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Review Article

REVIEW ARTICLE

# Global patterns of avian influenza A (H7): virus evolution and zoonotic threats

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**One sentence summary:** H7 avian influenza virus causes infections in birds and mammals and is of pandemic concern; our review brings together data from the ecology, veterinary and human health points of view and demonstrates the importance of 'One Heath' in the long-term management of this virus.

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## ABSTRACT

Avian influenza viruses (AIVs) continue to impose a negative impact on animal and human health worldwide. In particular, the emergence of highly pathogenic AIV H5 and, more recently, the emergence of low pathogenic AIV H7N9 have led to enormous socioeconomical losses in the poultry industry and resulted in fatal human infections. While H5N1 remains

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infamous, the number of zoonotic infections with H7N9 has far surpassed those attributed to H5. Despite the clear public health concerns posed by AIV H7, it is unclear why specifically this virus subtype became endemic in poultry and emerged in humans. In this review, we bring together data on global patterns of H7 circulation, evolution and emergence in humans. Specifically, we discuss data from the wild bird reservoir, expansion and epidemiology in poultry, significant increase in their zoonotic potential since 2013 and genesis of highly pathogenic H7. In addition, we analysed available sequence data from an evolutionary perspective, demonstrating patterns of introductions into distinct geographic regions and reassortment dynamics. The integration of all aspects is crucial in the optimisation of surveillance efforts in wild birds, poultry and humans, and we emphasise the need for a One Health approach in controlling emerging viruses such as AIV H7.

**Keywords:** avian influenza; influenza A virus; H7; One Health; virus evolution; zoonosis

## INTRODUCTION

Influenza A virus is a multihost virus and one of the most significant viruses affecting wildlife, domestic animals and human health (Webby and Webster 2001). Wild birds of the order Anseriformes (mainly ducks, swans and geese) and Charadriiformes (mainly gulls, terns and waders) appear to be central in the maintenance of influenza A virus, so-called avian influenza virus (AIV) (Webster et al. 1992; Olsen et al. 2006 ). From wild birds, AIV can be transmitted to domestic birds, causing a significant socioeconomical damage, and sporadically followed by transmission to humans, so-called zoonotic infections (Krammer *et al.* 2018).

Influenza A viruses belong to the family of *Orthomyxoviridae* and contain a single-stranded ribonucleic acid (RNA) genome composed of 8 gene segments encoding at least 11 viral proteins (Tollis and Di Trani 2002; Cheung and Poon 2007). The influenza A virus proteins can be categorised as 'surface proteins' (hemagglutinin [HA], neuraminidase [NA] and matrix protein 2 [M2]), 'internal proteins' (tripartite polymerase consisting of polymerase basic protein 2 [PB2], polymerase basic protein 1 [PB1], polymerase acidic protein [PA], nucleoprotein [NP], matrix protein 1 [M1] and nuclear export protein [NEP]) and 'nonstructural proteins' (NS1 and PB1-F2) (Webster *et al.* 1992; Brown 2000; Cheung and Poon 2007). Influenza A viruses are categorised based on their surface proteins, HA and NA, into 18 and 11 subtypes, respectively. Currently, AIVs of 16 HA (H1–H16) and 9 NA (N1–N9) subtypes have been identified in birds (Fouchier *et al.* 2005; ICTVdB 2006, Webster et al. 1992); however, the new HA (H17 and H18) and NA (N10 and N11) subtypes have been reported only in bats. Furthermore, AIVs can be categorised as low pathogenic AIVs (LPAIVs) or highly pathogenic AIVs (HPAIVs) based on their pathogenicity in chickens. This far, only AIVs of the H5 and H7 subtypes have shown the potential to mutate from LPAIV into HPAIV (Deshpande *et al.* 1987; Capua and Alexander 2007; Bonfanti *et al.* 2014).

Interspecies transmission is an important event in the evolution and ecology of AIV H7 (Joseph *et al.* 2017). These viruses are able to infect a broad range of species, from an array of wild bird species to poultry and mammals, including seals, pigs, horses and humans (Abdelwhab, Veits and Mettenleiter 2014; Fereidouni *et al.* 2016; Mostafa *et al.* 2018). In poultry, LPAIV H7 can circulate asymptomatically, and evolve into HPAIV H7, causing severe systemic diseases and mortality (Belser *et al.* 2018). From poultry, humans have shown to become infected sporadically with either LPAIV or HPAIV H7. These infections were mostly limited to ocular and/or mild respiratory signs, with one human death during an HPAIV H7N7 outbreak in the Netherlands in 2003 (Fouchier *et al.* 2004). In February 2013, LPAIV H7N9 emerged in poultry and humans in China. LPAIV H7N9 has caused seasonal waves of zoonotic infections in China and has led to lethal human infections. Human infections with H7N9 since 2013 has been far more severe than all other prior sporadic H7 human infections (i.e. 1567 confirmed human cases; 615 deaths; case fatality rate 39%) (as of March 2019) (Belser *et al.* 2018; WHO 2019a). So far, humans have become infected upon direct exposure to infected poultry, and no sustained interhuman transmission has been confirmed.

In this review, we address the current understanding of the evolution and emergence of AIV H7 in wild birds, poultry and humans. Specifically, we interrogate features of the wild–domestic bird interface, global virus evolution patterns and distributions, including a list of genetic changes associated with altered virus replication, pathogenesis and transmission in mammals. Overall, we demonstrate that AIV H7 is a One Health problem, requiring a One Health solution, including the control of AIV H7 in poultry and decreasing the potential for zoonotic transmission.

## H7 VIRUS GENESIS

### Different pathotypes and cleavage sites within H7 viruses

The characterisation of AIV as LPAIV or HPAIV is based on their capacity to cause disease in chickens upon experimental exposure and scored on an intravenous pathogenicity index (OIE 2019). Currently, the more common method to identify pathogenicity is by sequencing the HA gene segment as the presence of multiple basic amino acids at the HA cleavage site (HACS) [referred to as MBCS (Multiple Basic Cleavage Site)] indicates high pathogenicity (OIE 2019). Thus, while LPAIVs harbour a single basic amino acid (either arginine 'R' or lysine 'K') at of the cleavage site of the HA gene segment, HPAIVs possess motifs with more than one R and/or K (Table S1, Supporting Information) (OFFLU and OIE/FAO 2018). The insertion of an MBCS results in a broader tissue tropism of the virus, with HPAIVs being able to cause systemic infections (Garten and Klenk 2008), in contrast to LPAIVs, which are limited to the respiratory or digestive tract in birds or ocular and respiratory tract in mammals (Böttcher-Friebertshäuser *et al.* ).

