

Overview of the emergence and characteristics of the avian influenza A(H7N9) virus

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Summary

This is an overview of the emergence and characteristics of avian influenza A(H7N9) virus infecting humans in China in early 2013. The public health and animal health investigations of the outbreak were facilitated by rapid sharing of information and viruses. Epidemiologic studies and laboratory analyses of virus isolates have provided a vast amount of information in a very short time. Molecular and functional characterization of the virus revealed its possible origins and supported the development of diagnostic tests and vaccines as well as offering clinical guidance on antiviral therapy. Studies in animal models have started to shed light on pathogenicity and risk assessment. These activities have been essential in guiding disease control interventions and informing pandemic preparedness actions.

1. The outbreak

On 31 March 2013, the public health authorities of China reported three cases of laboratory-confirmed human infection with avian influenza A(H7N9) virus (hereafter H7N9). Two cases were detected in residents of the city of Shanghai and one in a resident of Anhui province. The first case was an 87 year old male patient from the city of Shanghai who reported onset of influenza-like symptoms on 19 February 2013. The second and third cases had illness onset dates of 27 February and 15 March. By 29 May 2013, approximately 2 months after the initial report, the number of laboratory-confirmed H7N9 infections reached 132, with 37 deaths, originating from these locations and seven additional provinces, Shandong, Zhejiang, Henan, Hunan, Fujian, Jiangxi, and Jiangsu, and the municipality of Beijing, in addition to one case reported by Taipei, Centres for Disease Control (CDC) (with a history of recent travel from Jiangsu).

Most patients initially developed an influenza-like illness (ILI) that subsequently progressed to respiratory distress syndrome resulting in hospitalization (Gao et al. 2013, Li et al. 2013). The case fatality proportion reached approximately 25%, which is a provisional value because many patients remain hospitalized as of 8 May 2013 and the number of mild cases remains unknown (Li et al. 2013). Six patients were identified through influenza-like illness surveillance, two of them with mild symptoms not requiring hospitalization (Xu et al. 2013). Underlying chronic conditions were reported in most cases. The median age was 61 years with a predominance of males (2.4:1 male to female ratio) (Li et al. 2013). In contrast, previous infections with subtype H7 avian influenza viruses have generally been mild and associated with conjunctivitis (Belser et al. 2009).

Investigations of H7N9 cases have so far revealed that except for four confirmed clusters of two or more cases that were in close contact, the patients did not appear to have known exposure to each other. However, most patients had a history of recent exposure to poultry, generally at live bird markets (Li et al. 2013, Chen et al. 2013). On April 5, 2013, the Ministry of Agriculture of China reported to the World Organization of Animal Health (OIE) the detection of low-pathogenic avian influenza A(H7N9) in a pigeon sampled at an agricultural wholesale market in the Shanghai municipality; this being the first H7N9 reported in birds in Asia since 2011 (OIE 2013b, Kageyama et al. 2013, Kim et al. 2012).

Surveillance for ILI among people in close contact with laboratory-confirmed H7N9 cases indicated that infected individuals are not a likely source of infection (Li et al. 2013). These preliminary studies suggested that despite numerous cases of H7N9 virus infection associated with poultry exposure, there is no evidence of sustained onwards virus transmission to other people (Li et al. 2013).

2. Clinical findings

Clinical findings in patients with confirmed H7N9 infection at hospital admission include high fever, non-productive as well as productive cough, shortness of breath, dyspnoea, hypoxia, and evidence of lower respiratory tract disease with opacities, consolidation, and infiltrates noted on chest imaging (Gao et al. 2013, Chen et al. 2013, Lu et al. 2013). Leukocyte counts have been normal or low, with leukopenia, lymphopenia, and moderate thrombocytopenia in some cases. Complications of H7N9 virus infection have included septic shock, respiratory failure, acute respiratory distress syndrome, refractory hypoxemia, acute renal dysfunction, multiple organ dysfunction, rhabdomyolysis, encephalopathy, and bacterial and fungal infections such as ventilator-associated pneumonia and blood-stream infection sometimes by multi-drug resistant bacteria (Gao et al. 2013,

Chen et al. 2013, Lu et al. 2013). The median time from onset to hospital admission is approximately 4.5 days, and a high proportion of patients with confirmed H7N9 infection have been admitted to intensive care (Li et al. 2013). The median time from illness onset to death is approximately 11 days, ranging from 7 to 20 days (Li et al. 2013). A small number of clinically mild H7N9 virus infections with uncomplicated influenza (febrile upper respiratory tract illness) have been identified in children and adults (Li et al. 2013, Xu et al. 2013). A recent study on hospitalized patients with pneumonia suggests that systemic high-dose steroid use may result in increased risk of prolonged viral replication and shedding providing a favourable condition to the emergence of antiviral resistance (Hu et al. 2013).

3. Laboratory diagnosis

Clinical specimens from the first three cases of H7N9 virus infection were initially reported as testing positive for influenza A viral RNA, but "unsubtypable" by the real-time reverse transcription RT-PCR test routinely used by public health laboratories (Jernigan et al. 2011). These tests were designed to determine whether the specimen contains influenza type A or B viral RNA from a respiratory source and, for type A positive samples, identify the HA gene as subtypes H1 or H3, from A(H1N1) or A(H3N2) seasonal influenza viruses, respectively, or H5 from avian influenza A(H5N1). Therefore, the results of real-time RT-PCR tests designed for currently circulating seasonal viruses or A(H5N1) were reported as influenza A viruses of unknown subtype by the municipal and provincial public health laboratories. Further real-time RT-PCR tests and sequence analysis of these clinical specimens at the China National Influenza Center in Beijing revealed that the HA belonged to the H7 subtype and the NA to the N9 subtype (Gao et al. 2013). Testing for other respiratory pathogens yielded negative results.

The real-time RT-PCR assay with primers and probes designed to detect the Eurasian H7 haemagglutinin is the method of choice to analyze respiratory specimens for diagnosis of H7N9 infection. This and similar assays have been developed, validated, and made available to public health laboratories (CDC 2013a, ECDC 2013, Xu et al. 2013). On 3 April 2013, the Chinese Center for Disease Control and Prevention in Beijing (China CDC) distributed primers and probes specific for H7N9 virus to all influenza surveillance network laboratories in China. Other WHO Collaborating Centres on influenza including the Centers for Disease Control and Prevention, United States of America and the National Institute for Infectious Diseases, Japan, have also developed and shared H7N9 specific PCR reagents.

Routine laboratory methods used for the propagation of influenza viruses include cultured Madin-Darby canine kidney cells supplemented with trypsin, and embryonated chicken eggs. Both systems support the growth of the H7N9 virus from clinical samples. The presence and quantity of virus in culture media can be measured by agglutination of erythrocytes derived from chicken, turkey, guinea pig, or horse, although turkey red blood cells are preferred in the WHO Global Influenza Surveillance and Response System (GISRS) laboratories (WHO 2002, WHO 2011).

Preliminary results indicate that infection also can be diagnosed retrospectively by haemagglutination-inhibition (HI) tests that detect a rise in specific antibodies to H7N9 virus in serum samples collected in the acute and convalescent periods of infection. HI tests with turkey erythrocytes and H7N9 virus propagated in the laboratory, as described previously, can provide satisfactory preliminary results (WHO 2011). The WHO GISRS and partner laboratories have developed both haemagglutination-inhibition and microneutralization laboratory protocols to detect specific H7N9 virus antibodies in human sera (WHO 2013a, WHO 2013b).

4. Laboratory biosafety

Biosafety guidance for work with H7N9 viruses in the laboratory should be based on existing frameworks and guidelines, such as applying the risk group classification in the WHO Laboratory biosafety manual (WHO 2004) and considering the bio-risk management approach provided in CEN CWA 15793 (The_European_Committee_for_Standardization 2008). Only laboratories that meet the appropriate biosafety level and conform to available bio-risk management standards (e.g. CWA 15793) should consider working with these viruses, with relevant national authority oversight. Final responsibility for the identification and implementation of appropriate risk assessment, mitigation, and containment measures for work with H7N9 viruses lies with individual countries and facilities. Accordingly, regulations may vary from country to country, and decisions should be taken in light of currently available knowledge, context, and applicable national requirements. A WHO interim biosafety risk assessment provides specific guidance in this regard (WHO 2013c). Compliance with the local animal and public health biosafety regulations applicable in each country is of the utmost importance to protect public and animal health.

5. Characterization of the A(H7N9) viruses

Complete genomic coding sequences from the first three H7N9 viruses isolated from humans in China were deposited into the GISAID database on 31 March, 2013. A nucleotide sequence alignment comparison of each of the eight genes indicated that the three viruses were very similar to each other and shared greatest identity with genes of avian influenza viruses that circulated recently in China (Shi et al. 2013). The HA genes had highest levels of sequence identity (95%) with H7N3 viruses detected recently in ducks at live bird markets in Eastern China (Wu et al. 2012, Shi et al. 2013). The NA genes were highly similar (96% identity) to N9 NA genes from viruses circulating recently in domestic ducks in China and Korea but featured a distinctive 15 nucleotide deletion (amino acids 69-73) beginning at position 215 (Shi et al. 2013). The remaining six viral genes (PB2, PB1, PA, NP, M and NS) had greatest identity (99%) with A(H9N2) poultry viruses that have been in circulation in China since 1994 (Shi et al. 2013, Chen et al. 2013).

