among poultry in Huzhou City, China, in the summer of 2013. *Int. J. Infect. Dis.* 26, 72–75.

Happold, J. R., I. Brunhart, H. Schwermer, and K. D. Stark, 2008: Surveillance of H5 avian influenza virus in wild birds found dead. *Avian Dis.* 52, 100–105.

Herfst, S., D. J. Smith, G. F. Rimmelzwaan, A. D. M. E. Osterhaus, R. A. M. Fouchier, E. J. A. Schrauwen, M. Linster, S. Chutinimitkul, E. de Wit, V. J. Munster, E. M. Sorrell, T. M. Bestebroer, and D. F. Burke, 2012: Airborne transmission of influenza A/H5N1 virus between ferrets. *Science* 336, 1534–1541.

Hien, T. T., N. T. Liem, N. T. Dung, L. T. San, P. P. Mai, N. V. V. Chau, P. T. Suu, V. C. Dong, L. T. Q. Mai, N. T. Thi, D. B. Khoa, L. P. Phat, N. T. Truong, H. T. Long, C. V. Tung, L. T. Giang, N. D. Tho, L. H. Nga, N. T. K. Tien, L. H. San, L. V. Tuan, C. Dolecek, T. T. Thanh, M. de Jong, C. Schultsz, P. Cheng, W. Lim, P. Horby, and J. Farrar, 2004: Avian influenza A (H5N1) in 10 Patients in Vietnam. *N. Engl. J. Med.* 350, 1179–1188.

Hoffmann, E., J. Stech, I. Leneva, S. Krauss, C. Scholtissek, P. S. Chin, M. Peiris, K. F. Shortridge, and R. G. Webster, 2000: Characterization of the influenza A virus gene pool in avian species in southern China: was H6N1 a derivative or a precursor of H5N1? *J. Virol.* 74, 6309–6315.

Horimoto, T., E. Rivera, J. Pearson, D. Senne, S. Krauss, Y. Kawaoka, and R. G. Webster, 1995: Origin and molecular changes associated with emergence of a highly pathogenic H5N2 influenza virus in Mexico. *Virology* 213, 223–230.

Horm, S. V., S. Sorn, L. Allal, and P. Buchy, 2013: Influenza A (H5N1) virus surveillance at live poultry markets, Cambodia, 2011. *Emerg. Infect. Dis.* 19, 305–308.

Huai, Y., N. Xiang, L. Zhou, L. Feng, Z. Peng, R. S. Chapman, T. M. Uyeki, and H. Yu, 2008: Incubation period for human cases of avian influenza A (H5N1) infection, China. *Emerg. Infect. Dis.* 14, 1819–1821.

Hulse-Post, D. J., T. D. Nguyen, H. T. Long, T. S. P. Naipospos, H. Chen, T. M. Ellis, Y. Guan, J. S. M. Peiris, R. G. Webster, K. M. Sturm-Ramirez, J. Humberd, P. Seiler, E. A. Govorkova, S. Krauss, C. Scholtissek, P. Puthavathana, and C. Buranathai, 2005: Role of domestic ducks in the propagation and biological evolution of highly pathogenic H5N1 influenza viruses in Asia. *Proc. Natl Acad. Sci. USA* 102, 10682–10687.

Imai, M., S. Watanabe, C. Li, E. Kawakami, S. Yamada, M. Kiso, Y. Suzuki, E. A. Maher, G. Neumann, Y. Kawaoka, T. Watanabe, M. Hatta, S. C. Das, M. Ozawa, K. Shinya, G. Zhong, A. Hanson, and H. Katsura, 2012: Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. *Nature* 486, 420.

Jiang, W. M., S. Liu, J. Chen, G. Y. Hou, J. P. Li, Y. F. Cao, Q. Y. Zhuang, Y. Li, B. X. Huang, and J. M. Chen, 2010: Molecular epidemiological surveys of H5 subtype highly pathogenic avian influenza viruses in poultry in China during 2007–2009. *J. Gen. Virol.* 91, 2491–2496.

Joannis, T. M., C. A. Meseko, A. T. Oladokun, H. G. Ularamu, A. N. Egbuji, P. Solomon, D. C. Nyam, D. A. Gado, P. Luka, M. E. Ogedengbe, M. B. Yakubu, A. D. Tyem, O. Akinyede, A. I. Shittu, L. K. Sulaiman, O. A. Owolodun, A. K. Olawuyi, E. T. Obishakin, and F. O. Fasina, 2008: Serologic and virologic surveillance of avian influenza in Nigeria, 2006–7. *Euro. Surveill.* 13, 11–15.

Jones, J. C., S. Sonnberg, Z. A. Kocer, K. Shanmuganatham, P. Seiler, Y. Shu, H. Zhu, Y. Guan, M. Peiris, R. J. Webby, and R. G. Webster, 2014: Possible role of songbirds and parakeets in transmission of influenza A(H7N9) virus to humans. *Emerg. Infect. Dis.* 20, 380–385.