### From low to high pathogenicity

Based on poultry outbreaks, a number of conceivable mechanisms for the emergence of HPAIV H7 from ancestral LPAIV H7 by converting a single basic cleavage site to an MBCS have been suggested (Table 1). *In vitro, in vivo* and/or *in ovo* experiments—including multiple virus passages and/or the use of reverse genetics—have been performed to investigate potential mechanisms involved in the emergence of HPAIV (Brugh 1988; Horimoto and Kawaoka 1995; Ito *et al.* 2001; Munster *et al.* 2010; Gohrbandt *et al.* 2011; Soda *et al.* 2011; Bottcher-Friebertshauser *et al.* 2014; Abdelwhab *et al.* 2016). Furthermore, in both natural

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**Table 1.** Overview of the proposed mechanism of H7 highly pathogenic AIVs detected during poultry outbreaks, which emerged from known ancestral low pathogenic AIVs, modified from Seekings (2017).

| Subtype | Country | Year | Host | Proposed mechanism |
|---|---|---|---|---|
| H7N1 | Italy | 1999–2000 | Turkeys; chickens; other | Recombination; minor variants in the LPAIV progenitor quasispecies |
| H7N3 | Pakistan | 1994–95 | Chicken | Nucleotide substitution and insertion |
| | Chile | 2002 | Chicken | Non-homologous recombination with NP |
| | Canada | 2004 | Chicken | Recombination with M1, nucleotide substitution mutation |
| | Canada | 2007 | Chicken | Recombination with host RNA |
| | Mexico | 2012 | Chicken | Recombination with host 28s rRNA |
| H7N7 | Australia | 1976 | Duck; chicken | Duplication insertion |
| | Netherlands | 2003 | Chicken | Presumed reassortment with LPAIV H7N3 2003 (HA) and LPAIV H10N7 2000 (NA) |
| | UK | 2008 | Chicken | Nucleotide substitution and insertion |
| | Spain | 2009–2010 | Chicken | Insertion of foreign nucleotides |
| | UK | 2015 | Chicken | Nucleotide substitution and insertion |
| | Germany | 2015 | Chicken | Substitution and insertion; minor variants in the LPAIV progenitor quasispecies |
| H7N8 | USA | 2016 | Turkey | Insertion |
| H7N9 | USA | 2017 | Chicken | Insertion |

and experimental settings, next-generation sequencing (NGS) has shown to be a useful technique to identify HPAIV minor variants among LPAIV quasispecies (Monne *et al.* 2014; Dietze *et al.* 2018).

So far, three molecular mechanisms for HPAIV genesis have been described. The most frequently described mechanism for HPAIV genesis from ancestral LPAIVs is the duplication of an existing AIV template by a polymerase stuttering mechanism (Pasick *et al.* 2005). This results in the insertion of series of A and G nucleotides, encoding basic amino acids at the HACS. This mechanism has been described in several occasions, including the Chinese LPAIV H7N9 outbreak in 2013, which mutated to HPAIVs in 2017 (Shi *et al.* 2017), and HPAIV H7N7 outbreaks in Germany in 2015, in the UK in 2008 and 2015, and in Spain in 2009–2010 (Defra 2008; Iglesias *et al.* 2010; Dietze *et al.* 2018; Seekings *et al.* 2018), HPAIV H7N8 outbreak in the USA in 2016 (Killian *et al.* 2016) and HPAIV H7N3 outbreaks in Pakistan in 1994–1995 and 2003 (Abbas *et al.* 2010). Another mechanism for HPAIV genesis is based on the non-synonymous mutation of one or more nucleotides in the HACS, leading to the coding of an R or K. However, this mechanism has only been observed in association with the insertion of nucleotides, as described for the HPAIV H7N7 outbreaks in the UK in 2008 and 2015 (Defra 2008; Seekings *et al.* 2018) and for the HPAIV H7N3 outbreak in Pakistan in 1994–1995 (Abbas *et al.* 2010). A third mechanism for HPAIV genesis is based on a non-homologous recombination. This mechanism is characterised by an insertion of nucleotides from another viral gene segment or other non-viral sources (e.g. host) into the HACS. Insertions of varying lengths have been described for multiple instances. For instance, the HACS of LPAIV H7N3 detected in Chile in 2002 and in Canada in 2004 had acquired several nucleotides from the M and the NP genes (Suarez *et al.* 2004; Pasick *et al.* 2005; Berhane *et al.* 2009). The HACS of LPAIV H7N3 as detected in Canada in 2007 and in Mexico in 2012 had acquired several nucleotides from chicken 28S rRNA (FAO 2012; Maurer-Stroh *et al.* 2013). Finally, the HACS of an LPAIV H7N1 in Italy mutated into unique HPAIV HACS motifs (PEIPK**RSRV**RR*GLF and PEIPK**GSRM**RR*GLF) in 1999–2000 and resulted in the insertion of four amino acids from an unknown source (Banks *et al.* 2001; Capua *et al.* 2002; Monne *et al.* 2014).

Remarkably, the emergence of HPAIV H7 appears to be mainly associated with the adaptation of LPAIV to poultry, especially chickens or turkeys (Richard *et al.* 2017). The majority of HPAIVs that emerged are of the H7 subtype compared to a relatively few of the H5 subtype (Richard *et al.* 2017); yet, the reason for this is still unknown. However, it highlights the risk of HPAIV H7 emergence and remains a major concern for the poultry industry globally, as the subclinical LPAIVs are continuing to circulate in wild birds.

## WILD–DOMESTIC BIRD INTERFACE OF H7 VIRUSES

Wild birds, in particular dabbling ducks, shorebirds and gulls, form the natural reservoir for most AIV subtypes (H1–H16, N1–N9). In wild birds, H7 has been detected in combination with N1–N9 (Olson *et al.* 2014). LPAIV H7 has been detected in wild birds in six continents and predominantly in autumn and winter, which is consistent with the ecology of all LPAIV subtypes in wild birds (Latorre-Margalef *et al.* 2014; Zhang *et al.* 2017). LPAIV H7 is most frequently reported in dabbling ducks, including mallards (*Anas platyrhynchos*), Northern pintails (*Anas acuta*), Northern shovelers (*Spatula clypeata*) and shorebirds, particularly ruddy turnstones (*Arenaria interpres*) (the latter at the AIV hotspot in Delaware Bay in North America only) (Zhang *et al.* 2017). Nevertheless, LPAIV H7 are relatively uncommon in wild birds, constituting only a small proportion of isolates in long term study systems (De Marco *et al.* 2003; Munster *et al.* 2005; Latorre-Margalef *et al.* 2014). Remarkably, no HPAIV H7 has been isolated from wild birds, in contrast to HPAIV H5, which has been detected in wild birds in association with outbreaks in poultry (Verhagen, Herfst and Fouchier 2015). Yet, avian influenza surveillance programmes are severely biased towards certain bird species—in particular mallards (Olsen *et al.* 2006)—leaving a wide range of bird species unexplored. Regardless, based on online sequence databases, LPAIV H7 has been detected in at least 65 bird species, demonstrating that a broad avian host range may be involved in the epidemiology of AIV H7 (Zhang *et al.* 2017).

