

REVIEW

Endemicity of H9N2 and H5N1 avian influenza viruses in poultry in China poses a serious threat to poultry industry and public health

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Abstract The H9N2 and H5N1 avian influenza viruses (AIVs) have been circulating in poultry in China and become endemic since 1998 and 2004, respectively. Currently, they are prevalent in poultry throughout China. This endemicity makes them actively involved in the emergence of the novel lineages of other subtypes of influenza viruses, such as the well-known viruses of the highly pathogenic avian influenza (HPAI) H5N2 and the 2013 novel H7N7, H7N9 and H10N8 subtypes, thereby threatening both the poultry industry and public health. Here, we will review briefly the prevalence and evolution, pathogenicity, transmission, and disease control of these two subtypes and also discuss the possibility of emergence of potentially virulent and highly transmissible AIVs to humans.

Keywords avian influenza virus, H9N2, H5N1, novel viruses, public health

waterfowl, particularly Anatidae (i.e., ducks, geese and swans) and Laridae (gulls and terns)^[1–6]. However, these viruses can occasionally infect other host species, including wild birds, terrestrial poultry, various kinds of mammals and human beings^[2,7–11].

The genome of the IAVs contains 8 gene segments encoding at least 18 proteins, including eight initially-identified proteins (PB2, PB1, PA, HA, NP, NA, M1 and NS1), two splicing variants of the M and NS genes (M2 and NS2)^[12–14], several previously identified accessory proteins, PB1-N40^[15], PB1-F2^[16], PA-X^[17], M42^[18], NS3^[19], PA-N155 and PA-N182^[20,21], and the more recently discovered PB2-S1^[22]. Undoubtedly, the presence of these accessory proteins further complicates the pathogenesis of IAVs. Also, the segmented genome feature of influenza viruses allows genome reassortment between different viruses, generating novel influenza viruses with pandemic potential. Since AIVs of the H9N2 and H5N1 subtype were first detected in China in the mid-1990s, new subtypes keep emerging due to the reassortment between different virus types^[23,24]. In the past 5 years, more lethal, pandemic candidates and/or pandemic subtypes of IAVs have been reassorted and emerged in wide geographical localities. These are represented by the Asian H5N1 variants of highly differentiated clades, the pandemic 2009 H1N1 virus and the new 2013 H7N9 subtype, which all posed a serious threat to human beings^[25–31].

In recent years, multiple HA subtypes of AIVs have been circulating in domestic poultry in China, including the H1, H2, H3, H4, H5, H6, H7, H9, H10, and H11 subtypes of viruses^[32]. However, the H9N2 and H5N1 AIVs are the most prevalent subtypes and have spread to most areas in China^[33]. The endemicity of these two subtypes in domestic poultry greatly increased the possibility of their reassortment with other subtypes of AIVs, leading to the generation of potential pandemic

1 Introduction

Influenza A viruses (IAVs) belong to the family of Orthomyxoviridae and are subtyped on the basis of the composition of the two major surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA). So far, at least 16 hemagglutinin subtypes (H1 to H16) and 9 neuraminidase subtypes (N1 to N9) have been detected, of which the majority of possible combinations have been isolated from avian species. The primary natural host reservoir of avian influenza viruses (AIVs) are wild

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virus, and thus poses a great threat to both the poultry industry and public health. Therefore, this review will focus on the situation of H5 and H9 viruses in China in recent years, describing their epidemiology, pathogenicity, transmission as well as disease control.

2 Prevalence and evolution of H9N2 AIVs

H9N2 AIVs were first isolated from diseased chickens in Guangdong Province in South China, in 1994^[23], and later in domestic poultry in other provinces of China^[34–37]. Since 1998, large scale vaccination of the flocks was carried out to reduce the impact of H9N2 infection in chickens. However, systematic surveillance of AIVs shows that H9N2 subtype influenza viruses still prevailed in chickens in mainland China from 1998 to 2014^[36,38–42]. In addition, the viruses have become much more complicated than 17 years ago. Since the first isolation in 1994, the H9N2 viruses have evolved into more than 102 genotypes and have spread to most poultry-raising areas of China^[32,33,43]. In addition, these viruses can reassort with the circulating H5N1 viruses, resulting in more than 13 genotypes of novel reassortant H9N2 influenza virus^[32] (Fig. 1). This phenomenon is very common due to coexistence of the H9N2 and H5N1 viruses in the same area of China. Such reassortments may directly or indirectly play a role in the emergence of the potential pandemic virus that threatens human health.