These findings indicate that H7N9 viruses from human cases were most closely related to a previously unidentified avian influenza virus with genes derived from several potential parental strains. A review of the literature indicated that human infections with H7N9 viruses have not been reported previously (Belser et al. 2009). Similarly, H7N9 viruses were not detected in animals from China before the start of this outbreak. On April 4, 2013, just days after the human outbreak was announced, the China Ministry of Agriculture reported detection of avian influenza H7N9 of low pathogenicity (LPAI) in avian species in the city of Shanghai (OIE 2013b). Three days later, on 7 April 2013, three genomic sequences from avian influenza H7N9 viruses isolated from a pigeon, a chicken and one environmental sample from Shanghai city and Jiangsu province were deposited in the GISAID database. The nucleotide sequences of the 8 genes from these viruses were nearly identical to each other and to genes of viruses isolated from human infections (Shi et al. 2013). The percent identity was 99% or greater for the majority of the genes (Shi et al. 2013, Chen et al. 2013). Simultaneous detection of nearly identical H7N9 viruses in peri-domestic birds and people in the same city suggested that human infections could be linked to exposure to birds.

Phylogenetic analyses of genomic sequences from H7N9 viruses and representative influenza viruses from diverse hosts provided a more detailed view of the origin and evolution of each of the virus genes. The HA genes of A/Shanghai/2/2013 clustered with A/chicken/Shanghai/S1053/2013 and A/pigeon/Shanghai /S1069/2013 as well as A/Hangzhou/1/2013 and A/Anhui/1/2013 human isolates

whereas A/Shanghai/1/2013 was more divergent. The HA genes from this outbreak clustered with A(H7N3) viruses from ducks sampled recently in this region, such as A/duck/Zhejiang/12/2011 (H7N3). Their genetic distances were consistent with limited unsampled evolution (Figure 1A). The NA genes also descend from an ancestor of duck viruses recently detected in the region such as A/wild bird/Korea/A9/2011 (H7N9) (Figure 1B). The 15 nucleotide deletion in the NA was absent in the avian viruses from China and Korea (Shi et al. 2013) suggesting that it may have been selected in the past three years or less. As in the case of HA, the NA genetic distances indicated very limited unsampled evolution. The remaining six genes share a very close ancestor with A(H9N2) viruses detected recently in poultry from Eastern China, such as A/chicken/Zhejiang/611/2011 (H9N2). Several H7N9 viruses have divergent genes that suggest a distinct evolutionary trajectory. The NP gene of the A/Shanghai/1/2013(H7N9) virus has a clearly distinct evolutionary history as compared to the other H7N9 viruses and likewise, A/Pigeon/Shanghai/S1069/2013(H7N9) shows a similarly divergent PB1 gene of distinct ancestry (Figures 1C to 1H). The PA genes of A/Zhejiang/DTID-ZJU01/2013 and A/Zhejiang/2/2013 are also distinct from those of the known H7N9 viruses. Additional viruses with reassortant genomes are likely to be identified as more sequence data become available.

Although the individual H7N9 genes were very similar to those of viruses that circulated recently in poultry from this region, viruses with the same genomic composition (genotype) were not identified in animals previously. Therefore, the genotype of H7N9 influenza viruses isolated from humans may have originated in China by reassortment of poultry A(H9N2) viruses with duck viruses carrying H7 and N9 genes (Figure 2).

A recent study (Jonges et al. 2013) compared the sequence divergence of HA, NA and PB2 genes observed during the Dutch A(H7N7) and Italian A(H7N1) outbreaks with the initial H7N9 virus sequences from the current outbreak in China. The study concluded that the genetic distance observed among the available genome sequences suggests that H7N9 viruses had circulated in the animal reservoir in Asia for several months prior to their detection in humans and animals.

The analysis of the 11 virus protein sequences deduced from gene sequences of the H7N9 viruses provided critical insight into their evolution and biological properties. The HA proteins are characterized by the presence of a single basic amino acid at the HA0 cleavage site that yields HA1 and HA2 (Figure 3). No amino acid insertions or deletions were detected in the HA sequence. The presence or absence of multiple basic amino acids or other sequence insertions at the cleavage site of the HA0 is one of the criteria used to determine the virulence potential of influenza viruses for chickens and other avian species (OIE 2009). In this case, the absence of such changes supports its classification as “low-pathogenic” for chickens, notwithstanding the capacity of these viruses to cause severe and fatal infections in people. The structure of the receptor binding site shows conservation of amino acids typical of avian H7 HAs, with the exception of Leu or Ile replacing Gln at position 217 (equivalent to 226 in H3 numbering) in most of the viruses isolated from humans and birds (Table 1). This change has been associated with the adaptation of avian viruses to humans, swine and terrestrial poultry as well as increased transmissibility in experimentally infected ferrets (Matrosovich et al. 2000, Rogers and Paulson 1983, Herfst et al. 2012, Imai et al. 2012, Wan and Perez 2007). The role of the Ala to Ser substitution at position 128 (137 in H3) in the HA of A/Shanghai/1/2013 is not well established, but merits further study.

The NA proteins of the human and avian isolates from the current outbreak have a deletion of five amino acids (positions 69–73) which shortens the stalk domain. Similar deletions in multiple subtypes of NA are a hallmark of aquatic bird viruses that become adapted to terrestrial poultry

(Banks et al. 2001, Matrosovich et al. 1999). The NA active site residues are conserved in all H7N9 outbreak viruses, with the exception of A/Shanghai/1/2013 which shows a Lys to Arg amino acid substitution at position 289 (292 in N2 numbering) which is predicted to affect susceptibility to neuraminidase inhibitor drugs (Gubareva et al. 1997, McKimm-Breschkin et al. 1998).

The PB2 proteins from some H7N9 viruses isolated from humans have mutations at positions 627 (Glu to Lys in the human isolates from Anhui, Hangzhou and Shanghai) or 701 (Asp to Asn in A/Zhejiang/DTID-ZJU01/2013) which impart enhanced replication at temperatures similar to that of the upper airway of mammalian hosts and possibly humans as well (Hatta et al. 2007, Massin et al. 2001). In contrast, the PB2s from H7N9 viruses isolated from birds retain Glu at position 627 and Asp at 701, strongly suggesting that the mutation is positively selected upon replication in the human host, as reported previously for zoonotic A(H7N7) and A(H5N1) infections (Le et al. 2009, de Wit et al. 2010). Additional markers of adaptation to non-avian hosts or virulence were noted in the PB1-F2, M1 and NS1 proteins as shown in Table 2. The M2 protein has a Ser to Asn mutation at position 31, which is associated with adamantane resistance (Hay et al. 1985).

6. Infection in animals

Natural infections with H7N9 viruses in chickens, ducks and other birds are asymptomatic and elicit an immune response that can be detected serologically. The virus replicates in the respiratory and digestive tracts and is transmitted by droplets or contact (direct or indirect). Preliminary experimental infections of chickens by the intranasal or intravenous route were also asymptomatic. Together with the molecular features of the HA (lack of multi-basic cleavage site), these biological properties are the basis for the categorization of the H7N9 outbreak viruses as low-pathogenic avian influenza (LPAI) by international veterinary sanitary authorities charged with protecting animal health (OIE 2009).

In response to the reported human infections with H7N9 virus, the Ministry of Agriculture of the People's Republic of China expanded and enhanced surveillance in live bird markets and poultry farms as well as in swine farms and slaughterhouses in the whole country, and especially in the affected region and surrounding provinces of eastern China. Because the H7N9 virus does not cause disease in poultry, sampling asymptomatic animals was necessary to detect the virus in respiratory/cloacal swabs or specific antibodies in serum by laboratory testing. This is a huge challenge in China, with the biggest human population in the world, as well as nearly 4.8 billion chickens. Within six weeks of the initial case report, testing of tens of thousands of samples from poultry and their environment has resulted in the identification of 51 H7N9 virus isolates from the provinces of Anhui, Henan, Zhejiang, Fujian, and Jiangsu as well as the Shanghai municipality, mostly from live poultry markets (OIE 2013a). The source(s) of infection in the markets where H7N9 viruses were detected have not yet been identified. It is important to note that some low pathogenic H7 viruses can evolve into highly pathogenic avian influenza viruses, as had been observed in Canada, Chile, Australia and various countries in Europe (Rott 1992, Suarez et al. 2004, Berhane et al. 2009, Senne et al. 2006). For this reason, the OIE guidance indicates that reporting of H7 subtype avian influenza virus detection in poultry is mandatory (Swayne et al. 2011).

Natural infection of swine with subtype avian influenza A(H7N2) viruses has been reported previously in Korea, prompting animal health authorities of China to perform surveillance in this species (Kwon et al. 2011). Several thousands of respiratory and serological samples collected from swine farms and swine slaughterhouses in Anhui, Zhejiang and Jiangsu provinces and the Shanghai municipality were reported all negative for H7N9 virus.

Little is known about the susceptibility of wild aquatic birds to the H7N9 virus. The dissemination of A(H5N1) virus among poultry and other birds throughout Asia, Africa and Europe in 2005-2006 may have been enhanced by wild bird migration (Kilpatrick et al. 2006). Therefore, continued targeted surveillance for H7N9 in domestic and wild avian and mammalian populations will be essential to detect and control the spread of this virus to reduce the probability of its further adaptation to humans.

7. Antiviral therapy

Based on the sequence of the M2 protein, H7N9 viruses are predicted to be resistant to adamantane antiviral drugs (Gao et al. 2013) which are therefore not recommended for use. In accord with the NA (neuraminidase) sequencing data, testing of the A/Anhui/1/2013 virus in the neuraminidase inhibition assay indicates that this virus is susceptible to neuraminidase inhibitor antiviral drugs oseltamivir and zanamivir (CDC 2013b) (Tables 3a and 3b). The arginine (R) to lysine (K) substitution at residue 292 (N2 numbering), which is likely to diminish efficacy of oseltamivir and zanamivir (McKimm-Breschkin 2013, Gubareva et al. 1997) (Tables 3a and 3b), was detected initially in the A/Shanghai/1/2013 virus (Gao et al. 2013). However, testing of A/Shanghai/1/2013 virus in the neuraminidase inhibition assay generated discrepant results, which may be attributed to a mixture of R and K at 292 residue of the virus (Table 3b). The clinical specimen containing Shanghai/1/2013 was collected two days after commencement of oseltamivir therapy (Gao et al. 2013).