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LPAIV H7 detected in poultry has their origin in wild waterfowls (Munster *et al.* 2005; Campitelli *et al.* 2008), and, globally, viruses of the H7 subtype are frequently detected in poultry (Senne, Pedersen and Panigrahy 2005). This may be due to a bias in poultry diagnostics towards H7 (and H5) viruses compared to other HA subtypes (Olson *et al.* 2014). HPAIV H7 emerges from LPAIVs in poultry; there is no evidence that HPAIVs have ever emerged in wild birds (Rohm *et al.* 1995). Furthermore, LPAIV H7 has been detected in poultry in six continents (Zhang *et al.* 2017). HPAIV H7 outbreaks in poultry have been observed year round, with varying severity (Alexander 2000; Capua and Marangon 2000; Naeem 2003; Hirst *et al.* 2004; Munster *et al.* 2005) and varying time intervals between the detection of ancestral LPAIVs and HPAIVs (e.g. less than one month for H7N3 in Chile and more than eight months for H7N1 in Italy) (Capua *et al.* 2002; Suarez *et al.* 2004; de Jong *et al.* 2009). Despite the regular emergence of H7 outbreaks in poultry, individual outbreaks appear to be limited in space and time (de Wit *et al.* 2004), with the exception of LPAIV H7N2 and LPAIV H7N9. LPAIV H7N2, which emerged in 1994, has been isolated across several years from birds sampled at live bird markets (LBMs) in Northeastern USA (Spackman *et al.* 2003; Suarez, Spackman and Senne 2003; Senne, Pedersen and Panigrahy 2005). LPAIV H7N9 has been maintained in the poultry population in China since 2013 and has been detected primarily in chickens and less frequently in domestic ducks, pigeons and quails (Chen *et al.* 2013; Pantin-Jackwood *et al.* 2014; Wang *et al.* 2014a; Millman *et al.* 2015). LPAIV H7N9, which is endemic in China (see the section titled 'H7N9'), contains genes solely of avian origin (Gao *et al.* 2013); yet, a virus with the same gene constellation has not been identified in wild birds, including waterfowls thus far (Zhao *et al.* 2014). This suggests that LPAIV H7N9 infection may not be widespread in wild birds (Millman *et al.* 2015). Furthermore, experimental infections suggest that there may be host-specific adaptions of LPAIV H7 in wild birds and chickens (Lebarbenchon and Stallknecht 2011; Kim *et al.* 2012; Lebarbenchon, Brown and Stallknecht 2013).

LPAIVs and HPAIVs of different avian origins have been studied experimentally to investigate virulence, pathogenesis, transmission and host range. Tissue tropism and receptor-binding profiles of LPAIV and HPAIV H7 have been characterised in different bird species (Mo *et al.* 1997; Hooper and Selleck 2003; Gambaryan *et al.* 2012). LPAIVs H7 of different origins have been shown to infect wild waterfowls (including mallards) (Ferreira *et al.* 2010; Pantin-Jackwood *et al.* 2016) and domestic birds (Lu and Castro 2004; Kaleta and Honicke 2005; Jourdain *et al.* 2010; Spackman *et al.* 2010). LPAIV H7N1 originating from chickens has been successfully transmitted to chickens via direct contact (Claes *et al.* 2013, 2015), and HPAIVs H7 of different origins have been shown to infect mallards (Pantin-Jackwood *et al.* 2016). With respect to the Chinese LPAIV H7N9, virus excretion was higher in chickens and quails than in rock pigeons (*Columba livia*), pekin ducks (*Anas platyrhynchos domesticus*), mallards, muscovy ducks (*Cairina moschata*) and embden geese (*Anser anser domesticus*). Furthermore, quails transmitted the virus through direct contacts, while pigeons and pekin ducks did not, which may suggest a limited ability to spread in these species (Pantin-Jackwood *et al.* 2014). Finally, LPAIV H7N9 was transmitted from finches to quails and chickens (Jones *et al.* 2015), suggesting that passerines cannot be excluded from the epidemiology of AIV H7.

The introduction and emergence of an AIV in poultry—in this case LPAIV H7N9—is not surprising. In China, chicken and duck meat production has increased by more than 600% from 1990 to 2015 (Gilbert, Xiao and Robinson 2017). Globally, the domestic chicken constitutes 70% of the bird biomass. Remarkably, the domestic duck constitutes a far greater biomass than the most common wild duck, the mallard (*Anas platyrhynchos*) (Gilbert, Xiao and Robinson 2017). This creates an enormous ecological niche for AIVs. Furthermore, LBMs are the primary source for poultry production and trading activities in China, where in 2013, 63% of the 190 million chickens consumed annually were purchased from LBMs (Wu *et al.* 2017b). Finally, the frequent contact between wild and domestic birds facilitates virus introduction and virus gene movement in and between the domestic and wild ecosystems. Despite the recognition that the wild–domestic bird interface is porous, there is a limited understanding of factors affecting viral introduction and the frequency of AIV gene movement across the interface. For instance, it was shown that contact rates between wild and domestic birds at a local scale varied per season (Cappelle *et al.* 2011), and that the proximity and abundance of water and wetlands have been associated with AIVs in poultry farms (Roche *et al.* 2009; Bouwstra *et al.* 2017; Verhagen *et al.* 2017). Currently, most studies limit their findings to an association in time between the presence of AIV and arrival of migratory birds in the area (e.g. the HPAIV H7N3 virus in poultry in Pakistan in December 1994 was associated with the arrival of migratory birds) (Naeem 2003). Thus, a combination of intensification of the poultry industry, poultry trade and close contact between wild and domestic birds creates a vulnerable system.

## ZOONOTIC AIV H7 INFECTIONS AND RELATED AMINO ACID SUBSTITUTIONS

Human infections caused by AIV H7 are placed on the top priority list among other zoonotic AIVs, including HPAIV H5N1 and LPAIV H9N2 (WHO 2018b). To date, reported human infections with AIV H7 have been caused by LPAIV H7N2, H7N3, H7N4, H7N7 and H7N9 and HPAIV H7N3, H7N7 and H7N9 (Fouchier *et al.* 2004; Abdelwhab, Veits and Mettenleiter 2014; Ke *et al.* 2017) (Table 2). More than 1600 LPAIV H7 human infections have been reported, in contrast to 840 HPAIV H5N1 and 55 LPAIV H9N2 human infections (WHO 2018c, 2019b; Ali *et al.* 2019). The ancestral viruses of LPAIV and HPAIV H7 isolated from humans were found in a variety of bird species, both wild and domestic (Elbers *et al.* 2004; Fouchier *et al.* 2004; Lam *et al.* 2013; ProMED-mail).

