

## ESSAY

## Novel human H7N9 influenza virus in China

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### Abstract

Outbreaks of H7N9 avian influenza in humans in 5 provinces and 2 municipalities of China have reawakened concern that avian influenza viruses may again cross species barriers to infect the human population and thereby initiate a new influenza pandemic. Evolutionary analysis shows that human H7N9 influenza viruses originated from the H9N2, H7N3 and H11N9 avian viruses, and that it is as a novel reassortment influenza virus. This article reviews current knowledge on 11 subtypes of influenza A virus from human which can cause human infections.

**Key words:** China, H7N9, human, influenza, virus

### INTRODUCTION

In Mar 2013, 3 patients in Shanghai and Anhui, China presented with rapidly progressing lower respiratory tract infections and were found to be infected with a novel avian influenza virus (AIV). On 21 Apr 2013, the National Health and Family Planning Commission of China (NHFPC) reported 102 confirmed human cases of infection of subtype H7N9, with 20 deaths. Cases have been reported from 5 provinces, Anhui, Jiangsu, Zhejiang, Shandong and Henan, and

2 municipalities, Beijing and Shanghai. All locations are in eastern and northern China. AIV is as an important pathogen in humans, and is of major current global health concern once again, having first emerged in 1997.

### EPIDEMIC OF H7N9 INFLUENZA VIRUS IN ANIMAL HOSTS

Influenza A viruses belong to the family Orthomyxoviridae. They have 8 negative-sense RNA segments encoding 11 known viral surface glycoproteins. Among them, hemagglutinin (HA) and neuraminidase (NA) variants lead to multiple serologically distinct virus subtypes. Over the past 3 decades, influenza A viruses of various HA and NA subtypes have been detected in birds, animal and humans throughout the world (Belser *et al.* 2009). A total of 16 HA and 9 NA subtypes have been confirmed in wild water birds. Wild water birds

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are the natural host for all influenza A viruses, and are known to infect domestic poultry and sometimes mammals. It is notable that in Asia, from 2004–2009, the mutations of HA protein amino acids coincided with human infections, with a ‘low–high–highest–high–low’ pattern, as indicated by the World Health Organization (Zhang & Lei 2010).

Currently, most H7N9 influenza viruses that infect wild or domestic birds cause no illness or death, are limited in scope and are characterized as being low pathogenicity avian influenza (LPAI) viruses. The transmission of H7N9 viruses to mammals, especially to humans, has not been reported previously in Asia, but such subtype viruses have been found in geese (in the Czech Republic in 2009 [Gonzalez-Reiche *et al.* 2012] and the USA in 2011), Eurasian teal (Spain 2008), blue-winged teal (in Guatemala in 2008 and in the USA in 2006), ducks (in Mongolia in 2008), guinea fowl (in the USA in 2011), mallards (in Spain in 2005 [Perez-Ramirez *et al.* 2010] and in Sweden in 2002 [Munster 2005]) and spot-billed ducks (in South Korea 2011 [Kim *et al.* 2012]). Thus, influenza viruses, such as H7N9, circulating in animal reservoirs, represent a potential source of pandemic viruses. (For more informa-

tion, see the database Influenza Virus Resource: <http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html>.)

## ORIGIN AND CHARACTERIZATION OF HUMAN H7N9 INFLUENZA VIRUS IN CHINA

A novel reassortant influenza A (H7N9) virus has been identified that is associated with severe human infection. Molecular analysis showed that the NA gene was closely related to that from another H7N9 virus (KO14), and further revealed that the HA gene was similar to that of an H7N3 virus A/chicken/Zhejiang/607/2011 from a nearby region, Zhejiang, China. All the internal gene segments were closely related to those from avian H9N2 viruses, particularly a virus isolated from a brambling in A/brambling/Beijing/16/2012. Thus, the human 2013 H7N9 viruses originate from a reassortment of viruses that are of avian origin only. In addition, the phylogenetic trees showed that A/Shanghai/1/2013 is phylogenetically distinct from A/Anhui/1/2013 and A/Shanghai/2/2013 across all gene segments, which suggests that there have been at least 2