Moreover, among the identified 102 genotypes of the H9N2 viruses, genotypes S (also known as genotype 57) appears to have a selective advantage in chickens in recent years^[40,44]. The genotype S virus was first detected in chickens in Jiangsu and Jiangxi Provinces in 2007, and it has been the predominant genotype in circulation throughout China ever since 2010^[40,44]. Owing to the high prevalence and wide host range of this genotype, the genotype S viruses can readily donate their internal genes to other IAVs in China, resulting in the generation of novel reassortant HPAI H5N2, H7N7, H7N9, and H10N8 viruses^[31,40,45] (Fig. 1). The acquisition of the gene segments from the H9N2 S genotype viruses may probably enable the H7N9 and H10N8 virus to survive and be repeatedly transmitted among poultry before adapting to humans. Moreover, the H7N9 and H10N8 viruses actively reassort with circulating H9N2 virus and other AIVs to generate multiple genotypes of H7N9 and H10N8 viruses^[31,46,47] (Fig. 1).

3 Prevalence and evolution of H5N1 AIVs

AIVs of the H5N1 subtype was first detected in sick geese in Guangdong Province in 1996^[24,48,49]. In 1997, H5N1 reassortant viruses harboring the HA gene from A/goose/Guangdong/1/96 (GS/GD/1/96)-like viruses and the other genes from H6N1 and/or H9N2 viruses caused lethal outbreaks in poultry and humans in Hong Kong^[50]. Since

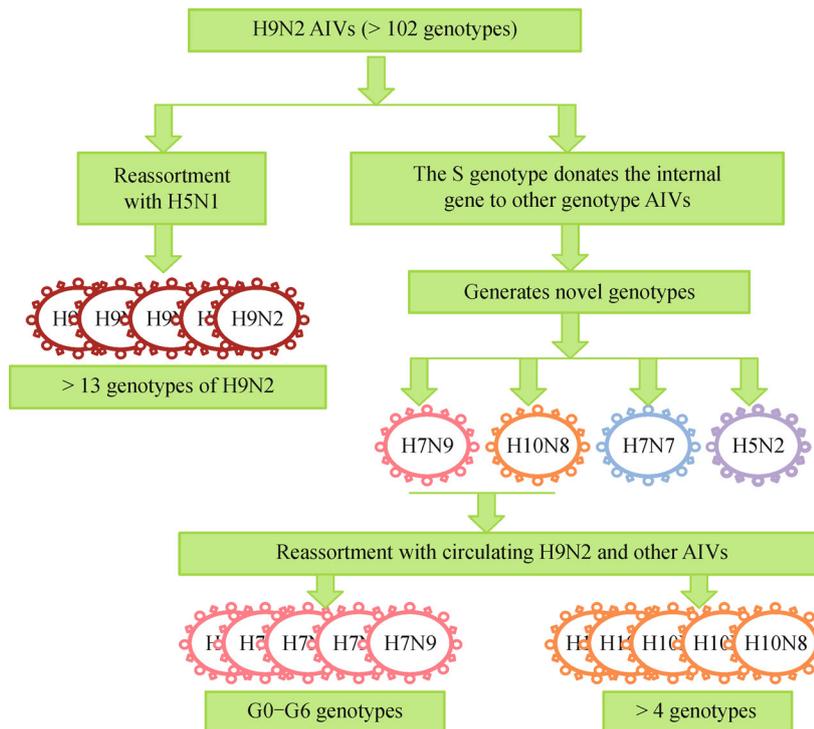


Fig. 1 The role of H9N2 avian influenza virus in the genesis of novel viruses in China. Viral subtypes are given as circles; different colors represent different types of viruses.

then, long-term active surveillance of influenza viruses in poultry has been performed, and multiple subtypes of influenza viruses have been detected in chickens, geese and ducks in China^[36,51,52].