The previously mentioned study by Hu et al (2013) on the hospitalised pneumonia patients found that reduction of viral load following antiviral treatment correlated with improved outcome. The R292K mutants were detected from two of the three poor responders to the neuraminidase inhibitor (NAI) antiviral therapy with persistently high viral load in the throat. In one of the two patients the NA had 292R on day 2 of antiviral therapy and 292K on day 9 suggesting selection of the resistant virus to dominate the infection.

While no data are available regarding early inhibitor treatment of persons infected with H7N9 virus, the potential severity of H7N9-associated illness warrants recommending that all confirmed cases, probable cases, and H7N9 cases under investigation receive antiviral treatment with a neuraminidase inhibitor drug as early as possible.

8. Vaccines

Preliminary antigenic characterization of an H7N9 virus with post-infection ferret serum revealed antigenic differences when compared with vaccine candidates for Eurasian or North American lineages of H7 subtype viruses (Table 4)(WHO 2013d). The WHO GISRS laboratories, public health research centers and the private sector are actively engaged in a global effort to develop H7N9 vaccines with a view to performing clinical trials to ascertain immunogenicity and establish the optimal vaccination regimen and dose. Ongoing work to develop candidate vaccine viruses based on the HA and NA genes of A/Anhui/1/2013-like H7N9 viruses reassorted with the internal genes from PR8 to enhance their growth in eggs and attenuate virulence has already resulted in candidate vaccine viruses (WHO 2013e). Several candidate vaccine viruses have recently been made available to interested vaccine manufacturers. (WHO 2013e). A parallel effort to develop candidate live attenuated influenza vaccine (LAIV) viruses has been initiated by joint efforts from public and private sectors. A document updating WHO biosafety risk assessment and guidelines for the production and quality control of human influenza vaccines against avian influenza H7N9 virus has been developed (WHO

2013f). In addition, new vaccine manufacturing technologies, such as tissue-cell-culture–derived vaccine antigens and recombinant HA may be utilized. These efforts are likely to reduce the timeline to produce and manufacture H7N9 vaccine if it is needed, however it will probably be many months before large quantities of a vaccine are available.

9. Risk factor assessment

The H7N9 viruses seem to transmit from animals to humans more readily than the Asian lineage A(H5N1) viruses, judging by the low frequency of detection in poultry and the relatively high number of human cases detected since the start of the outbreak (CDC 2013b). On 6 April 2013, as soon as the epidemiologic data suggested that H7N9 infections were associated with exposure to poultry at live bird markets, the municipal authorities of Shanghai ordered the closure of live bird markets. Similar action was taken by several major cities in eastern China. The rate of new human infections with H7N9 with onset of clinical symptoms in the following weeks has decreased substantially since markets closure, further suggesting that the primary risk factor is exposure to infected poultry, especially at markets where live poultry are sold (CDC 2013b).

At this time, investigations have not revealed evidence of sustained (ongoing) spread of this virus from person to person; however in a few small clusters of human H7N9 virus infections, the possibility of limited human-to-human spread cannot be excluded. The epidemiologic investigation of contacts relied on influenza-like symptom development to trigger collection of clinical specimens for laboratory diagnosis (Li et al. 2013, Xu et al. 2013). Therefore, asymptomatic infections resulting from contact with infected individuals may have escaped detection, and testing of serum samples collected from asymptomatic contacts with confirmed cases will be critical to address this question (CDC 2013b). Understanding of the denominator of the total number of H7N9 virus infections, including asymptomatic, clinically mild, severe, and fatal illness will help to inform assessment of the overall severity among the general population (Uyeki and Cox 2013). The WHO and member countries remain vigilant for evidence of events of high significance, including the following:

1. New human cases and clusters of H7N9 infection in China and outside of China
2. Human-to-human transmission of H7N9 virus
3. Mutations including those associated with receptor-binding affinity, antiviral susceptibility, virulence and transmissibility
4. Reassortment with human seasonal or avian A(H5N1) viruses

WHO, in its capacity of leading technical agency, is monitoring the situation very closely, developing and adjusting appropriate interventions in collaboration with its partners.

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Figures

Figure 1 (A-H). Phylogenetic analysis of the HA (panel A), NA (B), PB2 (C), PB1 (D), PA (E), NP (F), M (G), and NS (H) genes of H7N9 viruses from humans, birds and the environment (Accession numbers shown in Supplementary Table 1). The phylogenetic tree was constructed by Neighbor-Joining methods using MEGA5 software (Tamura et al. 2011) and includes representative closely related genes. The trees were drawn with midpoint rooting to North American-lineage genes as outgroups. The horizontal bar denotes the unit scale of nucleotide substitutions per site for the tree branch lengths. Genes from emerging H7N9 viruses isolated in 2013 are shown in pink.