### H7N9

Since the emergence of LPAIV H7N9 in China in March 2013, a total of 1567 laboratory-confirmed human cases (case fatality rate 615/1567, 39%) have been reported, including 40 instances of two to three human cases infected by a shared source (as of March 2019) (WHO 2019a). Human infections were acquired directly from poultry, which shed LPAIV H7N9 with no clinical signs of disease. Most of these transmission events from poultry to humans occurred in association with LBMs (Wu *et al.* 2017b). The vast majority of human H7N9 cases were detected in China, with two main epicentres: cities in the Yangtze River Delta and Pearl River Delta areas. In addition, cases have been detected in Malaysia (one case, imported from China) and Canada (two cases, imported from China) (WHO 2018b). Since 2013, there have been repeated waves of human infection of LPAIV H7N9 (Guo *et al.* 2018; FAO 2019), occurring mostly in the winter and spring months. Between March 2013 and March 2019, there have been seven waves of infection, although there have been no human, environmental or animal cases associated with the seventh wave to date (Fig. 1). Zoonotic LPAIV H7N9 orig-

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**Table 2.** Reported human infections with AIVs of the H7 subtype from 1959 to 2018.

| Pathotype | Subtype | Country | Year | Symptoms | Cases (deaths) | Reference |
|---|---|---|---|---|---|---|
| HP | H7N7 | USA | 1959 | Respiratory | 1 | (Belser *et al.* 2009) |
| HP | H7N7 | Australia | 1977 | Conjunctivitis | 1 | (Belser *et al.* 2009) |
| LP | H7N7 | USA | 1979 | Conjunctivitis | 4 | (Webster *et al.* 1981) |
| LP | H7N7 | UK | 1996 | Conjunctivitis | 1 | (Kurtz *et al.* 1996) |
| LP | H7N2 | USA | 2002 | Respiratory | 1 | (Terebuh *et al.* 2018) |
| LP | H7N2 | USA | 2003 | Respiratory | 1 | (Prevention 2004) |
| HP | H7N7 | Netherlands | 2003 | Conjunctivitis, pneumonia, fatal respiratory failure | 89 (1) | (Fouchier *et al.* 2004) |
| HP | H7N3 | Canada | 2004 | Conjunctivitis | 2 | (Tweed *et al.* 2004) |
| LP | H7N3 | UK | 2006 | Conjunctivitis | 1 | (Nguyen-Van-Tam *et al.* 2006) |
| LP | H7N2 | UK | 2007 | Conjunctivitis | 4 | (Editorial-team-Collective 2007) |
| HP | H7N3 | Mexico | 2012 | Conjunctivitis | 2 | (Lopez-Martinez *et al.* 2013) |
| HP | H7N7 | Italy | 2013 | Conjunctivitis | 3 | (Puzelli *et al.* 2014) |
| LP | H7N2 | USA | 2016 | Respiratory | 1 | (Marinova-Petkova *et al.* 2017) |
| LP / HP | H7N9 | China | 2013-2018 | Severe illness, fatal respiratory failure | 1567 (615) | (WHO 2018a) |
| LP | H7N4 | China | 2018 | Cough, fever, chills | 1 | (Tong *et al.* 2018) |

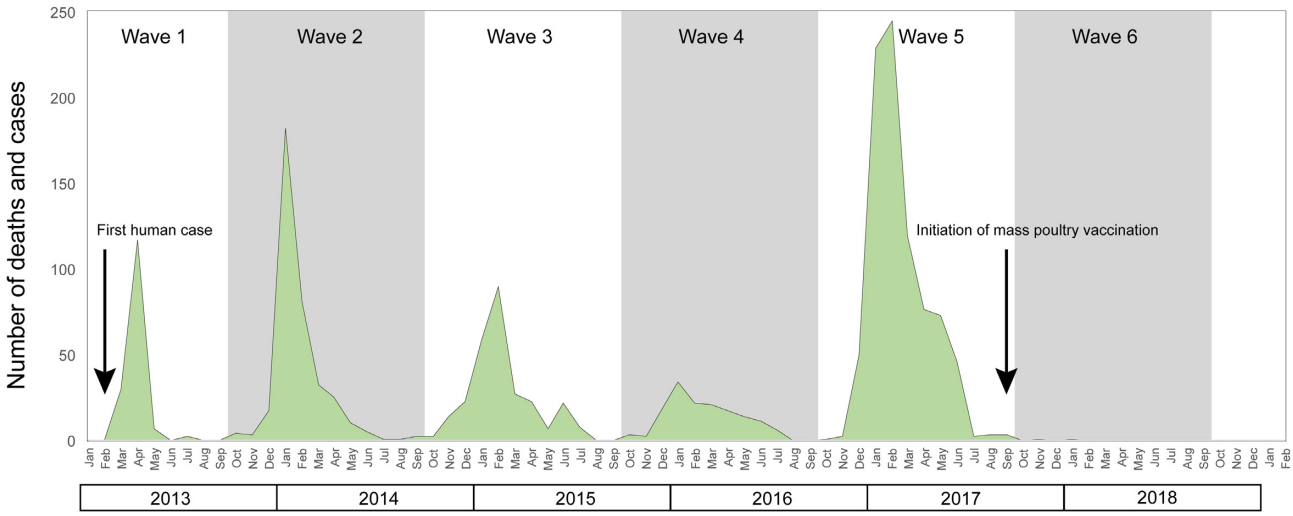


**Figure 1.** Seasonal waves of human infections with low pathogenic AIV H7N9 in China from 2013 to 2018. Data taken from Flutrackers.com (FluTrackers 2019), collated by Ian Mackay (Mackay 2019).

inated from multiple reassortment events between three different AIV subtypes: H7N7 (HA), H7N9 (NA) and H9N2 (internal segments) (Lam *et al.* 2013) (see the section titled 'Reassortment of LPAIV and HPAIV H7N9 affecting LBMs and humans in China'). Most AIV H7N9 cases reported have been of low pathogenicity; however, one fatal case of a patient in the Guangdong province in China was reported in January 2017 (fifth wave) with an H7N9 that had an MBCS at its HA cleavage site representing the first human HPAIV H7N9 case (Ke *et al.* 2017) (Fig. 1). In total, 32 human cases were identified to have HPAIV H7N9 (FAO 2019).

In response to the emergence of HPAIV H7N9, the closure of LBMs in several Chinese cities implemented in early waves, has shown a significant impact on the virus spread and reduced the incidence of human cases associated with LPAIV H7N9 (Fournie and Pfeiffer 2014); in September 2017, vaccination of poultry was initiated using a bivalent H5/H7 vaccine. This may consolidate the impact of closure of LBM in limiting LPAIV H7N9 spread in both poultry and humans (Zeng *et al.* 2018; Wu *et al.* 2019).