Kageyama, T., S. Fujisaki, E. Takashita, H. Xu, S. Yamada, Y. Uchida, G. Neumann, T. Saito, Y. Kawaoka, and M. Tashiro, 2013: Genetic analysis of novel avian A(H7N9) influenza viruses isolated from patients in China, February to April 2013. *Euro. Surveill.* 18, 20453.

Kandeel, A., S. Manoncourt, E. Abd el Kareem, A. N. Mohamed Ahmed, S. El-Refaie, H. Essmat, J. Tjaden, C. C. de Mattos, K. C. Earhart, A. A. Marfin, and N. El-Sayed, 2010: Zoonotic transmission of avian influenza virus (H5N1), Egypt, 2006–2009. *Emerg. Infect. Dis.* 16, 1101–1107.

Keawcharoen, J., K. Oraveerakul, T. Kuiken, R. A. Fouchier, A. Amonsin, S. Payungporn, S. Noppornpanth, S. Wattanodorn, A. Theamboonniers, R. Tantilertcharoen, R. Pattanarangsan, N. Arya, P. Ratanakorn, D. M. Osterhaus, and Y. Poovorawan, 2004: Avian influenza H5N1 in tigers and leopards. *Emerg. Infect. Dis.* 10, 2189–2191.

Kida, H., R. Yanagawa, and Y. Matsuoka, 1980: Duck influenza lacking evidence of disease signs and immune response. *Infect. Immun.* 30, 547–553.

Kilpatrick, A. M., A. A. Chmura, D. W. Gibbons, R. C. Fleischer, P. P. Marra, and P. Daszak, 2006: Predicting the global spread of H5N1 avian influenza. *Proc. Natl Acad. Sci. USA* 103, 19368–19373.

Kim, B. S., H. M. Kang, J. G. Choi, M. C. Kim, H. R. Kim, M. R. Paek, J. H. Kwon, and Y. J. Lee, 2011: Characterization of the low-pathogenic H5N1 avian influenza virus in South Korea. *Poult. Sci.* 90, 1449–1461.

Kim, H. R., C. K. Park, Y. J. Lee, J. K. Oem, H. M. Kang, J. G. Choi, O. S. Lee, and Y. C. Bae, 2012: Low pathogenic H7 subtype avian influenza viruses isolated from domestic ducks in South Korea and the close association with isolates of wild birds. *J. Gen. Virol.* 93, 1278–1287.

Klopfleisch, R., P. U. Wolf, C. Wolf, T. Harder, E. Starick, M. Niebuhr, T. C. Mettenleiter, and J. P. Teifke, 2007: Encephalitis in a stone marten (*Martes foina*) after natural infection with highly pathogenic avian influenza virus subtype H5N1. *J. Comp. Pathol.* 137, 155–159.

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* 450–451, 316–323.

Kwon, Y. K., H. W. Sung, S. J. Joh, Y. J. Lee, M. C. Kim, J. G. Choi, E. K. Lee, S. H. Wee, and J. H. Kim, 2005: An outbreak of highly pathogenic avian influenza subtype H5N1 in broiler breeders, Korea. *J. Vet. Med. Sci.* 67, 1193–1196.

Lam, T. T.-Y., J. Wang, Y. Shen, B. Zhou, L. Duan, C.-L. Cheung, C. Ma, S. J. Lycett, C. Y.-H. Leung, X. Chen, L. Li, W. Hong, Y. Chai, L. Zhou, H. Liang, Z. Ou, Y. Liu, A. Farooqui, D. J. Kelvin, L. L. M. Poon, D. K. Smith, O. G. Pybus, G. M. Leung, Y. Shu, R. G. Webster, R. J. Webby, J. S. M. Peiris, A. Rambaut, H. Zhu, and Y. Guan, 2013: The genesis and source of the H7N9 influenza viruses causing human infections in China. *Nature* 502, 241–244.

Le, T. H., and N. T. Nguyen, 2014: Evolutionary dynamics of highly pathogenic avian influenza A/H5N1 HA clades and vaccine implementation in Vietnam. *Clin. Exp. Vaccine Res.* 3, 117–127.

Lebarbenchon, C., S. Sreevatsan, M. A. Ramakrishnan, R. Poulson, V. Goekjian, J. J. Di Matteo, B. Wilcox, and D. E. Stallknecht, 2010: Influenza A viruses in American White Pelican (*Pelecanus erythrorhynchos*). *J. Wildl. Dis.* 46, 1284–1289.

Lee, Y.-J., Y.-K. Choi, Y.-J. Kim, M.-S. Song, O.-M. Jeong, E.-K. Lee, W.-J. Jeon, W. Jeong, S.-J. Joh, K.-S. Choi, M. Her, M.-C. Kim, A. Kim, M.-J. Kim, E. h. Lee, T.-G. Oh, H.-J. Moon, D.-W. Yoo, J.-H. Kim, M.-H. Sung, H. Poo, J.-H. Kwon, and C.-J. Kim, 2008: Highly pathogenic avian influenza virus (H5N1) in domestic poultry and relationship with migratory birds, South Korea. *Emerg. Infect. Dis.* 14, 487–490.