HA



Fig. 1B
NA

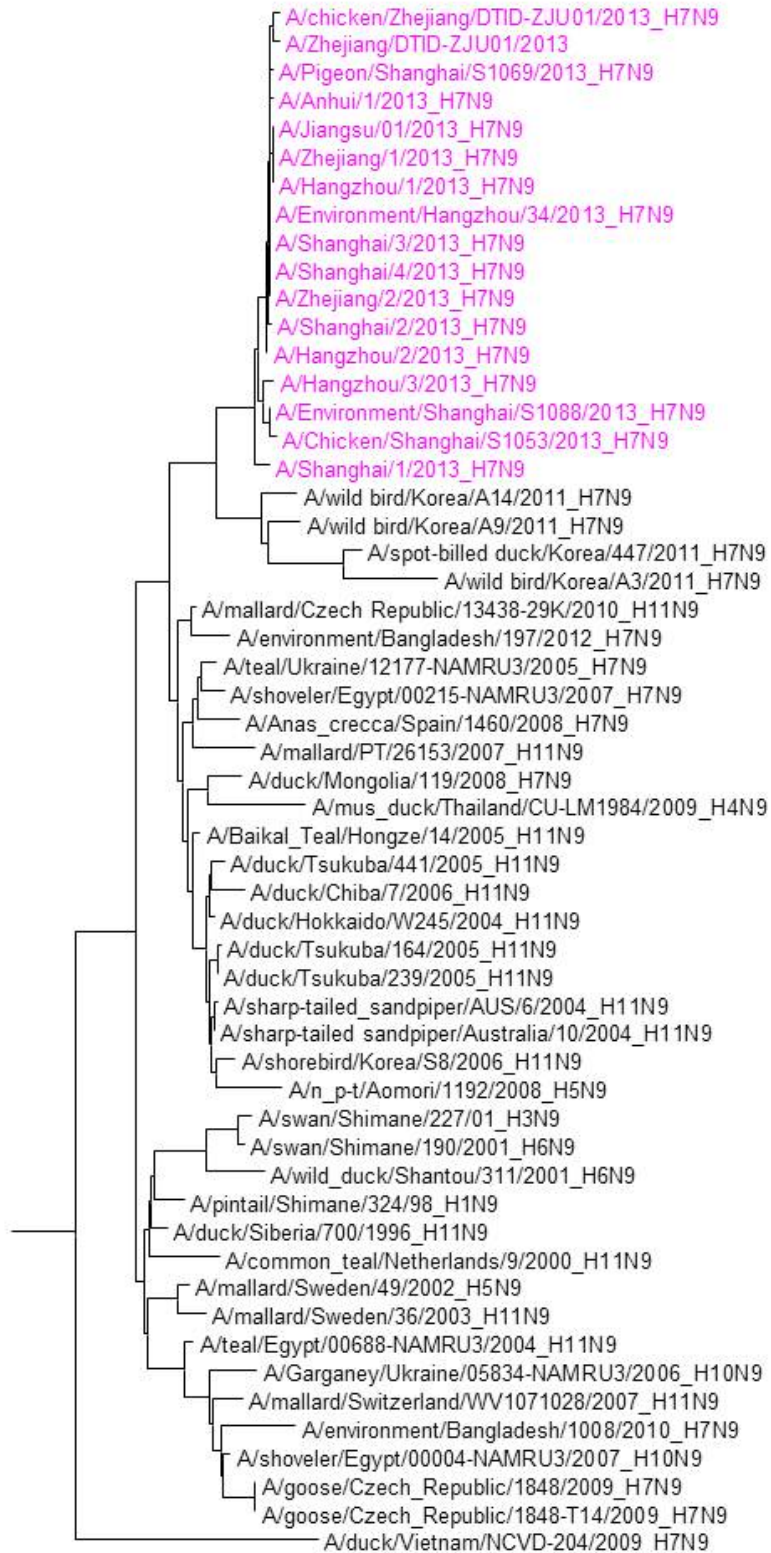


Fig. 1C
PB2

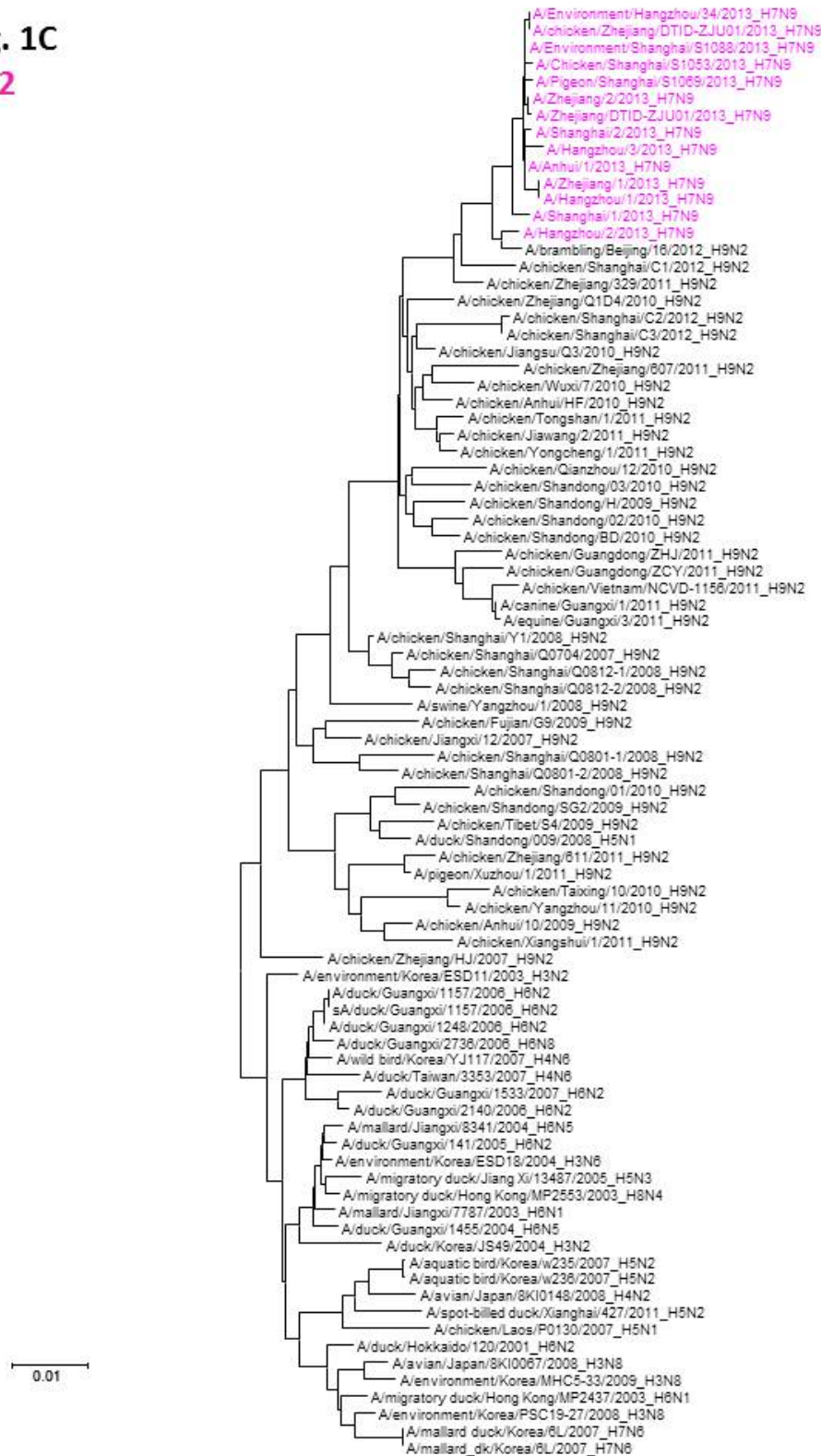


Fig. 1D
PB1

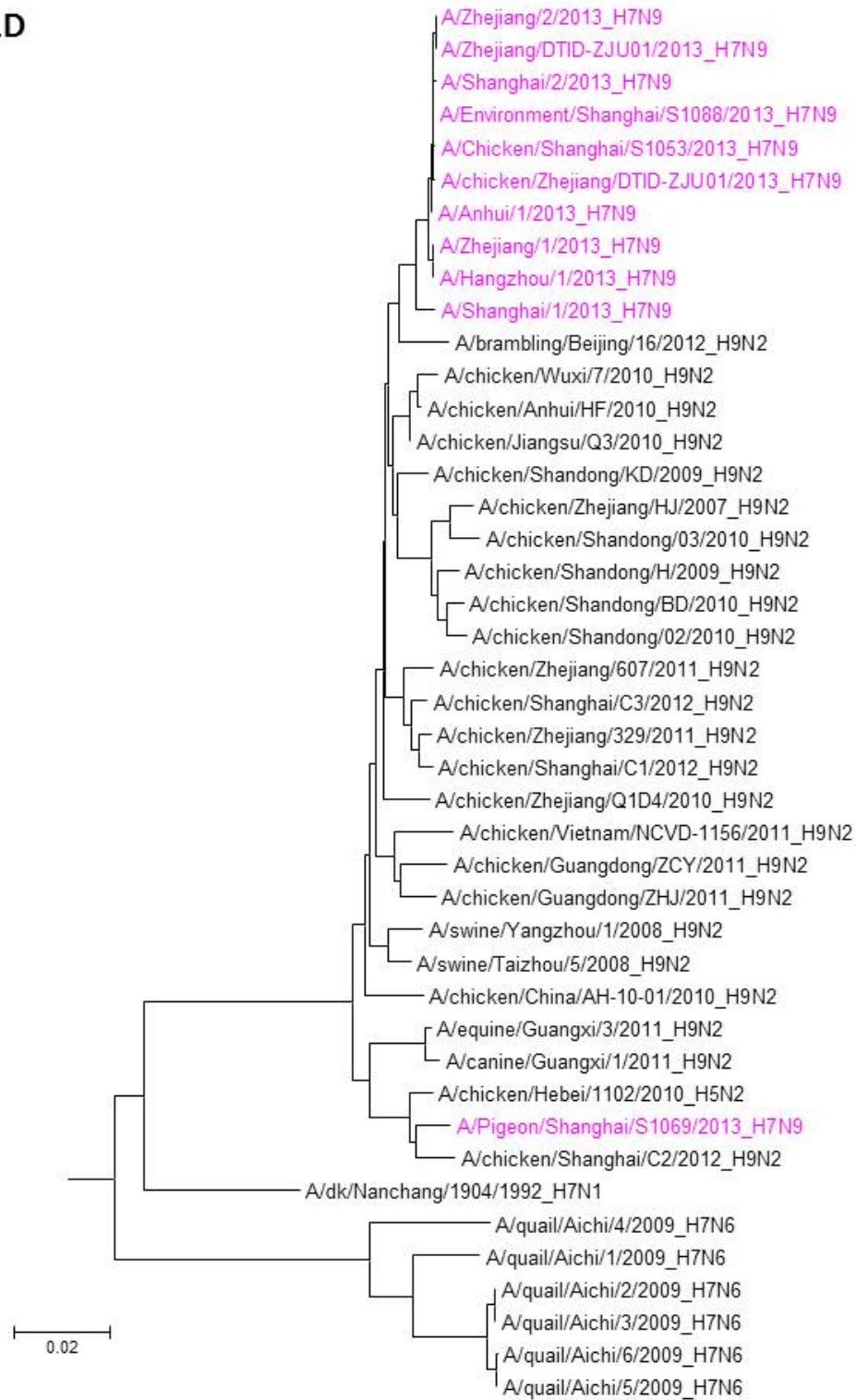


Fig. 1E
PA

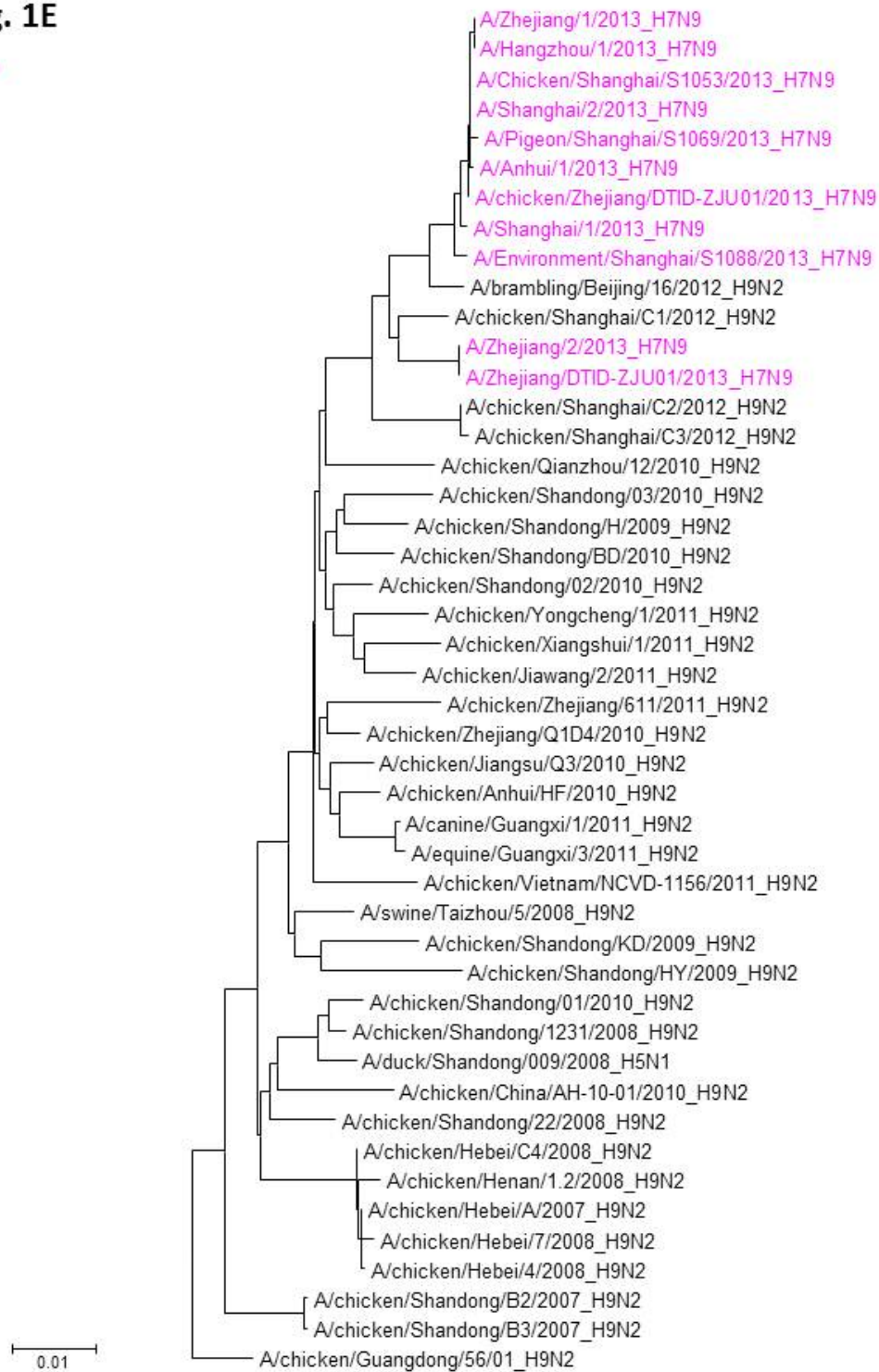


Fig. 1F
NP

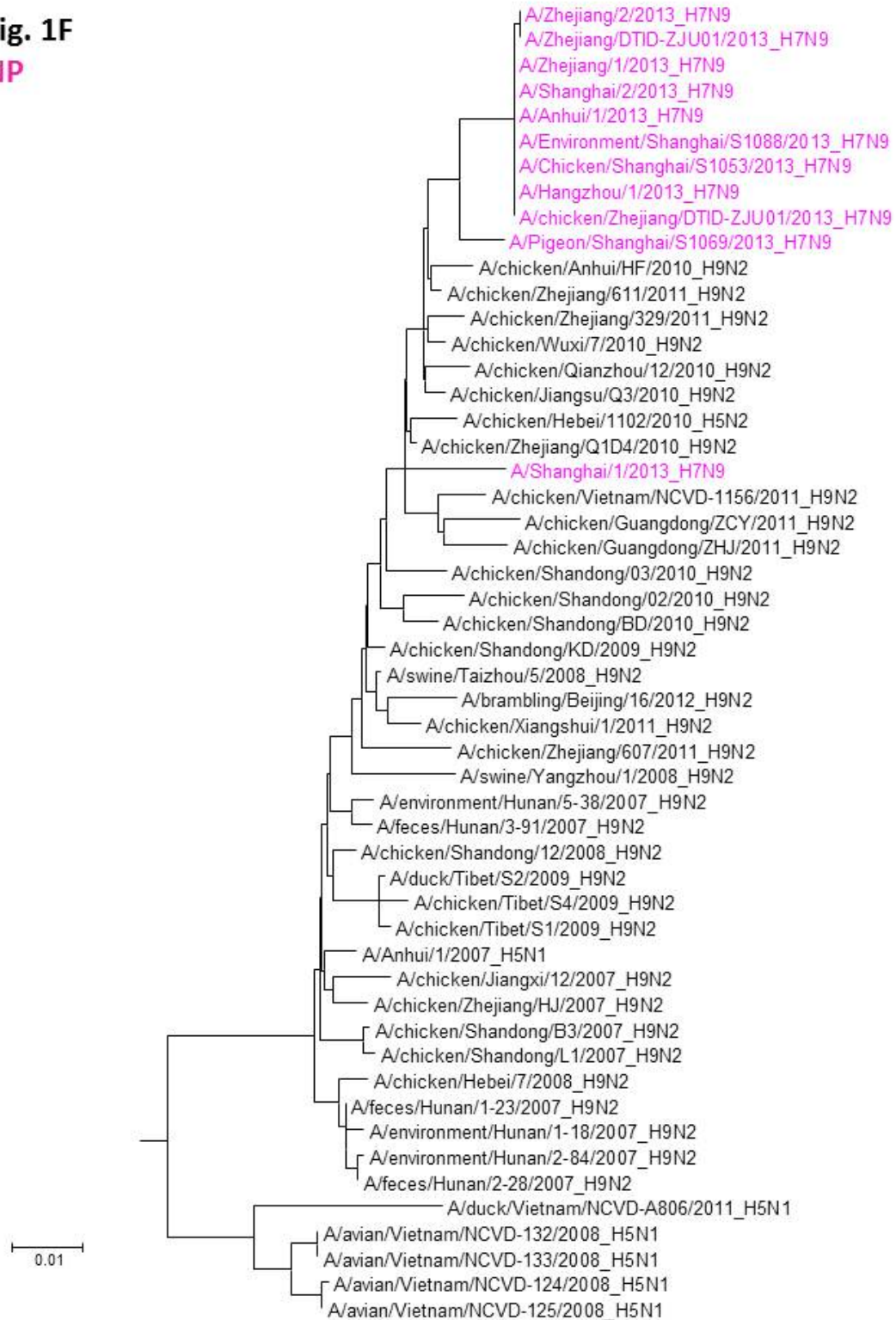


Fig. 1G
M

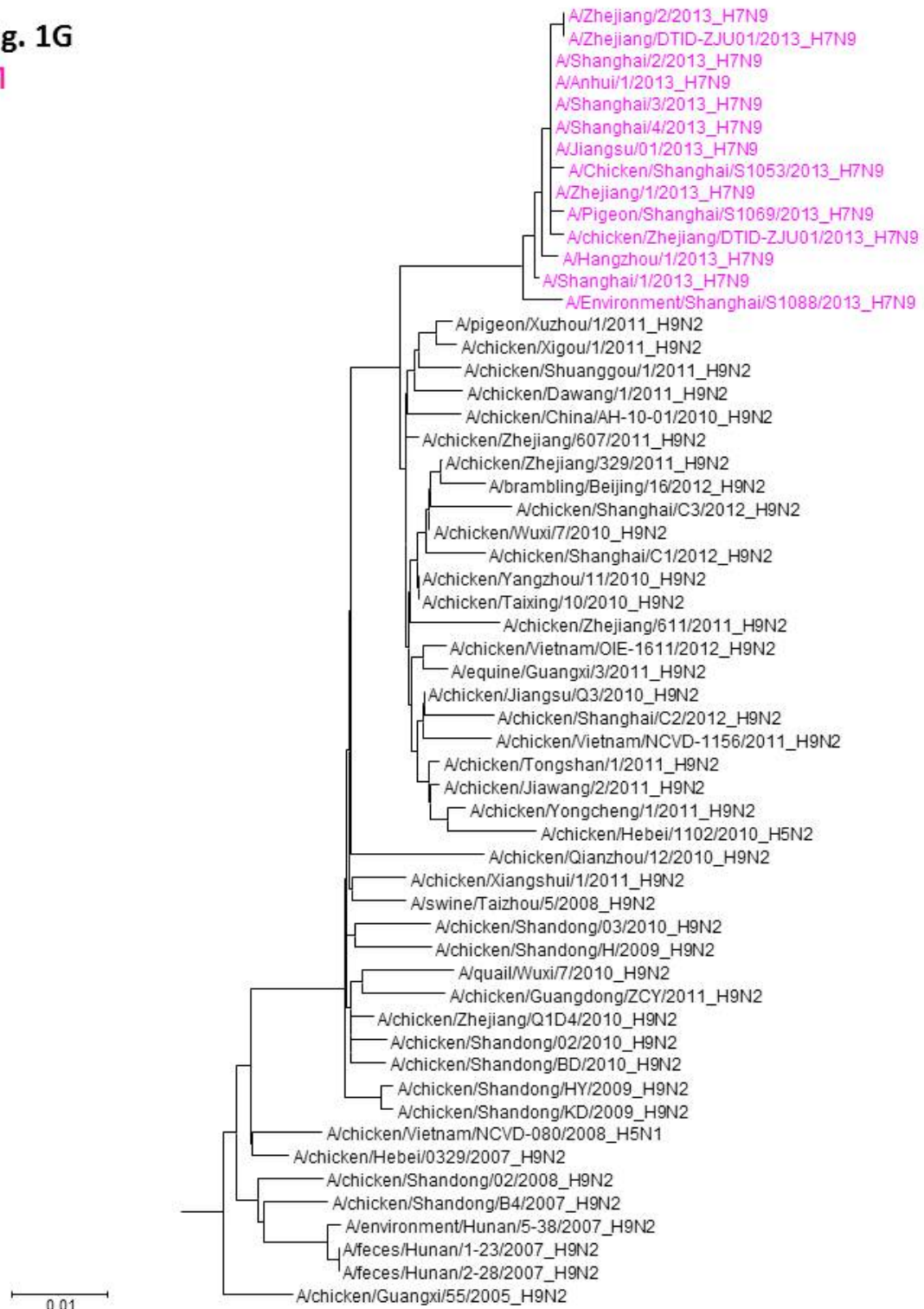


Fig. 1H
NS

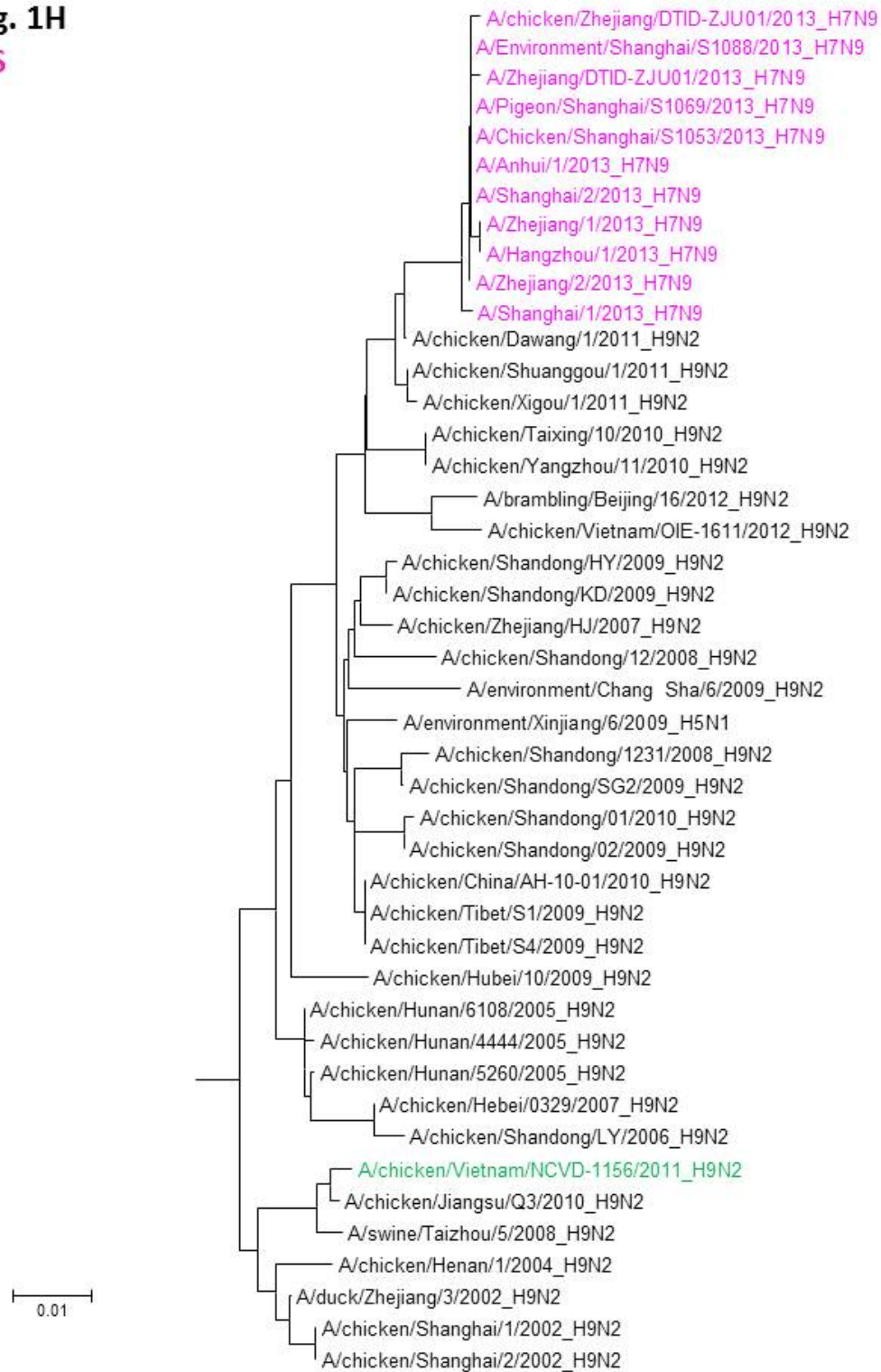
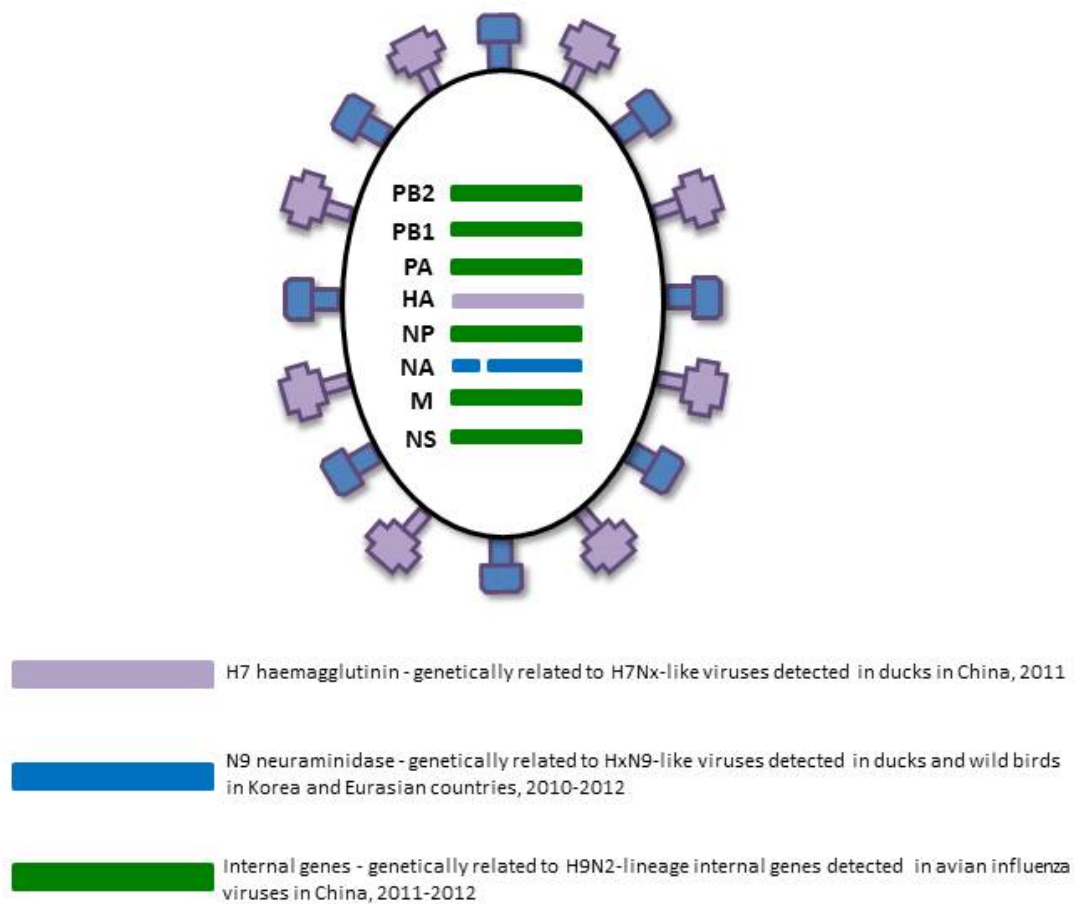


Figure 2. Genesis of H7N9 viruses in China. Poultry H9N2 viruses circulating recently in China were the donors of 6 of the 8 genes. The H7 gene was derived from duck viruses that circulated in domestic ducks in China in recent years. The N9 gene is postulated to originate from duck viruses that circulated recently in China, though the duck viruses did not carry the NA stalk deletion.



H7 HA

HAO
cleavage
↓

Tables

Table 1. Amino acid substitutions in the HA associated with receptor binding