In the past 20 years, the HA gene of the highly pathogenic H5N1 AIVs has evolved frequently by point mutation, leading to a number of genetically and antigenically distinct clades and subclades. Currently, the virus have evolved into at least 10 major clades (i.e., clades 0–9) and other multiple second, third, fourth and fifth-tier subclades based upon their variation of the HA genes^[53]. Notably, in recent years, the most prevalent clades in China, including clade 2.3.2, 2.3.4 and 7.2, have gained ecologic niches and continued circulating by further evolving into new sub-clades, represented by the newly emerged variants of clade 2.3.4.4 (formerly defined as clade 2.3.4.6)^[53,54]. On the other hand, the H5N1 viruses can also reassort with circulating H9N2 viruses and other AIVs, resulting in more than 47 genotypes^[55–61] (Fig. 2). Thus, the currently circulating highly pathogenic H5N1 viruses represent a diverse group of viruses. More importantly, the virus has evolved a novel mechanism for generating HPAI H5 viruses of various NA subtypes with potential threat to the public in China through reassortment of endemic HPAI H5N1 viruses from clade 2.3.2.1, clade 2.3.4.4 and clade 7.2, typical representatives are H5N2, H5N6 and H5N8^[62–65] (Fig. 2). In addition, these viruses

have been regularly detected in domestic ducks, geese, quail, and chickens, causing great economic losses to the poultry industry^[20,63,64,66–69]. Also, it seems troubling that these novel reassortants bearing the genetic backbone of clade 2.3.4.4 H5N1 variants have been undergoing extensive reassortment with circulating viruses, such as H3, H5, H6, H7, H9, and H11 AIVs, and the resulting novel viruses are becoming increasingly prevalent in domestic birds^[70] (Fig. 2).

4 Pathogenicity of the H9N2 AIVs

The H9N2 subtype avian influenza viruses (AIVs) was first isolated and characterized in turkeys in 1966^[71], then spread to birds^[72–74], pigs and humans^[75–86]. In chickens, H9N2 infection often resulted in respiratory syndrome, declined egg production, immunosuppression and variable rates of morbidity and mortality^[34,36,87–91]. Human infection of H9N2 AIVs generally results in mild respiratory tract inflammation and often goes unnoticed^[75,80,86]. However, infection of swine with H9N2 viruses causes significant morbidity and mortality^[84]. Most of the diseased pigs showed typical respiratory syndrome, including fever, nasal and ocular discharge, coughing and dyspnoea. In some cases, paralysis associated with fatal disease was also observed^[76].

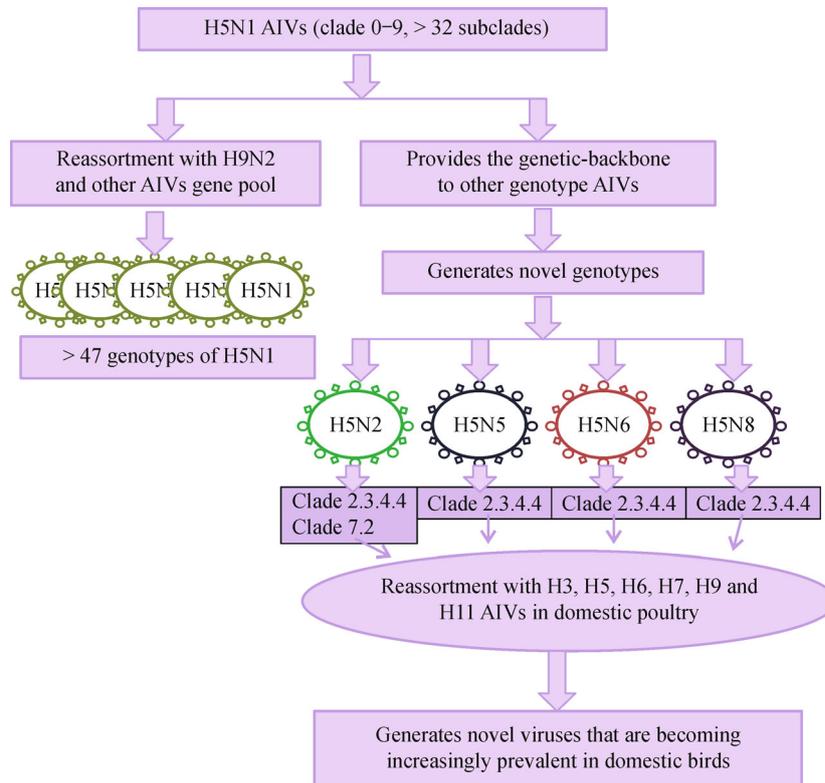


Fig. 2 The role of H5N1 avian influenza virus in the genesis of novel viruses in China. Viral subtypes are given as circles; different colors represent different types of viruses.