Lee, D. H., J. K. Park, H. N. Youn, Y. N. Lee, T. H. Lim, M. S. Kim, J. B. Lee, S. Y. Park, I. S. Choi, and C. S. Song, 2011: Surveillance and isolation of HPAI H5N1 from wild Mandarin Ducks (*Aix galericulata*). *J. Wildl. Dis.* 47, 994–998.

Leschnik, M., J. Weikel, K. Mostl, S. Revilla-Fernandez, E. Wodak, Z. Bago, E. Vanek, V. Benetka, M. Hess, and J. G. Thalhammer, 2007: Subclinical infection with avian influenza A (H5N1) virus in cats. *Emerg. Infect. Dis.* 13, 243–247.

Li, K. S., Y. Guan, J. Wang, G. J. Smith, K. M. Xu, L. Duan, A. P. Rahardjo, P. Puthavathana, C. Buranathai, T. D. Nguyen, A. T. Estoepangestie, A. Chaisingh, P. Auewarakul, H. T. Long, N. T. Hanh, R. J. Webby, L. L. Poon, H. Chen, K. F. Shortridge, K. Y. Yuen, R. G. Webster, and J. S. Peiris, 2004: Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. *Nature* 430, 209–213.

Li, Q., L. Zhou, M. Zhou, Z. Chen, F. Li, H. Wu, N. Xiang, E. Chen, F. Tang, D. Wang, L. Meng, Z. Hong, W. Tu, Y. Cao, L. Li, F. Ding, B. Liu, M. Wang, R. Xie, R. Gao, X. Li, T. Bai, S. Zou, J. He, J. Hu, Y. Xu, C. Chai, S. Wang, Y. Gao, L. Jin, Y. Zhang, H. Luo, H. Yu, X. Wang, L. Gao, X. Pang, G. Liu, Y. Yan, H. Yuan, Y. Shu, W. Yang, Y. Wang, F. Wu, T. M. Uyeki, and Z. Feng, 2014: Epidemiology of human infections with avian influenza A(H7N9) virus in China. *N. Engl. J. Med.* 370, 520–532.

Liang, L., B. Xu, Y. Chen, Y. Liu, W. Cao, L. Fang, L. Feng, M. F. Goodchild, and P. Gong, 2010: Combining spatial-temporal and phylogenetic analysis approaches for improved understanding on global H5N1 transmission. *PLoS One* 5, e13575.

Liem, N. T., C. V. Tung, N. D. Hien, T. T. Hien, N. Q. Chau, H. T. Long, N. T. Hien, Q. Mai le, W. R. Taylor, H. Wertheim, J. Farrar, D. D. Khang, and P. Horby, 2009: Clinical features of human influenza A (H5N1) infection in Vietnam: 2004–2006. *Clin. Infect. Dis.* 48, 1639–1646.

Ling, F., E. Chen, Q. Liu, Z. Miao, and Z. Gong, 2014: Hypothesis on the source, transmission and characteristics of infection of avian influenza A (H7N9) virus – based on analysis of field epidemiological investigation and gene sequence analysis. *Zoonoses Public Health* 62, 29–37.

Liu, J., H. Xiao, F. Lei, Q. Zhu, K. Qin, X. W. Zhang, X. L. Zhang, D. Zhao, G. Wang, Y. Feng, J. Ma, W. Liu, J. Wang, and G. F. Gao, 2005: Highly pathogenic H5N1 influenza virus infection in migratory birds. *Science* 309, 1206.

Liu, D., W. Shi, Y. Shi, D. Wang, H. Xiao, W. Li, Y. Bi, Y. Wu, X. Li, J. Yan, W. Liu, G. Zhao, W. Yang, Y. Wang, J. Ma, Y. Shu, F. Lei, and G. F. Gao, 2013: Origin and diversity of novel avian influenza A H7N9 viruses causing human infection:

phylogenetic, structural, and coalescent analyses. *Lancet* 381, 1926–1932.

Loth, L., M. Gilbert, M. G. Osmani, A. M. Kalam, and X. Xiao, 2010: Risk factors and clusters of Highly Pathogenic Avian Influenza H5N1 outbreaks in Bangladesh. *Prev. Vet. Med.* 96, 104–113.

Lu, L., S. J. Lycett, and A. J. Leigh Brown, 2014: Reassortment patterns of avian influenza virus internal segments among different subtypes. *BMC Evol. Biol.* 14, 16.