## H7N7

LPAIV H7N7 was detected in a 43-year-old woman with conjunctivitis in the UK in 1996 (Kurtz, Manvell and Banks 1996). Human infections with HPAIV H7N7 have been mostly associated with conjunctivitis, and have been reported in 1959, 1977 and 1979 (Webster *et al.* 1981; Belser *et al.* 2009). In the spring of 2003, HPAIV H7N7 was detected in commercial poultry farms in the Netherlands, resulting in a massive, country-wide poultry outbreak. During the outbreak, 89 humans became infected with HPAIV H7N7. The majority of the patients suffered from conjunctivitis and a few had mild influenza-like illness. This outbreak included the first reported human death (a veterinarian) due to HPAIV H7N7 infection (Fouchier *et al.* 2004). The genes of the Dutch HPAIV H7N7 were of avian origin, genetically related to previously reported LPAIVs in ducks in the same region in 2000 (Table 1) (Fouchier *et al.* 2004). In 2013, three human cases of HPAIV H7N7 were detected among poultry workers in Italy associated with the culling of HPAIV H7N7 infected poultry and clinical signs were limited to conjunctivitis (Puzelli *et al.* 2014).

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Genetically, all gene segments of this virus were closely related to the H7N7 viruses isolated from affected chicken farms (Puzelli *et al.* 2014).

### H7N4

In February 2018, LPAIV H7N4 was isolated from a 68-year-old woman in Jiangsu Province in China (Tong *et al.* 2018), representing the first human LPAIV H7N4 case. It was suggested that the infection was acquired after direct exposure to poultry in an LBM (Tong *et al.* 2018). The genes of the LPAIV H7N4 were of avian origin (Gao *et al.* 2018; Tong *et al.* 2018).

### H7N3

LPAIV H7N3 has been detected in one poultry worker associated with an LPAIV H7N3 outbreak in poultry in the UK in 2006. Symptoms were limited to conjuntivitis (Nguyen-Van-Tam *et al.* 2006). There is serological evidence of a separate LPAIV H7N3 in poultry workers during the H7N3 epizootic in Italy in 2003 (Puzelli *et al.* 2005), although no symptoms were reported at that time. HPAIV H7N3 caused two human infections in British Columbia, Canada, which were laboratory-confirmed and isolated in 2004 (Tweed *et al.* 2004). In 2012, two laboratory-confirmed mild infections of humans with HPAIV H7N3 were reported to be associated with exposure to infected poultry in Jalisco, Mexico (Lopez-Martinez *et al.* 2013).

### H7N2

Evidence of human infections with LPAIV H7N2 was first reported based on a positive serological analysis of workers with a history of exposure to infected poultry in the USA in 2002 (Terebuh *et al.* 2018). LPAIV H7N2 was first isolated from an immunecompromised man who suffered from fever and acute respiratory symptoms in the USA in 2003 (Ostrowsky *et al.* 2012). LPAIV H7N2 was also detected in four humans showing clinical signs, including conjunctivitis and influenza-like illness, in Wales, UK, in 2007 (Editorial-team-Collective 2007). In December 2016, LPAIV H7N2 led to an outbreak in a cat shelter in the USA, during which a veterinarian exposed to the infected cats in this animal shelter became infected, representing the first human infection with LPAIV H7N2 in North America since 2003 (Belser *et al.* 2017; Marinova-Petkova *et al.* 2017).

### Amino acid substitution of H7 viruses associated with mammalian adaptation

While H7N9 is an avian-adapted virus, a main concern is the emergence of sustained human–human transmission; amino acid substitutions are required for the adaptation from avian to mammalian hosts (de Vries *et al.* 2017; Shao *et al.* 2017). Regardless of subtype, key amino acid substitutions are critical in (1) changing receptor specificity from avian-type to human-type receptors, $\alpha$2.3-to $\alpha$2.6-linked sialic acids (SAs), respectively; (2) increased HA thermostability and pH stability; (3) increased replication of influenza viruses *in vitro* and *in vivo* at temperatures equivalent to those of the mammalian upper respiratory tract; and (4) changing the expression of RNA transcripts by the viral polymerase complex, resulting in increased replication (Wang *et al.*2014b). Many of these changes were described as early as 2014, and Wang *et al.* proposed a system of 'genetic tuning' in the emergence of H7N9, whereby there were continuous substitutions mediating adaption to mammalian hosts (Wang *et al.* 2014a). To date, substitutions falling into all of the above categories have been described in both field isolates and animal experiments, suggesting it is imperative to continue to closely monitor the evolution of this virus (Table S2, Supporting Information).

## SPATIAL DIFFUSION OF H7 VIRUSES

As with other AIV subtypes, there is strong evidence of geographically structured viral diffusion of H7, both on a global and a regional scale. Using a dataset of 606 nucleotide sequences of the full HA gene segment of LPAIV and HPAIV H7 isolated from avian and mammalian hosts [obtained from the Genbank and Global Initiative on Sharing All Influenza Data (GISAID) platforms], Bayesian phylogeographic analysis was conducted to investigate the spatial diffusion and routes of transmission of this subtype (see Supporting Information for details). From a global perspective, currently circulating AIV H7 may have expanded from Europe to East Asia, and represent a separate gene pool from AIV H7 in North America (Figs 2 and 3). Across all AIV subtypes and segments, there are two different geographically segregated gene pools: North American and Eurasian. This genetic segregation is driven by patterns of bird migration, wherein waterfowl, the main reservoir for AIVs, tend to have migratory patterns within each continental region (Olsen *et al.* 2006). There are, of course, exceptions, often driven by transhemispheric introductions followed by a competitive exclusion of previously circulating lineages (Bahl *et al.* 2009). Based on online databases (Shu and McCauley 2017; GenBank 2019), the most common H7 subtype combinations in the European and North American wild bird reservoirs are H7N7 and H7N3, respectively, whereas there has been a transition in the East Asian reservoir from H7N7 prior to 2013 to H7N9 thereafter (see Table S3, Supporting Information). These regional-specific dominating HA–NA subtypes are highly correlated to, and hence feed, the evolution of other subtypes within each reservoir (see Fig. S2, Table S4, Supporting Information) (Banks *et al.* 2000; Escalera-Zamudio *et al.* 2018). This spatially independent evolution may also result in the parallel evolution of HPAIVs from their LPAIV counterparts (Escalera-Zamudio *et al.* 2018). That is, we see the genesis of HPAIV H7 as a reoccurring event, rather than a single transition to HPAIV H7 followed by a global spread (see the section titled 'Wild–domestic bird interface of H7 viruses').