In laboratory experiments, studies have shown that the H9N2 viruses were able to infect mice without prior adaptation and resulted in different levels of replication and lethality^[34,43,53,92–96]. Moreover, the molecular basis of mammalian adaptation of the H9N2 AIVs was associated mainly with the PB2^[94,97–99], HA and NA genes^[100]. Experimental studies also have shown that domestic cats and dogs are susceptible to H9N2 AIVs^[101,102], thus may serve as host species contributing to the adaptation of H9N2 viruses in mammals. In ferrets, H9N2 infection results in high replication and efficient transmission by direct contact^[103] and leads to mild to moderate lesions in lung tissue when infected by H9N2 AIVs with different genomic features^[104]. In guinea-pigs, the H9N2 virus was restricted to the respiratory system and shed at high titers through the nasal tracts^[105]. In a non-human primate model, rhesus macaque was developed to study H9N2 virus infections and clinical signs such as biphasic fever and viral pneumonia were observed^[106]. Other animal models, such as Japanese quail and turkeys^[107], chukar partridges^[108], sparrows^[109], and farmed minks^[110,111], were also confirmed to be susceptible to H9N2 viral infection and might serve as the H9N2 virus carriers, although no death were observed.

5 Pathogenicity of H5 AIVs

In chickens and turkeys, the H5 highly pathogenic AIVs cause systemic disease and high mortality that can reach up to 100%. Other gallinaceous birds produced 75%–100% mortality within 10 days, but may survive longer and present neurological signs^[112]. In its natural host, wild waterfowl, infection with the highly pathogenic avian influenza viruses (HPAIVs) generally, leads to minimal or no disease signs^[113–115]. However, since 2002, accumulating field observations and experimental studies have determined the increased virulence of the currently circulating H5N1 HPAIVs in both waterfowl and wild

birds^[116–130]. Our team previously isolated a highly pathogenic H5N1 strain that exhibited high virulence in chickens, ducks, mice and guinea-pigs^[64]. We have shown that critical amino acids, 101G and 237E in the PA protein, contributed to its high virulence in ducks^[120]. Interestingly, the PA gene also accounts for the high virulence of this H5N1 strain in mice and the amino acid 353R acts as the critical molecular marker^[51].

In addition to the H5N1 subtype, the novel reassortants H5N2, H5N6 and H5N8 viruses (H5N_x) also have attracted a lot of attention. Studies have shown that viruses isolated in China show low to high pathogenicity in chickens; mild to high virulence in ducks; and moderate to highly pathogenicity in mammals (virulence differs among different virus strains)^[63,69,131–135] (Table 1). However, viruses isolated from other countries, such as South Korea, the USA and some European countries, exhibited low to moderate virulence in mammals^[148,151,156,157] (Table 1). In addition, although these viruses are highly pathogenic in chickens, some of them show lower transmissibility and pathogenicity than those of previously-isolated H5N1 HPAIVs^[62,63,131,151,158]. It seems likely that because of the extensive genetic divergence and reassortment between other subtypes, influenza viruses undergo genetic evolution and a change of virulence in the host. Therefore, continuous monitoring along with characteristic analysis of AIVs is needed to predict future changes of these viruses.