L'Vov D, K., M. Shchelkanov, P. G. Deriabin, T. V. Grebennikova, A. G. Prilipov, E. A. Nepoklonov, G. G. Onishchenko, N. A. Vlasov, T. I. Aliper, A. D. Zaberezhnyi, D. E. Kireev, O. P. Krasheninnikov, S. T. Kiriukhin, E. I. Burtseva, and A. N. Slepushkin, 2006: Isolation of influenza A/H5N1 virus strains from poultry and wild birds in West Siberia during epizooty (July 2005) and their depositing to the state collection of viruses (August 8, 2005). *Vopr. Virusol.* 51, 11–14.

Macken, C. A., R. J. Webby, and W. J. Bruno, 2006: Genotype turnover by reassortment of replication complex genes from avian influenza A virus. *J. Gen. Virol.* 87, 2803–2815.

Martin, V., M. Gilbert, X. Zhou, E. Marshall, B. Jia, G. Fusheng, M. A. FrancoDixon, N. DeHaan, D. U. Pfeiffer, and R. J. Soares Magalhães, 2011: Risk-based surveillance for avian influenza control along poultry market chains in South China: the value of social network analysis. *Prev. Vet. Med.* 102, 196–205.

Mase, M., K. Tsukamoto, T. Imada, K. Imai, N. Tanimura, K. Nakamura, Y. Yamamoto, T. Hitomi, T. Kira, T. Nakai, M. Kiso, T. Horimoto, Y. Kawaoka, S. Yamaguchi, M. Mase, K. Tsukamoto, T. Imada, K. Imai, N. Tanimura, K. Nakamura, Y. Yamamoto, T. Hitomi, T. Kira, T. Nakai, M. Kiso, T. Horimoto, Y. Kawaoka, and S. Yamaguchi, 2005: Characterization of H5N1 influenza A viruses isolated during the 2003–2004 influenza outbreaks in Japan. *Virology* 332, 167–176.

Ministry of Agriculture, PSROC, 2014: H7N9 monitoring topics, monitoring and epidemic dynamics, veterinary authority, Chaoyang District, Beijing Agricultural Exhibition. Available at http://www.syj.moa.gov.cn/dwyqdt/jczt/ (accessed August 5 2014).

Morris, R. S., and R. Jackson, 2005: Historical background on Avian Influenza and Emergence of the H5N1 strain. Epidemiology of H5N1 Avian Influenza in Asia and Implications for Regional Control. A contracted report for the Food and Agriculture Organization of the United Nations Covering the period January 2003 to February 11, 2005, pp. 2–3. Food and Agriculture Organization of the UN, Rome, Italy.

Munster, V. J., A. Wallensten, C. Baas, G. F. Rimmelzwaan, M. Schutten, B. Olsen, A. D. M. E. Osterhaus, R. A. M. Fouchier, V. Molekylär, and Hälsouniversitetet and m. Institutionen för klinisk och experimentell, 2005: Mallards and highly pathogenic avian influenza ancestral viruses, northern Europe. *Emerg. Infect. Dis.* 11, 1545–1551.

Murhekar, M., Y. Arima, P. Horby, K. A. Vandemaele, S. Vong, F. Zijian, C. K. Lee, A. Li, and World Health Organization Regional Office for the Western Pacific Event Management Team, 2013: Avian influenza A(H7N9) and the closure of live bird markets. *Western Pac. Surveill. Response J.* 4, 4–7.

Nagy, A., L. Černíková, H. Jiřincová, M. Havlíčková, and J. Horníčková, 2014: Local-Scale Diversity and Between-Year Frozen Evolution of Avian Influenza A Viruses in Nature. *PLoS ONE* 9, e103053.

Nguyen, D. C., T. M. Uyeki, S. Jadhao, T. Maines, M. Shaw, Y. Matsuoka, C. Smith, T. Rowe, X. Lu, H. Hall, X. Xu, A. Balish, A. Klimov, T. M. Tumpey, D. E. Swayne, L. P. Huynh, H. K. Nghiem, H. H. Nguyen, L. T. Hoang, N. J. Cox, and J. M. Katz, 2005: Isolation and characterization of avian influenza viruses, including highly pathogenic H5N1, from poultry in live bird markets in Hanoi, Vietnam, in 2001. *J. Virol.* 79, 4201–4212.

Nidom, C. A., R. Takano, S. Yamada, Y. Sakai-Tagawa, S. Daulay, D. Aswadi, T. Suzuki, Y. Suzuki, K. Shinya, K. Iwatsuki-Horimoto, Y. Muramoto, and Y. Kawaoka, 2010: Influenza A (H5N1) viruses from pigs, Indonesia. *Emerg. Infect. Dis.* 16, 1515–1523.

Olsen, S., K. Ungchusak, L. Sovann, T. M. Uyeki, S. F. Dowell, N. J. Cox, W. Aldis, and S. Chunsutthiwat, 2005: Family Clustering of Avian Influenza A (H5N1). *Emerg. Infect. Dis.* 11, 1799–1801.