Virus	Positions 226 and 228 [¶]	Function
A/Shanghai/1/2013 A/chicken/Zhejiang/DTDID-ZJU01/2013	226Gln / 228Gly	typical avian receptor binding [‡]
A/Shanghai/2/2013 A/Anhui/1/2013 A/Zhejiang/DTID-ZJU01/2013 A/Hangzhou/2/2013 A/Hangzhou/3/2013 A/Shanghai/3/2013 A/Shanghai/4/2013 A/Zhejiang/2/2013 A/pigeon/Shanghai/S1069/2013 A/environment/Shanghai/S1088/2013 A/chicken/Jiangsu/K89/2013 A/chicken/Shanghai/S1053/2013 A/chicken/Jiangsu/K27/2013 A/environment/Hangzhou/34/2013	226Leu / 228Gly	correlated with decreased binding to α 2-3 receptors and increased binding to α 2-6 receptors
A/Hangzhou/1/2013 A/Jiangsu/01/2013 A/Zhejiang/1/2013	226Ile / 228Gly	

[‡] Alternative structure involving A137S is possible.

[¶] H3 numbering

Table 2. Markers of mammalian adaptation in internal proteins of viruses of avian origin

Protein	Amino acid sequence/position	Function
PB2	89Val all isolates	Selected by human host. Correlated with enhanced polymerase activity and increased virulence in mice. (Li et al. 2009, Hatta et al. 2001, Le et al. 2009)
	627Lys most human isolates	
	701Asn one human isolate	
PB1	368Val all isolates except A/Shanghai/1/2013	Correlated with H5 virus transmission among ferrets (Herfst et al. 2012)
PB1-F2 protein	Stop codon at position 21 in A/Pigeon/Shanghai/S1069/2013 (all other isolates full length)	Truncation partially correlated with adaptation to mammalian hosts (Zamarin et al. 2006)
M1	Asn30Asp; all viruses	Increased virulence in mice (Fan et al. 2008)
	Thr215Ala all viruses	
NS1	Pro42Ser; all isolates	Correlated with increased virulence in mice (Jiao et al. 2008)
	C-terminal deletion of PDZ ligand; all isolates	Potential adaptation to non-avian host (Jackson et al. 2008)

Table 3a. IC₅₀ (nM) of neuraminidase inhibitor antiviral drugs using the fluorescent neuraminidase inhibition assay.