6 Transmission of the H9N2 AIVs

The H9N2 virus can be transmitted by airborne droplets to chickens which may account partially for their fast spread among flocks and to individual birds^[66,159,160]. Zhang et al. have shown that most of the H9N2 viruses isolated before 2000 fail to be transmitted efficiently to aerosol contact groups of chickens^[66]. However, a number of viruses isolated from 2001 onwards not only replicate efficiently in the infected chickens but also transmit

Table 1 Virulence of the novel H5N_x reassortants

Virus	Virulence			
	Chickens	Ducks	Mice	Other animal species
H5N1	High ^[56]	Low to high ^[120,123,136,137]	Low to high ^[56,136]	Variability of virulence in migratory waterfowl ^[138] ; Lethal to quails ^[139,140] , budgerigars ^[140] , geese ^[141] , cats ^[8,142] , tigers ^[9,11] and dogs ^[10] ; Nonlethal to guinea-pigs ^[143] , pigs ^[140,144] and pigeons ^[121,145]
H5N2	Low to high ^[63] ; High ^[146,147]	Low to high ^[63]	Low to moderate ^[148] ; Moderate ^[146]	Nonlethal to dogs ^[149]
H5N5	High ^[62,131]	Mild to moderate ^[131]	Moderate ^[62,131]	/
H5N6	High ^[133,134,150]	/	Low ^[151] ; Moderate ^[133]	Lethal to cats and swan geese ^[132] ; Lethal to human ^[152]
H5N8	High ^[131] ; Low ^[153]	Moderate ^[154] ; High ^[135]	Low to moderate ^[148] ; Moderate to high ^[135]	Lethal to quails ^[155] ; Nonlethal to ferrets ^[153,156]

Note: “/” means no reference has reported the associated findings.

efficiently by aerosol contact in chickens^[66]. Zhong et al. further identified that the amino acids 363K in the HA gene and 672L in the PA gene contribute to the airborne transmissibility of the H9N2 AIVs in chickens and they also confirmed the importance of these two residues by evaluating the airborne transmission ability of 18 casually chosen natural H9N2 viruses carrying these two residues in chickens^[160]. Notably, the proportion of strains with both PA 672L and HA 363K increased in 1998, which coincided with the epidemicity of H9N2 viruses in China^[39]. The efficient transmission of the H9N2 virus may further accelerate the reassortment between the H9N2 virus and other subtypes viruses, providing opportunities for emergence of novel influenza viruses that may extend the host range or increase the virulence of the original virus, thereby threatening both the poultry industry and public health.

As for mammalian models, some of the naturally isolated H9N2 AIVs have acquired the ability to transmit efficiently in ferrets by respiratory droplet^[161], by contact and the respiratory droplet route in mice^[162], while others can transmit among cats^[91], guinea-pigs^[163], and ferrets^[103] by direct contact. Therefore, there is an increasing public health concern posed by H9N2 AIVs regarding its potential for host-range extension, virulence enhancement, providing internal genes for novel emerging influenza virus and high transmission efficiency in mammals^[44,80,161,164–166].

7 Transmission of the H5 AIVs

Currently, the naturally isolated H5N1 AIVs have not yet acquired the airborne transmissibility in avian species and mammals. However, experimental studies have shown that the H5N1 viruses can gain the ability for airborne transmission in mammals either by reassortment with human IAVs or by acquiring adaptive mutations in HA and PB2 genes^[167–170]. It was reported that the A/Indonesia/5/2005 avian A/H5N1 influenza virus required as few as five amino acid substitutions^[169] and the A/Vietnam/1203/2004 A/H5N1 influenza virus required four substitutions and reassortment with 2009 pandemic H1N1 virus^[170], to become transmissible via respiratory droplets between ferrets. Also, some of the H5N2 and H5N6 AIVs belonging to clade 2.3.4.4 viruses have acquired the ability to bind both the α -2,3 (avian type) and α -2,6 receptor (human type), and can transmit efficiently in ferrets via the direct contact route^[171,172]. Therefore, there is a high possibility that the H5 virus may integrate both high virulence and effective transmission in mammals and thus pose a serious risk to public health.