Oner, A. F., A. Bay, S. Arslan, H. Akdeniz, H. A. Sahin, Y. Cesur, S. Epcacan, N. Yilmaz, I. Deger, B. Kizilyildiz, H. Karsen, and M. Ceyhan, 2006: Avian influenza A (H5N1) infection in eastern Turkey in 2006. *N. Engl. J. Med.* 355, 2179–2185.

Pantin-Jackwood, M. J., P. J. Miller, E. Spackman, D. E. Swayne, L. Susta, M. Costa-Hurtado, and D. L. Suarez, 2014: Role of poultry in the spread of novel H7N9 influenza virus in China. *J. Virol.* 88, 5381–5390.

Peiris, J. S. M., M. D. de Jong, and Y. Guan, 2007: Avian Influenza Virus (H5N1): a threat to human health. *Clin. Microbiol. Rev.* 20, 243–267.

Pinsent, A., I. M. Blake, M. T. White, and S. Riley, 2014: Surveillance of low pathogenic novel H7N9 avian influenza in commercial poultry barns: detection of outbreaks and estimation of virus introduction time. *BMC Infect. Dis.* 14, 427.

Prosser, D. J., P. Cui, J. Y. Takekawa, M. Tang, Y. Hou, B. M. Collins, B. Yan, N. J. Hill, T. Li, Y. Li, F. Lei, S. Guo, Z. Xing, Y. He, Y. Zhou, D. C. Douglas, W. M. Perry, and S. H. Newman, 2011: Wild bird migration across the Qinghai-Tibetan plateau: a transmission route for highly pathogenic H5N1. *PLoS One* 6, e17622.

Qiu, C., S. Yuan, D. Tian, Y. Yang, A. Zhang, Q. Chen, Y. Wan, Z. Song, J. He, L. Li, J. Sun, M. Zhou, C. Qiu, Z. Zhang, S. Lu, X. Zhang, Y. Hu, and J. Xu, 2014: Epidemiologic report and serologic findings for household contacts of three cases of influenza A (H7N9) virus infection. *J. Clin. Virol.* 59, 129–131.

Rabinowitz, P. M., D. Galusha, S. Vegso, J. Michalove, S. Rinne, M. Scotch, and M. Kane, 2012: Comparison of human and animal surveillance data for H5N1 influenza A in Egypt 2006–2011. *PLoS One* 7, e43851.

Rimmelzwaan, G. F., D. van Riel, M. Baars, T. M. Bestebroer, G. van Amerongen, R. A. Fouchier, A. D. Osterhaus, and T.

Kuiken, 2006: Influenza A virus (H5N1) infection in cats causes systemic disease with potential novel routes of virus spread within and between hosts. *Am. J. Pathol.* 168, 176–183; quiz 364.

Sedyaningsih, E. R., S. Isfandari, V. Setiawaty, L. Rifati, S. Harun, W. Purba, S. Imari, S. Giriputra, P. J. Blair, S. D. Putnam, T. M. Uyeki, and T. Soendoro, 2007: Epidemiology of cases of H5N1 virus infection in Indonesia, July 2005–June 2006. *J. Infect. Dis.* 196, 522–527.

Senne, D. A., B. Panigrahy, Y. Kawaoka, J. E. Pearson, J. Suss, M. Lipkind, H. Kida, and R. G. Webster, 1996: Survey of the hemagglutinin (HA) cleavage site sequence of H5 and H7 avian influenza viruses: amino acid sequence at the HA cleavage site as a marker of pathogenicity potential. *Avian Dis.* 40, 425–437.

Shi, J., G. Deng, P. Liu, J. Zhou, L. Guan, W. Li, X. Li, J. Guo, G. Wang, J. Fan, J. Wang, Y. Li, Y. Jiang, L. Liu, G. Tian, C. Li, and H. Chen, 2013: Isolation and characterization of H7N9 viruses from live poultry markets — Implication of the source of current H7N9 infection in humans. *Chin. Sci. Bull.* 58, 1857–1863.

Shortridge, K. F., N. N. Zhou, Y. Guan, P. Gao, T. Ito, Y. Kawaoka, S. Kodihalli, S. Krauss, D. Markwell, K. G. Murti, M. Norwood, D. Senne, L. Sims, A. Takada, and R. G. Webster, 1998: Characterization of avian H5N1 influenza viruses from poultry in Hong Kong. *Virology* 252, 331–342.

Shriner, S. A., K. K. VanDalen, N. L. Mooers, J. W. Ellis, H. J. Sullivan, J. J. Root, A. M. Pelzel, and A. B. Franklin, 2012: Low-pathogenic avian influenza viruses in wild house mice. *PLoS One* 7, e39206.

Sims, L., and M. Jeggo, 2014: Avian influenza from an ecohealth perspective. *EcoHealth* 11, 4–14.

Sims, L. D., T. M. Ellis, K. K. Liu, K. Dyrting, H. Wong, M. Peiris, Y. Guan, and K. F. Shortridge, 2003: Avian influenza in Hong Kong 1997–2002. *Avian Dis.* 47, 832–838.