Within Eurasia, AIV H7N7 sampled in European countries are more likely to constitute the ancestral viruses from which new lineages have evolved compared to AIV H7N7 isolated in other regions, linking viruses sampled in European and East Asian countries and guiding the worldwide viral diffusion. There is an important caveat here, whereby H7N7 sequences from Europe (2002–2009) predate the ever-increasing number of sequences generated in China since 2013 with the emergence of LPAIV H7N9. Within Asia, AIV H7N7 in Japan and South Korea drives the spatial transmission pattern, with bidirectional gene flow between the two countries, and diffusions to the Yangtze River area of China (see Fig. S1, Tables S5 and S6, Supporting Information). The substantial H7N9 human infections occurring in China since 2013 (see the section titled 'H7N9') correspond in time and space with the shift of the most prevalent subtype in East Asia from H7N7 to H7N9. Both Yangtze River and Pearl River Delta regions have a relatively high probability of being the origin of viruses within China, indicating the establishment of two epicentres (Wang *et al.* 2016; Li *et al.* 2018). In particular, AIVs H7N9 isolated in the Yangtze River area form significant

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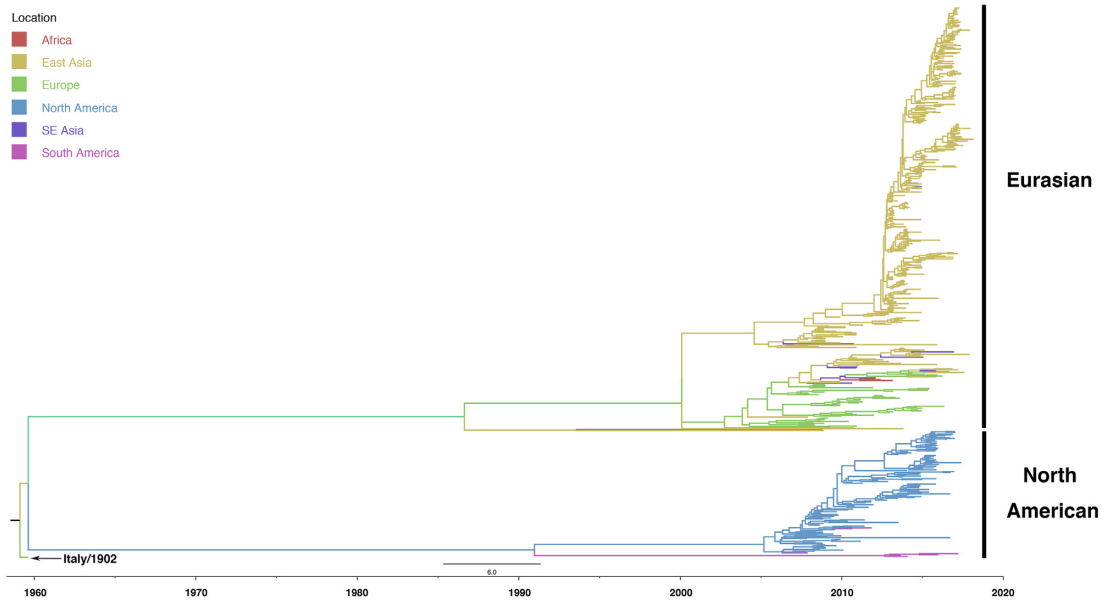


**Figure 2.** Phylogenetic relationship of the HA gene segment of H7 AIVs isolated from different geographical regions. The whole HA gene segment was used from viruses reported from 2008 to 2018, with ancestral virus A/chicken/Brescia/1902 (H7N7).The locations of virus isolation are classified into different regions. Branches are distinguished by different colours based on the region of viruses.

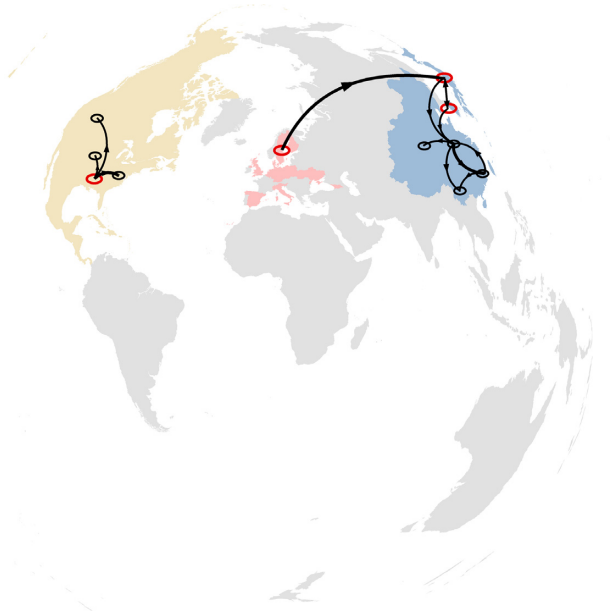

**Figure 3.** Hierarchical transmission network of H7 AIVs in the period from 2008 to 2018. Based on available sequences, three viral reservoirs located in Europe (pink), East Asia (blue) and North America (yellow) were identified (as shown in Fig. 2) and indicated here. Statistically supported pathways among regions on the global level and among subregions within two viral reservoirs are shown by arrow lines. The corresponding pairwise locations are shown using circles. Pathways with the highest significance and locations with the highest probability as transmission origins are highlighted by thick arrow lines and red circles.

transmission routes to other parts of China, including Southern, Southwest, Northeast and the Yellow River areas. Of these diffusions, dissemination from the Yangtze River to the Pearl River Delta region is more probable than from the Pearl River Delta area to the Yangtze River Delta (see Table S4, Supporting Information). In contrast, the viral evolution and gene flow within the North American reservoir depicts a more compact pattern, which can be characterised by expansions from the Mississippi to other flyways (see Fig. S2, Tables S5 and S6, Supporting Information). Differences in transmission patterns between Asia and North America of AIV H7 may be due, in part, to the specific epidemiological and socioeconomic conditions of each region, indicating its role in the maintenance of virus on the local scale. Based on the intensive poultry population and high demand/consumption of live poultry in Southern and Eastern China, LBMs and poultry trading have been considered a major driver in the dissemination of the most prevalent AIV subtypes, including H5N1, H5N6, H7N9 and H9N2 viruses (Soares Magalhaes *et al.* 2012; Jin *et al.* 2014; Zhou *et al.* 2015; Bi *et al.* 2016). Correspondingly, the higher density of commercial poultry farms in the Mississippi flyways also serves as one of the prerequisites for the increased number of poultry outbreaks (Belkhiria, Alkhamis and Martinez-Lopez 2016) and, hence, viral transmissions.

## EVOLUTIONARY GENETICS OF AIV H7

### Reassortment of LPAIV H7 in wild birds

Reassortment is the process whereby, following co-infection, viral progeny may contain various combinations of gene segments from the different parental viruses. Thus, given an infection with two AIVs, each with eight segments, 256 different genetic progenies are theoretically possible, generating a significant viral diversity. In wild birds, reassortment of LPAIVs is frequent and occurs among co-circulating viruses (Wille *et al.* 2013).