Virus Name	Subtype	Oseltamivir	Peramivir	Zanamivir	Laninamivir
A/Anhui/1/2013*	H7N9	0.41	0.24	1.06	1.39
A/Anhui/1/2013	H7N9	0.17	0.06	0.33	0.46
<i>Reference Viruses</i>					
A/Fukui/20/2004, E119 (ISIRV-AVR)	H3N2	0.13	0.19	1.03	0.63
A/Fukui/45/2004, E119V (ISIRV-AVR)	H3N2	37.00	0.26	1.01	0.73
A/Washington/01/2007, R292	H3N2	0.07	0.08	0.23	0.29
A/Bethesda/956/2006, R292K	H3N2	1511.51	16.27	6.84	2.51

* Tested at the WHO CC in Melbourne, Australia; remaining viruses were tested at the WHO CC in Atlanta, United States of America.

Table 3b. IC₅₀ (nM)* of neuraminidase-inhibitor antiviral drugs using chemiluminescence-based NA-XTD assay .

Virus Name	Subtype	Oseltamivir	Peramivir	Zanamivir	Laninamivir
A/Anhui/1/2013	H7N9	0.43	0.02	0.21	0.34
<i>Reference Viruses</i>					
A/Fukui/20/2004,119E (ISIRV-AVG)	H3N2	0.14	0.03	0.18	0.49
A/Fukui/45/2004, E119V (ISIRV-AVG)	H3N2	3.10	0.03	0.14	0.34
A/Kagoshima/2/2012, R292K	H3N2	1262.74	22.27	1.82	0.63

*Tested at the WHO CC in Tokyo, Japan.

Table 4. Antigenic characterization of A/Anhui/1/2013 (H7N9) by haemagglutination-inhibition.

Virus Name	Ferret Antisera		
	turkey/Virg/4529	mallard/Neth/12	Anhui/1/13
A/turkey/Virginia/4529/2002 (H7N2)	<u>160</u>	80	40
A/mallard/Netherlands/12/00 (H7N3)	10	<u>640</u>	80
A/Anhui/1/2013 (H7N9)	10	160	<u>160</u>

Table 5. Sequence data used in this report were downloaded from GISAID.

We acknowledge the authors, originating and submitting laboratories of the sequences from GISAID's EpiFlu™ Database on which this research is based. The list is detailed below. All submitters of data may be contacted directly via the GISAID website www.gisaid.org

Segment ID	Segment	Country	Collection date	Isolate name	Originating Lab	Submitting Lab	Authors
EPI440694	NP	China	2013-Apr-02	A/Pigeon/Shanghai/S1069/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440695	NS	China	2013-Apr-02	A/Pigeon/Shanghai/S1069/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440696	MP	China	2013-Apr-02	A/Pigeon/Shanghai/S1069/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440697	PA	China	2013-Apr-02	A/Pigeon/Shanghai/S1069/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440698	PB2	China	2013-Apr-02	A/Pigeon/Shanghai/S1069/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440699	PB1	China	2013-Apr-02	A/Pigeon/Shanghai/S1069/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440700	NA	China	2013-Apr-02	A/Pigeon/Shanghai/S1069/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440701	HA	China	2013-Apr-02	A/Pigeon/Shanghai/S1069/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440686	NP	China	2013-Apr-03	A/Environment/Shanghai/S1088/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440687	NS	China	2013-Apr-03	A/Environment/Shanghai/S1088/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440688	MP	China	2013-Apr-03	A/Environment/Shanghai/S1088/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440689	PA	China	2013-Apr-03	A/Environment/Shanghai/S1088/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440690	PB2	China	2013-Apr-03	A/Environment/Shanghai/S1088/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440691	PB1	China	2013-Apr-03	A/Environment/Shanghai/S1088/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440692	NA	China	2013-Apr-03	A/Environment/Shanghai/S1088/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	

Segment ID	Segment	Country	Collection date	Isolate name	Originating Lab	Submitting Lab	Authors
EPI440693	HA	China	2013-Apr-03	A/Environment/Shanghai/S1088/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI442716	HA	China	2013-Apr-04	A/Environment/Hangzhou/34/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI442717	NA	China	2013-Apr-04	A/Environment/Hangzhou/34/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI442715	PB2	China	2013-Apr-04	A/Environment/Hangzhou/34/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI443574	NS	China	2013-Apr-04	A/Environment/Hangzhou/34/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI443572	NP	China	2013-Apr-04	A/Environment/Hangzhou/34/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI443571	PA	China	2013-Apr-04	A/Environment/Hangzhou/34/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI443573	MP	China	2013-Apr-04	A/Environment/Hangzhou/34/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI443570	PB1	China	2013-Apr-04	A/Environment/Hangzhou/34/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI443039	PB2	China	2013-Apr-03	A/Zhejiang/2/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443040	PB1	China	2013-Apr-03	A/Zhejiang/2/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443041	PA	China	2013-Apr-03	A/Zhejiang/2/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ

Segment ID	Segment	Country	Collection date	Isolate name	Originating Lab	Submitting Lab	Authors
EPI443042	HA	China	2013-Apr-03	A/Zhejiang/2/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443043	NP	China	2013-Apr-03	A/Zhejiang/2/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443044	NA	China	2013-Apr-03	A/Zhejiang/2/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443045	MP	China	2013-Apr-03	A/Zhejiang/2/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443046	NS	China	2013-Apr-03	A/Zhejiang/2/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443031	PB2	China	2013-Mar-24	A/Zhejiang/1/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443032	PB1	China	2013-Mar-24	A/Zhejiang/1/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443033	PA	China	2013-Mar-24	A/Zhejiang/1/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443034	HA	China	2013-Mar-24	A/Zhejiang/1/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443035	NP	China	2013-Mar-24	A/Zhejiang/1/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443036	NA	China	2013-Mar-24	A/Zhejiang/1/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI443037	MP	China	2013-Mar-24	A/Zhejiang/1/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ

Segment ID	Segment	Country	Collection date	Isolate name	Originating Lab	Submitting Lab	Authors
EPI443038	NS	China	2013-Mar-24	A/Zhejiang/1/2013	Zhejiang Provincial Center for Disease Control and Prevention	Zhejiang Provincial Center for Disease Control and Prevention	Sun, Y; Zhang, YJ
EPI442713	HA	China	2013-Apr-02	A/Hangzhou/3/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI442712	PB2	China	2013-Apr-02	A/Hangzhou/3/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI442714	NA	China	2013-Apr-02	A/Hangzhou/3/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI442711	NA	China	2013-Mar-25	A/Hangzhou/2/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI442710	HA	China	2013-Mar-25	A/Hangzhou/2/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI442709	PB2	China	2013-Mar-25	A/Hangzhou/2/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Jing-Cao, Pan
EPI441599	PA	China	2013-Mar-24	A/Hangzhou/1/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Li,J; Sun,YX; Pu,XY; Yu,XF; Chen,QJ; Kou,Y; Ding,SJ; Zhou,YY; Pan,JC
EPI441601	PB2	China	2013-Mar-24	A/Hangzhou/1/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Li,J; Sun,YX; Pu,XY; Yu,XF; Chen,QJ; Kou,Y; Ding,SJ; Zhou,YY; Pan,JC
EPI440095	HA	China	2013-Mar-24	A/Hangzhou/1/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Li,J; Sun,YX; Pu,XY; Yu,XF; Chen,QJ; Kou,Y; Ding,SJ; Zhou,YY; Pan,JC
EPI441000	NP	China	2013-Mar-24	A/Hangzhou/1/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Li,J; Sun,YX; Pu,XY; Yu,XF; Chen,QJ; Kou,Y; Ding,SJ; Zhou,YY; Pan,JC
EPI441001	NS	China	2013-Mar-24	A/Hangzhou/1/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Li,J; Sun,YX; Pu,XY; Yu,XF; Chen,QJ; Kou,Y; Ding,SJ; Zhou,YY; Pan,JC

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EPI440096	NA	China	2013-Mar-24	A/Hangzhou/1/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Li,J; Sun,YX; Pu,XY; Yu,XF; Chen,QJ; Kou,Y; Ding,SJ; Zhou,YY; Pan,JC
EPI440097	MP	China	2013-Mar-24	A/Hangzhou/1/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Li,J; Sun,YX; Pu,XY; Yu,XF; Chen,QJ; Kou,Y; Ding,SJ; Zhou,YY; Pan,JC
EPI441600	PB1	China	2013-Mar-24	A/Hangzhou/1/2013	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	Li,J; Sun,YX; Pu,XY; Yu,XF; Chen,QJ; Kou,Y; Ding,SJ; Zhou,YY; Pan,JC
EPI441796	NP	China	2013-Apr-03	A/Zhejiang/DTID-ZJU01/2013		Other Database Import	Chen,H.-L.; Yuen,K.-Y.; Chen,Y.; Wu,N.P.; Yang,S.G.; Wo,J.E.; Yao,H.P.; Liang,W.F.; Cui,D.W.; Wu,H.B.; Li,L.J.
EPI441799	NS	China	2013-Apr-03	A/Zhejiang/DTID-ZJU01/2013		Other Database Import	Chen,H.-L.; Yuen,K.-Y.; Chen,Y.; Wu,N.P.; Yang,S.G.; Wo,J.E.; Yao,H.P.; Liang,W.F.; Cui,D.W.; Wu,H.B.; Li,L.J.
EPI441800	PB1	China	2013-Apr-03	A/Zhejiang/DTID-ZJU01/2013		Other Database Import	Chen,H.-L.; Yuen,K.-Y.; Chen,Y.; Wu,N.P.; Yang,S.G.; Wo,J.E.; Yao,H.P.; Liang,W.F.; Cui,D.W.; Wu,H.B.; Li,L.J.
EPI441801	PB2	China	2013-Apr-03	A/Zhejiang/DTID-ZJU01/2013		Other Database Import	Chen,H.-L.; Yuen,K.-Y.; Chen,Y.; Wu,N.P.; Yang,S.G.; Wo,J.E.; Yao,H.P.; Liang,W.F.; Cui,D.W.; Wu,H.B.; Li,L.J.
EPI441795	PA	China	2013-Apr-03	A/Zhejiang/DTID-ZJU01/2013		Other Database Import	Chen,H.-L.; Yuen,K.-Y.; Chen,Y.; Wu,N.P.; Yang,S.G.; Wo,J.E.; Yao,H.P.; Liang,W.F.; Cui,D.W.; Wu,H.B.; Li,L.J.