**Table 1** Subtypes of influenza A virus in human infection

Subtype	First isolated	Virulence	Host
H1N1	1918, human	Seasonal influenza in human (Department of Health and Human Services Centers for Disease Control and Prevention 2005)	Avian, human, camel, canine, cat, cheetah, ferret, giant anteater, mink, seal, swine
H1N2	1976, murre	HPAI (Ferrari <i>et al.</i> 2010)	Avian, human, swine
H2N2	1957, human	Seasonal influenza in human (Scholtissek <i>et al.</i> 1978)	Avian, human
H3N2	1969, turkey	Seasonal influenza in human (Department of Health and Human Services Centers for Disease Control and Prevention 2005)	Avian, human, canine, feline, ferret, mink, swine
H5N1	1959, chicken	HAPI (Department of Health and Human Services Centers for Disease Control and Prevention 2005)	Avian, human, blow fly, canine, cat, cheetah, civet, equine, ferret, leopard, mink, pika, raccoon dog, stone marten, swine, tiger
H7N2	1978, duck	LPAI (Belser <i>et al.</i> 2009)	Avian, human, swine
H7N3	1963, turkey	LPAI/HPAI (Belser <i>et al.</i> 2009)	Avian, human
H7N7	1902, chicken	LPAI/HPAI (Belser <i>et al.</i> 2009)	Avian, human, equine, seal
H7N9	1988, turkey	LPAI	Avian, human
H9N2	1966, turkey	LPAI (Peiris <i>et al.</i> 1999)	Avian, human, canine, equine, swine
H10N7	1949, chicken	LPAI (Arzey <i>et al.</i> 2012)	Avian, human

HPAI, highly pathogenic avian influenza; LPAI, low pathogenicity avian influenza.

introductions to humans (Gao *et al.* 2013) (Fig. S1). Genetic mutation analysis revealed that the NA amino acid sequence of a patient had no H275Y and R294K substitutions, indicating that it was sensitive to Tamiflu. M1 protein was found in virulence sites (N30D) and T215A. The M2 protein was found to exit S31N substitution, indicating resistance to Adamantanes (amantadine and rimantadine).

## SUBTYPES OF AN INFLUENZA VIRUS-INFECTED HUMAN

Since 1996, a few isolated cases (>100) of human infection with virus A subtype H7 (H7N2, H7N3 and H7N5) have been reported, but none have been fatal. The largest outbreak of subtype H7 infections in humans to date occurred in 2003, in the Netherlands, and was caused by highly pathogenic avian influenza (HPAI) H7N7, with 89 patients (Hirst *et al.* 2004; Nguyen-Van-Tam *et al.* 2006; Eurosurveillance Editorial Team 2007). Human infections with avian influenza A viruses, which usually occur after recent exposure to poultry, have caused a wide spectrum of illness, ranging from conjunctivitis and upper respiratory tract disease to pneumonia and multiorgan failure (Arzey *et al.* 2012). However, the H7N9 subtype virus can gain genes, which significantly increases its virulence and the death rate in human. These viruses are branded as HPAI viruses according to the intravenous pathogenicity index method described by the World Organization for Animal Health (Cullen & Linnance 1996). LPAI viruses (H9N2) are also considered to have pandemic potential in poultry in many countries (Peiris *et al.* 1999). Poultry, as an intermediate host, may play an important role in the transmission of influenza viruses from wild birds to humans (Sharp *et al.* 1997). So far, there are 11 subtypes of influenza A virus isolated from humans that can cause human infections (Table 1). Of great concern to humans are the occasional highly contagious H5N1 viruses circulating in avian populations. Equally worrying was the appearance of a 2009 swine-origin H1N1 influenza A virus in humans (Fraser *et al.* 2009; Neumann *et al.* 2009; Novel Swine-Origin Influenza A [H1N1] Virus Investigation Team 2009). In Mar 2013, the 2013 A (H7N9) virus was first detected in humans, and has since been declared a pandemic by the NHFPCC. Complex processes between virus and host have been put in place to control viral cross-infection to the human population (Neumann *et al.* 2009). The possible source of infection and mode of transmission of the current outbreak in China is

still inclusive. Until the source is identified, more cases of human infection in China are expected. In addition, no effective vaccine has been identified. So far, there is no evidence of sustained human-to-human transmission. However, the genetic changes seen among these viruses suggest that adaptation to mammals is of concern, and further adaptation may occur.