As noted in the section titled 'Wild–domestic bird interface of H7 viruses', H7 is a naturally occurring virus in wild birds, and is consistently detected in surveillance schemes, albeit at low frequencies (Sharp *et al.* 1997; Munster *et al.* 2007; Wilcox *et al.* 2011; Latorre-Margalef *et al.* 2014). Reassortment of LPAIV H7 from wild birds has been assessed in two studies. First, it was demonstrated that like other LPAIV subtypes, there is large incongruence across phylogenetic trees of each segment, and genome constellations with the H7 HA are transient rather than stable (Xu *et al.* 2016). Lu *et al.* further demonstrated that LPAIV

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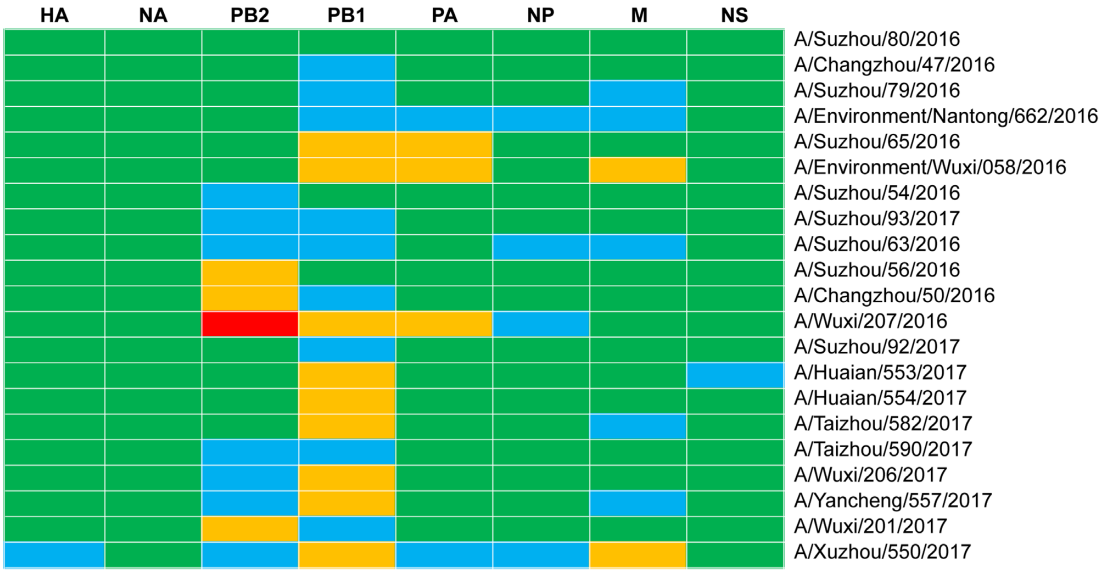


**Figure 4.** Reassortment patterns with H7 low pathogenic AIVs. Co-circulation of 21 different genome constellations of H7N9 in humans and LBMs of China in 2016–2017. Genome segments are arranged by HA and NA, followed by the 'internal' segments in order of size. Each colour corresponds to a unique genetic lineage. Adapted from (Qi *et al.* 2018a).

H7 reassort no more frequently or infrequently than other AIV subtypes. Interestingly, reassortment rates were correlated to prevalence in anseriform (waterfowl) vs gallinaceous (chickens, quail) birds, such that LPAIV H7N3, found mostly in gallinaceous birds, had a lower reassortment rate than LPAIV H7N7, found mostly in anseriform birds (Lu, Lycett and Brown 2014).

## Reassortment of LPAIV and HPAIV H7N9 affecting LBMs and humans in China

The genesis of LPAIV H7N9 in China is a story of reassortment. Prior to the emergence of H7N9, H9N2 had been circulating in domestic birds in Asia for many years (Li *et al.* 2005; Bahl *et al.* 2016). It has been hypothesised that LPAIV H7N9 was the result of numerous reassortment events, whereby the six internal protein genes were derived from at least two separate H9N2 lineages, with wild-bird origin H7 and N9 segments (Gao *et al.* 2013; Wu *et al.* 2013; Lam *et al.* 2013; Pu *et al.* 2015; Wang *et al.* 2016). Despite the maintenance of the HA and NA subtypes, LPAIVs H7N9 detected in LBMs and human infections have a high degree of diversity in the internal genes. Cui *et al.* (2014) described a remarkable diversity, reporting 27 genotypes within three months of emergence. They further proposed a dynamic reassortment model for LPAIV H7N9 evolution (Cui *et al.* 2014). This reassortment and diversity have not abated since the first wave, although the number of genotypes has decreased. An analysis by Qi *et al.* demonstrated that in the fifth wave there were 18 genotypes present in 41 sequenced viruses from the Yangtze River Delta clade (Ding *et al.* 2017; Qi *et al.* 2018a,b). This diversity is likely maintained due to reassortment combined with the diversity of AIV in poultry markets and farms (Shi *et al.* 2018). Indeed, there has been reported reassortment between H5N6, H6N6 and H7N9, suggesting not all internal genes are derived from the H9N2 internal gene cassette (Jin *et al.* 2017; Wu *et al.* 2017a) (Fig. 4).

In mid-2016, HPAIV H7N9 emerged in mainland China in poultry. Phylogenetic analysis demonstrated that the HA and NA sequences of these HPAIVs clustered together. However the internal genes did not cluster together, suggesting that these HPAIVs H7N9 had undergone complex reassortment with LPAIVs H7N9/H9N2 and that multiple genotypes were co-circulating in poultry (Shi *et al.* 2018; Qi *et al.* 2018a,b). Alternatively, this was due to a number of independent transitions from LPAIV to HPAIV.

Despite continued circulation for five years and presumably high levels of reassortment of the internal genes, the HA–NA subtype combination has remained stable. However, this lineage of H7 has been with N9 for a number of years, and other lineages of LPAIV H7 are indeed promiscuous. As outlined in the WHO Candidate Vaccine Virus report (2018/10) and previous studies, LPAIV H7N6 in China and Chile, and LPAIV H7N3 in Japan, has been evolved from the H7N9 gene pool (Wu *et al.* 2017a; WHO 2018a; Jimenez-Bluhm *et al.* 2019; Shibata *et al.* 2019). Similar recent evidence has been noted with H5 viruses (2.3.4.4 lineage), where a number of different NAs have been detected (Claes, Morzaria and Donis 2016).