8 Disease control

The H9N2 subtype influenza viruses have been constantly

detected in different host species in many countries for several decades^[71–86]. However, their eradication is not a priority for animal disease control in China owing to their low pathogenicity in poultry, which has allowed them to continue to evolve and spread. Since 1998, vaccination with commercially available inactivated H9N2 vaccines, including A/chicken/Guangdong/SS/1994 (Ck/GD/SS/94), A/chicken/Shandong/6/1996 (Ck/SD/6/96), and A/chicken/Shanghai/F/1998 (Ck/SH/F/98)^[39], has been implemented. Although these H9N2 vaccines initially limited the outbreaks and virus spread and reduced the clinical losses, the H9N2 influenza virus continues to circulate in vaccinated chicken flocks and has caused sporadic disease outbreaks^[39,52,66,173–175]. Moreover, the continuous existence and evolution of the H9N2 AIVs in flocks facilitate the genesis of novel subtypes of the influenza virus, such as H7N9, H5N2 and H10N8 virus^[40,44].

For H5N1, most countries use stamping-out programs in poultry to eradicate H5N1 HPAI. However, 15 affected countries (including China) have used vaccination as a part of the control strategy. It has been reported that greater than 113 billion doses of vaccines have been used from 2002 to 2010, five countries/regions have utilized nationwide routine vaccination programs, which account for 99% of vaccine usage: China (90.9%), Egypt (4.6%), Indonesia (2.3%), Vietnam (1.4%), and Hong Kong Special Administrative Region (< 0.01%)^[176]. Since 2004, large-scale vaccination has been conducted for the control of H5N1 HPAIVs infection in poultry in China. While this strategy has been effective in reducing the incidence of H5N1 HPAIVs in poultry and in markedly reducing the number of human cases, it is impossible to vaccinate every single bird due to the enormous poultry population. Moreover, although vaccines can reduce mortality, relieve the clinical symptoms, and decrease viral replication and virus shedding, they cannot eliminate virus infection. Thus, persistent circulation of the virus in birds poses a potential risk of virus spread among poultry flocks and transmission to humans^[136,177–179]. Also, vaccination failure has frequently occurs in vaccinated flocks owing to virus variation. Therefore, in order to keep up with the virus evolution, on-going vaccine development must be a high priority. Taking H5N1 vaccination as an example, it can be seen that from the initial Re-1 to the recent Re-8 (Re, abbreviation of recombinant virus), the requirement to update the vaccine has been accelerating in China (Fig. 3).

In fact, the most effective way to control AI is immediate eradication through a four-component strategy: (1) destruction of the infected animals at the beginning of an outbreak or before any spread of the disease, (2) quarantine of live poultry markets or periodic thorough disinfections of these markets, (3) continuous surveillance for potentially-infected birds in production facilities and wild populations, and (4) strengthening biosecurity measures. In addition, vaccination should be used as an