Skowronski, D. M., N. Z. Janjua, T. L. Kwindt, and G. De Serres, 2013: Virus-host interactions and the unusual age and sex distribution of human cases of influenza A(H7N9) in China, April 2013. *Euro. Surveill.* 18, 20465.

Songserm, T., A. Amonsin, R. Jam-on, N. Sae-Heng, N. Pariyothorn, S. Payungporn, A. Theamboonlers, S. Chutinimitkul, R. Thanawongnuwech, and Y. Poovorawan, 2006a: Fatal avian influenza A H5N1 in a dog. *Emerg. Infect. Dis.* 12, 1744–1747.

Songserm, T., R. Jam-on, N. Sae-Heng, N. Meemak, D. J. Hulse-Post, K. M. Sturm-Ramirez, and R. G. Webster, 2006b: Domestic ducks and H5N1 influenza epidemic, Thailand. *Emerg. Infect. Dis.* 12, 575–581.

Sorrell, E. M., H. Song, L. Pena, and D. R. Perez, 2010: A 27-amino-acid deletion in the neuraminidase stalk supports replication of an avian H2N2 influenza A virus in the respiratory tract of chickens. *J. Virol.* 84, 11831–11840.

Spackman, E., C.-W. Lee, D. Stallknecht, R. Slemons, H. S. Ip, T. Deliberto, D. E. Swayne, D. L. Suarez, D. A. Senne, J. C. Pedersen, M. L. Killian, J. Pasick, K. Handel, and S. P. S. Pillai, 2007: Characterization of low-pathogenicity H5N1 avian influenza viruses from North America. *J. Virol.* 81, 11612–11619.

Spekreijse, D., A. Bouma, G. Koch, and J. A. Stegeman, 2011: Airborne transmission of a highly pathogenic avian influenza virus strain H5N1 between groups of chickens quantified in an experimental setting. *Vet. Microbiol.* 152, 88–95.

Stallknecht, D. E., and S. M. Shane, 1988: Host range of avian influenza virus in free-living birds. *Vet. Res. Commun.* 12, 125–141.

Sturm-Ramirez, K. M., T. Ellis, B. Bousfield, L. Bissett, K. Dyrting, J. E. Rehg, L. Poon, Y. Guan, M. Peiris, and R. G. Webster, 2004: Reemerging H5N1 influenza viruses in Hong Kong in 2002 are highly pathogenic to ducks. *J. Virol.* 78, 4892–4901.

Sturm-Ramirez, K. M., D. J. Hulse-Post, E. A. Govorkova, J. Humberd, P. Seiler, P. Puthavathana, C. Buranathai, T. D. Nguyen, A. Chaisingh, H. T. Long, T. S. Naipospos, H. Chen, T. M. Ellis, Y. Guan, J. S. Peiris, and R. G. Webster, 2005: Are ducks contributing to the endemicity of highly pathogenic H5N1 influenza virus in Asia? *J. Virol.* 79, 11269–11279.

Su, S., P. Zhou, X. Fu, L. Wang, M. Hong, G. Lu, L. Sun, W. Qi, Z. Ning, K. Jia, Z. Yuan, H. Wang, C. Ke, J. Wu, G. Zhang, G. C. Gray, and S. Li, 2014: Virological and epidemiological evidence of avian influenza virus infections among feral dogs in live poultry markets, china: a threat to human health? *Clin. Infect. Dis.* 58, 1644–1646.

Subbarao, K., H. Chen, D. Swayne, L. Mingay, E. Fodor, G. Brownlee, X. Xu, X. Lu, J. Katz, N. Cox, and Y. Matsuoka, 2003: Evaluation of a genetically modified reassortant H5N1 influenza A virus vaccine candidate generated by plasmid-based reverse genetics. *Virology* 305, 192–200.

Takekawa, J. Y., D. J. Prosser, B. M. Collins, D. C. Douglas, W. M. Perry, B. Yan, L. Ze, Y. Hou, F. Lei, T. Li, Y. Li, and S. H. Newman, 2013: Movements of wild ruddy shelducks in the central asian flyway and their spatial relationship to outbreaks of highly pathogenic avian influenza H5N1. *Viruses* 5, 2129–2152.

Tang, X., G. Tian, J. Zhao, and K. Y. Zhou, 1998: Isolation and characterization of prevalent strains of avian influenza viruses in China. *Chin. J. Anim. Poult. Infect. Dis.* 20, 1–5.

Tiensin, T., M. Nielen, H. Vernooij, T. Songserm, W. Kalpravidh, S. Chotiprasatintara, A. Chaisingh, S. Wongkasemjit, K. Chanachai, W. Thanapongtham, T. Srisuvan, and A. Stegeman, 2007: Transmission of the highly pathogenic avian influenza virus H5N1 within flocks during the 2004 epidemic in Thailand. *J. Infect. Dis.* 196, 1679–1684.