Segment ID	Segment	Country	Collection date	Isolate name	Originating Lab	Submitting Lab	Authors
EPI441794	HA	China	2013-Apr-03	A/Zhejiang/DTID-ZJU01/2013		Other Database Import	Chen,H.-L.; Yuen,K.-Y.; Chen,Y.; Wu,N.P.; Yang,S.G.; Wo,J.E.; Yao,H.P.; Liang,W.F.; Cui,D.W.; Wu,H.B.; Li,L.J.
EPI441797	NA	China	2013-Apr-03	A/Zhejiang/DTID-ZJU01/2013		Other Database Import	Chen,H.-L.; Yuen,K.-Y.; Chen,Y.; Wu,N.P.; Yang,S.G.; Wo,J.E.; Yao,H.P.; Liang,W.F.; Cui,D.W.; Wu,H.B.; Li,L.J.
EPI441798	MP	China	2013-Apr-03	A/Zhejiang/DTID-ZJU01/2013		Other Database Import	Chen,H.-L.; Yuen,K.-Y.; Chen,Y.; Wu,N.P.; Yang,S.G.; Wo,J.E.; Yao,H.P.; Liang,W.F.; Cui,D.W.; Wu,H.B.; Li,L.J.
EPI443028	HA	China	2013-Mar-25	A/Zhejiang/01/2013		WHO Chinese National Influenza Center	
EPI443029	NA	China	2013-Mar-25	A/Zhejiang/01/2013		WHO Chinese National Influenza Center	
EPI443030	MP	China	2013-Mar-25	A/Zhejiang/01/2013		WHO Chinese National Influenza Center	
EPI443025	HA	China	2013-Mar-09	A/Shanghai/4/2013		WHO Chinese National Influenza Center	
EPI443026	NA	China	2013-Mar-09	A/Shanghai/4/2013		WHO Chinese National Influenza Center	
EPI443027	MP	China	2013-Mar-09	A/Shanghai/4/2013		WHO Chinese National Influenza Center	
EPI443022	HA	China	2013-Feb-27	A/Shanghai/3/2013		WHO Chinese National Influenza Center	
EPI443024	MP	China	2013-Feb-27	A/Shanghai/3/2013		WHO Chinese National Influenza Center	
EPI443023	NA	China	2013-Feb-27	A/Shanghai/3/2013		WHO Chinese National Influenza Center	
EPI439503	PA	China	2013-Mar-20	A/Anhui/1/2013		WHO Chinese National Influenza Center	
EPI439504	PB2	China	2013-Mar-20	A/Anhui/1/2013		WHO Chinese National Influenza Center	

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EPI439505	NP	China	2013-Mar-20	A/Anhui/1/2013		WHO Chinese National Influenza Center	
EPI439508	PB1	China	2013-Mar-20	A/Anhui/1/2013		WHO Chinese National Influenza Center	
EPI439506	MP	China	2013-Mar-20	A/Anhui/1/2013		WHO Chinese National Influenza Center	
EPI439507	HA	China	2013-Mar-20	A/Anhui/1/2013		WHO Chinese National Influenza Center	
EPI439509	NA	China	2013-Mar-20	A/Anhui/1/2013		WHO Chinese National Influenza Center	
EPI439510	NS	China	2013-Mar-20	A/Anhui/1/2013		WHO Chinese National Influenza Center	
EPI439495	PB2	China	2013-Mar-05	A/Shanghai/2/2013		WHO Chinese National Influenza Center	
EPI439498	PA	China	2013-Mar-05	A/Shanghai/2/2013		WHO Chinese National Influenza Center	
EPI439496	NP	China	2013-Mar-05	A/Shanghai/2/2013		WHO Chinese National Influenza Center	
EPI439497	MP	China	2013-Mar-05	A/Shanghai/2/2013		WHO Chinese National Influenza Center	
EPI439499	NS	China	2013-Mar-05	A/Shanghai/2/2013		WHO Chinese National Influenza Center	
EPI439500	NA	China	2013-Mar-05	A/Shanghai/2/2013		WHO Chinese National Influenza Center	
EPI439501	PB1	China	2013-Mar-05	A/Shanghai/2/2013		WHO Chinese National Influenza Center	
EPI439502	HA	China	2013-Mar-05	A/Shanghai/2/2013		WHO Chinese National Influenza Center	
EPI439488	PB2	China	2013-Feb-26	A/Shanghai/1/2013		WHO Chinese National Influenza Center	
EPI439493	MP	China	2013-Feb-26	A/Shanghai/1/2013		WHO Chinese National Influenza Center	
EPI439489	PB1	China	2013-Feb-26	A/Shanghai/1/2013		WHO Chinese National Influenza Center	
EPI439490	PA	China	2013-Feb-26	A/Shanghai/1/2013		WHO Chinese National Influenza Center	

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EPI439486	HA	China	2013-Feb-26	A/Shanghai/1/2013		WHO Chinese National Influenza Center	
EPI439487	NA	China	2013-Feb-26	A/Shanghai/1/2013		WHO Chinese National Influenza Center	
EPI439491	NP	China	2013-Feb-26	A/Shanghai/1/2013		WHO Chinese National Influenza Center	
EPI439494	NS	China	2013-Feb-26	A/Shanghai/1/2013		WHO Chinese National Influenza Center	
EPI442707	HA	China	2013-Apr-01	A/chicken/Jiangsu/K89/2013	China Animal Health and Epidemiology Center	China Animal Health and Epidemiology Center	
EPI442706	HA	China	2013-Apr-01	A/chicken/Jiangsu/K27/2013	China Animal Health and Epidemiology Center	China Animal Health and Epidemiology Center	Chen, J; Liu, L.; Zhuang, Q.; Hou, G.; Li, J.; Jiang, W.; Wang, K.
EPI442708	HA	China	2013-Apr-01	A/chicken/Jiangsu/K27/2013	China Animal Health and Epidemiology Center	China Animal Health and Epidemiology Center	Chen, J; Liu, L.; Zhuang, Q.; Hou, G.; Li, J.; Jiang, W.; Wang, K.
EPI442718	PB2	China	2013-Apr-01	A/chicken/Zhejiang/DTID-ZJU01/2013		Other Database Import	Wu,H.; Wu,N.; Yao,H.; Chen,H.; Song,W.; Wang,P.; Zheng,M.; Lau,S.; Li,L.
EPI442719	PB1	China	2013-Apr-01	A/chicken/Zhejiang/DTID-ZJU01/2013		Other Database Import	Wu,H.; Wu,N.; Yao,H.; Chen,H.; Song,W.; Wang,P.; Zheng,M.; Lau,S.; Li,L.
EPI442720	PA	China	2013-Apr-01	A/chicken/Zhejiang/DTID-ZJU01/2013		Other Database Import	Wu,H.; Wu,N.; Yao,H.; Chen,H.; Song,W.; Wang,P.; Zheng,M.; Lau,S.; Li,L.
EPI442721	HA	China	2013-Apr-01	A/chicken/Zhejiang/DTID-ZJU01/2013		Other Database Import	Wu,H.; Wu,N.; Yao,H.; Chen,H.; Song,W.; Wang,P.; Zheng,M.; Lau,S.; Li,L.
EPI442722	NP	China	2013-Apr-01	A/chicken/Zhejiang/DTID-ZJU01/2013		Other Database Import	Wu,H.; Wu,N.; Yao,H.; Chen,H.; Song,W.; Wang,P.; Zheng,M.; Lau,S.; Li,L.
EPI442723	NA	China	2013-Apr-01	A/chicken/Zhejiang/DTID-ZJU01/2013		Other Database Import	Wu,H.; Wu,N.; Yao,H.; Chen,H.; Song,W.; Wang,P.; Zheng,M.; Lau,S.; Li,L.
EPI442724	MP	China	2013-Apr-01	A/chicken/Zhejiang/DTID-ZJU01/2013		Other Database Import	Wu,H.; Wu,N.; Yao,H.; Chen,H.; Song,W.; Wang,P.; Zheng,M.; Lau,S.; Li,L.

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EPI442725	NS	China	2013-Apr-01	A/chicken/Zhejiang/DTID-ZJU01/2013		Other Database Import	Wu,H.; Wu,N.; Yao,H.; Chen,H.; Song,W.; Wang,P.; Zheng,M.; Lau,S.; Li,L.
EPI440678	NP	China	2013-Apr-03	A/Chicken/Shanghai/S1053/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440679	NS	China	2013-Apr-03	A/Chicken/Shanghai/S1053/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440680	MP	China	2013-Apr-03	A/Chicken/Shanghai/S1053/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440681	PA	China	2013-Apr-03	A/Chicken/Shanghai/S1053/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440682	PB2	China	2013-Apr-03	A/Chicken/Shanghai/S1053/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440683	PB1	China	2013-Apr-03	A/Chicken/Shanghai/S1053/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440684	NA	China	2013-Apr-03	A/Chicken/Shanghai/S1053/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	
EPI440685	HA	China	2013-Apr-03	A/Chicken/Shanghai/S1053/2013	Harbin Veterinary Research Institute	Harbin Veterinary Research Institute	