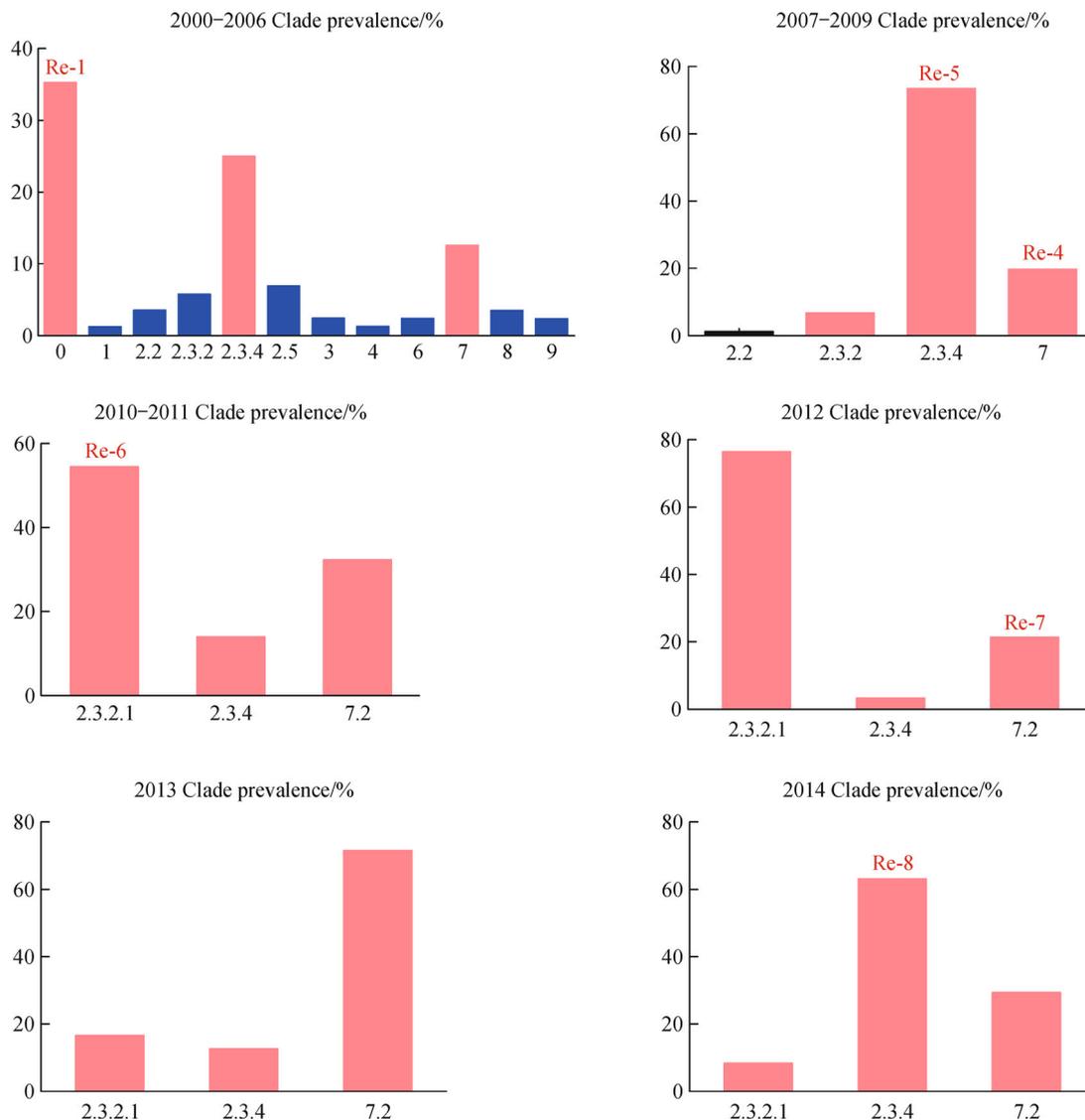


Fig. 3 Clade prevalence of the H5N1 subtype in Eastern China from 2000 to 2014. The percentages of clade prevalence are based upon unpublished data of our routine epidemiology survey during 2000 to 2014.

additional tool when immediate eradication is not feasible, which will maintain livelihoods and food security, and control clinical disease until a primary strategy can be developed and implemented to achieve eradication. Currently, considering the H9N2 and H5N1 influenza virus are still endemic in poultry and wild birds in China, and the poor biosecurity condition of the poultry farms, the vaccination measures still need to be used as a part of a comprehensive control strategy. In addition, when a vaccination strategy is implemented in an endemic area, the vaccine seed strain should be selected based on the surveillance data, genetic and antigenic characterization of the filed strains to try to get the longest possible protection.

9 Conclusions and perspectives

The endemicity of the H9N2 and H5N1 AIVs in poultry in

China accelerates the emergence of the novel lineages of other subtypes of influenza virus, such as the H5N2, H7N7, H7N9, H10N8, and H5Nx reassortant viruses and constitutes a continuous and serious threat to the poultry industry and public health. Moreover, the possibility of emergence of other potentially virulent and highly transmissible AIVs to humans, which could arise from the circulating H9N2 and H5N1 viruses, should not be ignored. The influenza viruses in poultry that have caused wide public concern over their potential to create a pandemic, H5N1, H7N9, H5N6, and H10N8, have caused human deaths, and H6N1 and H9N2 have caused mild illness. Other subtypes of avian influenza viruses, such as H1, H3, H4, and H11, have not yet been found that have gained the ability to infect humans. However, we are not sure whether these subtypes can overcome the host barriers to infect humans. Therefore, we need to constantly keep an eye on the hidden threats on the emergence of the

unexpected novel subtypes. Also, considering the epidemiology and virology, there may be no more complex infectious disease problems than those posed by AI. However, the complexity of the AI in China challenges us to integrate virology and public health research and surveillance at the animal-human interface.

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