To, K. K., J. F. Chan, H. Chen, L. Li, and K. Y. Yuen, 2013: The emergence of influenza A H7N9 in human beings 16 years after influenza A H5N1: a tale of two cities. *Lancet Infect. Dis.* 13, 809–821.

Ungchusak, K., P. Auewarakul, S. F. Dowell, R. Kitphati, W. Auwanit, P. Puthavathana, M. Uiprasertkul, K. Boonnak, C. Pittayawonganon, N. J. Cox, S. R. Zaki, P. Thawatsupha, M. Chittaganpitch, R. Khontong, J. M. Simmerman, and S. Chunsutthiwat, 2005: Probable person-to-person

transmission of avian influenza A (H5N1). *N. Engl. J. Med.* 352, 333–340.

Van Kerkhove, M. D., S. Vong, J. Guitian, D. Holl, P. Mangtani, S. San, and A. C. Ghani, 2009: Poultry movement networks in Cambodia: implications for surveillance and control of highly pathogenic avian influenza (HPAI/H5N1). *Vaccine* 27, 6345–6352.

Wan, X. F., L. Dong, Y. Lan, L. P. Long, C. Xu, S. Zou, Z. Li, L. Wen, Z. Cai, W. Wang, X. Li, F. Yuan, H. Sui, Y. Zhang, J. Dong, S. Sun, Y. Gao, M. Wang, T. Bai, L. Yang, D. Li, W. Yang, H. Yu, S. Wang, Z. Feng, Y. Wang, Y. Guo, R. J. Webby, and Y. Shu, 2011: Indications that live poultry markets are a major source of human H5N1 influenza virus infection in China. *J. Virol.* 85, 13432–13438.

Wang, C., J. Wang, W. Su, S. Gao, J. Luo, M. Zhang, L. Xie, S. Liu, X. Liu, Y. Chen, Y. Jia, H. Zhang, H. Ding, and H. He, 2014a: Relationship between domestic and wild birds in live poultry market and a novel human H7N9 virus in China. *J. Infect. Dis.* 209, 34–37.

Wang, D., L. Yang, R. Gao, X. Zhang, Y. Tan, A. Wu, W. Zhu, J. Zhou, S. Zou, X. Li, Y. Sun, Y. Zhang, Y. Liu, T. Liu, Y. Xiong, J. Xu, L. Chen, Y. Weng, X. Qi, J. Guo, X. Li, J. Dong, W. Huang, Y. Zhang, L. Dong, X. Zhao, L. Liu, J. Lu, Y. Lan, H. Wei, L. Xin, Y. Chen, C. Xu, T. Chen, Y. Zhu, T. Jiang, Z. Feng, W. Yang, Y. Wang, H. Zhu, Y. Guan, G. F. Gao, D. Li, J. Han, S. Wang, G. Wu, and Y. Shu, 2014b: Genetic tuning of the novel avian influenza A(H7N9) virus during interspecies transmission, China, 2013. *Euro. Surveill.* 19, 33–49.

Webster, R. G., Y. Guan, M. Peiris, D. Walker, S. Krauss, N. N. Zhou, E. A. Govorkova, T. M. Ellis, K. C. Dyrting, T. Sit, D. R. Perez, and K. F. Shortridge, 2002: Characterization of H5N1 influenza viruses that continue to circulate in Geese in Southeastern China. *J. Virol.* 76, 118–126.

Wee, S. H., J. H. Lee, C. S. Kim, C. K. Park, H. M. Nam, C. H. Kim, H. Yoon, S. J. Kim, E. S. Lee, B. Y. Lee, and J. H. Kim, 2006: Outbreaks of highly pathogenic avian influenza (H5N1) in the Republic of Korea in 2003/04. *Vet. Rec.* 158, 341–344.

World Health Organization, 2011: H5N1 avian influenza: timeline of major events. Available at http://www.who.int/influenza/human_animal_interface/avian_influenza/H5N1_avian_influenza_update.pdf (accessed April 4, 2014).

World Health Organization, 2014a: Cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO, 2003–2014. Available at http://www.who.int/influenza/human_animal_interface/H5N1_cumulative_table_archives/en/index.html. (accessed April 4, 2014).

World Health Organization, 2014b: Global outbreak and alert response network archives. Available at http://www.who.int/csr/don/archive/year/2014/en/ (accessed April 20, 2014).

World Health Organization, 2014c: H7N9 data reports. Available at http://www.who.int/influenza/human_animal_interface/influenza_h7n9/Data_Reports/en/ (accessed April 20, 2014).

World Organisation for Animal Health, 2014: OIE Immediate notifications and follow-up reports. Available at http://www.oie.int/wahis_2/public/wahid.php/Wahidhome/Home (accessed July 31, 2014).

Xu, X., K. Subbarao, N. J. Cox, and Y. Guo, 1999: Genetic characterization of the pathogenic influenza A/Goose/Guangdong/1/96 (H5N1) virus: similarity of its hemagglutinin gene to those of H5N1 viruses from the 1997 outbreaks in Hong Kong. *Virology* 261, 15–19.