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## REFERENCES

- Arzey GG, Kirkland PD, Arzey KE *et al.* (2012). Influenza virus A (H10N7) in chickens and poultry abattoir workers, Australia. *Emerging Infectious Diseases* **18**, 814–6.
- Belser JA, Bridges CB, Katz JM, Tumpey TM (2009). Past, present and possible future human infection with influenza virus A subtype H7. *Emerging Infectious Diseases* **15**, 859–65.
- Cullen GA, Linnance S, eds (1996). *Manual of Standards for Diagnostic Tests and Vaccines*, 3rd edn. The Organisation, Paris.
- Department of Health and Human Services Centers for Disease Control and Prevention (2005). Avian influenza (bird flu). [Cited 14 Apr 2013.] Available from URL: <http://www.cdc.gov/flu/avian/gen-info/flu-viruses.htm>
- Eurosurveillance Editorial Team (2007). Avian influenza A/(H7N2) outbreak in the United Kingdom. *Euro Surveillance*; 12:E070531.2. [Cited 18 Apr 2013.] Available from URL: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=3206>
- Ferrari M, Borghetti P, Foni E *et al.* (2010). Pathogenesis and subsequent cross-protection of influenza virus infection in pigs sustained by an H1N2 strain. *Zoonoses Public Health* **574**, 273–80.
- Fraser C, Donnelly CA, Cauchemez S *et al.* (2009). Pandemic potential of a strain of influenza A (H1N1): early findings. *Science* **324**, 1557–61.
- Gao R, Cao B, Hu Y, Feng Z *et al.* (2013). Human infection with a novel avian-origin influenza A (H7N9) virus. *New England Journal of Medicine*. **368**, 1888–97.

- Gonzalez-Reiche AS, Morales-Betoulle ME, Alvarez D *et al.* (2012). Influenza A viruses from wild birds in Guatemala belong to the North American lineage. *PLOS ONE* **7**, e32873.
- Hirst M, Astell CR, Griffith M *et al.* (2004). Novel avian influenza H7N3 strain outbreak, British Columbia. *Emerging Infectious Diseases* **10**, 2192–5.
- Kim HR, Park CK, Lee YJ *et al.* (2012). Low pathogenic H7 subtype avian influenza viruses isolated from domestic ducks in South Korea and the close association with isolates of wild birds. *Journal of General Virology* **93**, 1278–87.
- Munster VJ, Wallensten A, Baas C *et al.* (2005). Mallards and highly pathogenic avian influenza ancestral viruses, northern Europe. *Emerging Infectious Diseases* **11**, 1545–51.
- Neumann G, Noda T, Kawaoka Y (2009). Emergence and pandemic potential of swine origin H1N1 influenza virus. *Nature* **459**, 931–9.
- Nguyen-Van-Tam JS, Nair P, Acheson P *et al.* (2006). Outbreak of low pathogenicity H7N3 avian influenza in UK, including associated case of human conjunctivitis. *Euro Surveillance* **11**, E060504.2.
- Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team (2009). Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *New England Journal of Medicine* **360**, 2605–15.
- Peiris M, Yuen KY, Leung CW, Chan KH, Ip PL, Lai RW (1999). Human infection with influenza H9N2. *Lancet* **354**, 916–7.
- Perez-Ramirez E, Gerrikagoitia X, Barral M, Hofle U (2010). Detection of low pathogenic avian influenza viruses in wild birds in Castilla-La Mancha (south central Spain). *Veterinary Microbiology* **146**, 200–8.
- Scholtissek C, Rohde W, Von Hoyningen V *et al.* (1978). On the origin of the human influenza virus subtypes H2N2 and H3N2. *Virology* **87**, 13–20.
- Sharp GB, Kawaoka Y, Jones DJ *et al.* (1997). Coinfection of wild ducks by influenza A viruses: distribution patterns and biological significance. *Journal of Virology* **71**, 6128–35.
- Zhang J, Lei F (2010). Analysis of human infectious avian influenza virus: hemagglutinin genetic characteristics in Asia and Africa from 2004 to 2009. *Integrative Zoology* **5**, 264–71.

## SUPPORTING INFORMATION

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**Figure S1** Phylogenetic trees of the novel influenza A (H7N9) viruses, China.

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