## Evolutionary rates of H7 viruses

In addition to genetic reassortment, AIVs evolve through genetic drift. Genetic drift is the process of mutation, which is due to an error-prone RNA-dependant RNA polymerase, which lacks proof-reading ability, resulting in genetic changes. Influenza A viruses have an extraordinary rapid rate of mutations, with an average of $3.41 \times 10^{-3}$ substitutions per site per year (subs/site/year) (Chen and Holmes 2006). To put this in perspective, the rate of RNA virus mutation is a million times greater than that of vertebrates (Pybus and Rambaut 2009). Different factors can affect nucleotide substitution rates within the viral genome. For example, Worobey *et al.* demonstrated that influenza A viruses have different mutation rates in different broad host groups (Worobey, Han and Rambaut 2014), and, crucially, that there are different rates between poultry and wild birds (Fourment and Holmes 2015). Lebarbenchon, Brown and Stallknecht (2013) found that rates obtained for viruses circulating in wild birds were higher than for those isolated from domestic birds, albeit this study was undertaken prior to the emergence of LPAIV H7N9 (Lebarbenchon and Stallknecht

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2011). Ward *et al.* (2013) showed no differences in evolutionary rates of AIVs H7 across different host types (waterfowl vs galliformes), and, furthermore, found no difference between LPAIVs and HPAIVs H7 (Ward *et al.* 2013). A study by Rejmanek *et al.* (2015) showed that the nucleotide substitution rate of H7N7 and H7N3 ($11.62 \times 10^{-3}$ subs/site/year and $8 \times 10^{-3}$ subs/site/year, respectively) was significantly higher than that of LPAIV H3N8, a very common LPAIV subtype combination found in wild birds ($1.43 \times 10^{-3}$ subs/site/year) (Rejmanek *et al.* 2015). Focussing on only H7N9, there are different rates across the different reported lineages (Lu *et al.* 2018; Zhu *et al.* 2018). These rates range from 0.60 (lineage A) to 3.12 (lineage C2) adaptive substitutions per year, suggesting a faster adaption in the 2C clades compared to the A and B lineages (Lu *et al.* 2018). Furthermore, the evolutionary rate of the 2C clades is higher than for seasonal human influenza (H1N1, 1.02 adaptive substitutions per year; H3N2, 1.52 adaptive substitutions per year) (Bhatt, Holmes and Pybus 2011). Despite high rates of substitutions, it is mutations occurring at key regions, many of which are adjacent to or in the receptor binding site of the HA protein that allows for an antigenic drift, as shown for human H3N2 viruses (Koel *et al.* 2013). Antigenic drift allows for escape from antibody-mediated neutralisation acquired following infection (Koel *et al.* 2013) or vaccination (Lee, Senne and Suarez 2004; Escorcia *et al.* 2008; Nguyen *et al.* 2017). As such, one important concern with the reports of elevated rates, particularly in H7N9, is the potential of these viruses to escape from the vaccine-induced immunity, which is an ongoing problem in global efforts to contain HPAIV H5 (Connie Leung *et al.* 2013). Nevertheless, a conserved motif at the antigenic site A was found in the HA of all H7 sequences. It has been shown that mouse monoclonal antibodies produced from hemagglutinin of A/Shanghai/1/2013 (H7N9) do cross-react with different H7 isolates of the North American and Eurasian lineages, including the recent Chinese H7N9 virus from 2016–2017 (Stadlbauer *et al.* 2018). This suggests that the existing H7N9 vaccine candidate could protect against divergent H7 strains (Krammer *et al.* 2014; Tan *et al.* 2016).

## CONCLUSION AND FUTURE PERSPECTIVES

The emergence of HPAIV H5 of the goose/Guangdong lineage put AIV, colloquially referred to as 'Bird Flu', on the map. These viruses caused the destruction of millions of domestic birds with large socioeconomic ramifications. However, these viruses resulted in limited human cases, which is in stark contrast to AIV H7. Given repeated spillover into mammals, particularly humans, there has been an increasing concern that human AIV H7 infections may lead to local epidemics or, given transmissibility between humans, a global pandemic. Influenza pandemics in the last century, for example, H2N2/1957 and H3N2/1968, arose from reassortment events between two or more viruses, including AIVs (Fuller *et al.* 2013). Therefore, even if AIV H7 with a complete avian genome never does become transmissible between humans, reassortment of human seasonal influenza with AIV H7 may allow the emergence of a new influenza virus variant in the human population (Zhu *et al.* 2013; Zhang *et al.* 2015; Huo *et al.* 2017).

The current reservoir for LPAIV H7N9 is commercial poultry, particularly in LBMs in China, despite ancestral LPAIVs circulating among wild birds. It has been suggested that LPAIV H7N9 emerged in LBMs (Wu *et al.* 2017b), and in the initial years, it was entirely restricted to cities. As such, combined with other factors, these viruses have not expanded into wild birds, and the control and surveillance in LBMs played a crucial role in controlling this virus. To control LPAIV H7N9 and other emerging AIVs, it is imperative to reconsider poultry management and practices on a global scale. Measures such as increased biosecurity and hygiene controls throughout the entire poultry supply chain and improved biosecurity in live poultry retail markets may help to reduce the risk for human exposure to AIV, and further to other zoonotic pathogens. More drastically, poultry vaccination strategies are crucial in decreasing the viral burden, therefore lowering potential human contact with poultry viruses, although imperfect vaccination does drive viral evolution. Interventions in the reservoir are crucial to limit zoonotic spillover; of note is that the seventh wave of H7N9 has not materialized in poultry, the environment or humans, and this may be attributable to strict LBM control and massive poultry vaccination schemes, which may also be important in decreasing the viral burden, therefore lowering potential human contact with poultry viruses. This clearly demonstrates that a 'One Health' approach—including wildlife, domestic animal and human health—is critical in controlling zoonotic viruses, such as AIV H7.

To get ahead of AIV H7, we will need to continue surveillance of birds, the environment and humans. From surveillance, virus characterisation and timely sharing of virus sequence data remains imperative, which can be integrated into models of virus epidemiology and evolution. Timely data sharing has played a central role in managing and understanding outbreaks, with notable examples in the outbreak of Zika Virus in the Americas (De Carvalho *et al.* 2016) and Ebola Virus in West Africa (Diehl *et al.* 2016, Urbanowicz *et al.* 2016). Real-time epidemiological and sequence data were rapidly fed into models to demonstrate transmission patterns and virus evolution, and platforms such as Nextstrain (Hadfield *et al.* 2018), which allows for dissemination to researchers and the general public. To better understand the interspecies transmission of AIV H7, comparative *in vitro* and *in vivo* studies are required to reveal H7 virulence, pathogenesis, transmission and to identify genetic markers (van Riel *et al.* 2006; Koel *et al.* 2013), which are key to the interpretation of sequence and surveillance data. Studies from ecology are crucial in better describing the host range and bird migration patterns and strategies. Studies tracking wild birds have demonstrated their extraordinary capacity to link broad geographical regions and potentially disperse viruses (Gilbert *et al.* 2010; Van Toor *et al.* 2018). A multifaceted One Health approach is imperative for creating early warning systems to detect emerging, re-emerging and endemic viruses, particularly AIVs, that are prone to cross-species barriers.

## SUPPLEMENTARY DATA

Supplementary data are available at *FEMSRE* online

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