Xu, L., Y. Yao, Q. Lv, J. Yuan, F. Li, L. Bao, P. Yu, and C. Qin, 2013: Complete Genome Sequence of an H9N2 Avian Influenza Virus Isolated from *Fringilla montifringilla* Brambling in Northern China. Available at http://www.uniprot.org/uniprot/M1GN45 (accessed January 6, 2015).

Yang, Y., M. Halloran, J. Sugimoto, and I. Longini, 2007a: Detecting Human-to-Human Transmission of Avian Influenza A (H5N1). *Emerg. Infect. Dis.* 13, 1348–1353.

Yang, Y., M. E. Halloran, J. D. Sugimoto, and I. M. Jr Longini, 2007b: Detecting human-to-human transmission of avian influenza A (H5N1). *Emerg. Infect. Dis.* 13, 1348–1353.

Yu, H., J. T. Wu, B. J. Cowling, Q. Liao, V. J. Fang, S. Zhou, P. Wu, H. Zhou, E. H. Y. Lau, D. Guo, M. Y. Ni, Z. Peng, L. Feng, H. Jiang, H. Luo, Q. Li, Z. Feng, Y. Wang, W. Yang, and G. M. Leung, 2014a: Effect of closure of live poultry markets on poultry-to-person transmission of avian influenza A H7N9 virus: an ecological study. *Lancet* 383, 541–548.

Yu, X., T. Jin, Y. Cui, X. Pu, J. Li, J. Xu, G. Liu, H. Jia, D. Liu, S. Song, Y. Yu, L. Xie, R. Huang, H. Ding, Y. Kou, Y. Zhou, Y. Wang, X. Xu, Y. Yin, J. Wang, C. Guo, X. Yang, L. Hu, X. Wu, H. Wang, J. Liu, G. Zhao, J. Zhou, J. Pan, G. F. Gao, R. Yang, and J. Wang, 2014b: Influenza H7N9 and H9N2 viruses: coexistence in poultry linked to human H7N9 infection and genome characteristics. *J. Virol.* 88, 3423–3431.

Zeng, X., W. Mai, B. Shu, L. Yi, J. Lu, T. Song, H. Zhong, H. Xiao, D. Guan, J. Wu, L. Liang, C. Monagin, X. Zhang, and C. Ke, 2014: Mild Influenza A/H7N9 Infection among Children in Guangdong Province. *Pediatr. Infect. Dis. J.* 34, 104–107.

Zhang, L., Z. Zhang, and Z. Weng, 2013: Rapid reassortment of internal genes in avian influenza A(H7N9) virus. *Clin. Infect. Dis.* 57, 1059–1061.

Zhao, Z. M., K. F. Shortridge, M. Garcia, Y. Guan, and X. F. Wan, 2008: Genotypic diversity of H5N1 highly pathogenic avian influenza viruses. *J. Gen. Virol.* 89, 2182–2193.

Zhao, B., L. Yang, D. Wang, Y. Shu, F. Wu, X. Zhang, W. Zhu, Z. Teng, X. Yu, Y. Gao, D. Wu, E. Pei, and Z. Yuan, 2014: Novel Avian Influenza A(H7N9) virus in Tree Sparrow, Shanghai, China, 2013. *Emerg. Infect. Dis.* 20, 850.

Zhu, Q., H. Yang, W. Chen, W. Cao, G. Zhong, P. Jiao, G. Deng, K. Yu, C. Yang, Z. Bu, Y. Kawaoka, and H. Chen, 2008: A naturally occurring deletion in its NS gene contributes to the attenuation of an H5N1 swine influenza virus in chickens. *J. Virol.* 82, 220–228.

Zhuang, Q., S. Wang, M. Wu, S. Liu, W. Jiang, G. Hou, J. Li, K. Wang, J. Yu, J. Chen, and J. Chen, 2013: Epidemiological and risk analysis of the H7N9 subtype influenza outbreak in China at its early stage. *Chin. Sci. Bull.* 58, 3183–3187.

Zou, S., J. Guo, R. Gao, L. Dong, J. Zhou, Y. Zhang, J. Dong, H. Bo, K. Qin, and Y. Shu, 2013: Inactivation of the novel avian influenza A (H7N9) virus under physical conditions or chemical agents treatment. *Virol. J.* 10, 289.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Number of laboratory-confirmed human cases and outbreaks in domestic poultry and wild birds due to H5N1, by country of report and year of illness onset, 1997 to 31 July 2014.

Table S2. Number of laboratory-confirmed human cases and outbreak reports in domestic poultry and wild birds due to H7N9 by country of report and month of illness onset, 1997 to 31 July 2014.

Table S3. Virus detection rates of H7N9 in birds (unspecified species) in China according to publically available Ministry of Agriculture National Animal H7N9 bird flu monitoring reports (Ministry of Agriculture, 2014).

