Emerging Problems in Infectious Diseases

The Third Wave: H7N9 Endemic Reassortant Viruses and Patient Clusters

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Abstract

Southern China experienced few cases of H7N9 during the first wave of human infections in the spring of 2013. The second and now the third waves of H7N9 infections have been localized mostly in Southern China with the Guangdong province an epicenter for the generation of novel H7N9 reassortants. Clusters of human infections show human-to-human transmission to be a rare but well-documented event. A recent cluster of infections involving hospital health care workers stresses the importance of care givers utilizing personal protective equipment in treating H7N9 infected or suspected patients.

Key words: H7N9; Influenza; Pnuemonia

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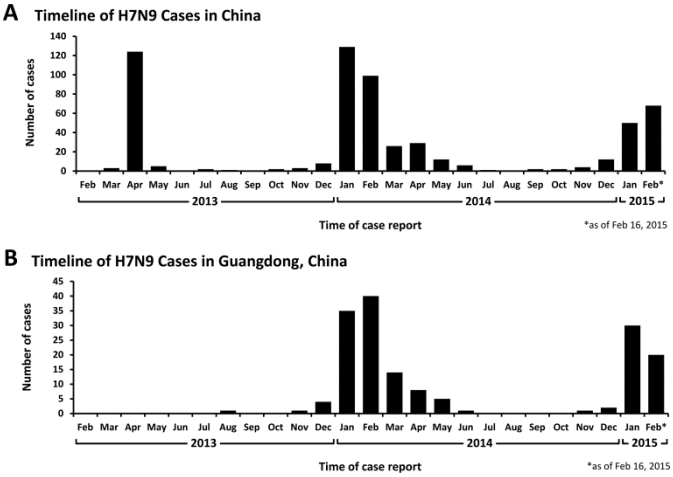
The third wave of the H7N9 outbreak of human infections in China began in late 2014 and has continued with increasing numbers of human cases through the early months of the 2015 calendar year (Figure 1A). Interestingly, the largest number of human cases has been reported in Southern China, with the Guangdong province accounting for more than 50 patients in January and February alone (Figure 1B). This contrasts the absence of any reported cases in the Guangdong province during the first wave and now underscores a major shift in geographical distribution of H7N9 cases and genotypic diversity of the H7N9 virus.

The first wave of H7N9 infections began on 31 March 2013, when Chinese public health officials issued the first report of human infection with novel avian-origin reassortant influenza A (H7N9) detected in three patients from Anhui and Shanghai, China [1]. The subsequent first wave of H7N9 lasted until May 2013 and resulted in 133 confirmed cases with 45 deaths concentrated in the Eastern Chinese provinces of Shanghai, Zhejiang, and Jiangsu [2, 3]. Patients typically presented with fever and cough, and while the majority developed pneumonia, a number of patients further developed acute respiratory distress syndrome (ARDS) which often led to refractory hypoxemia and death [4]. The simultaneous H7N9

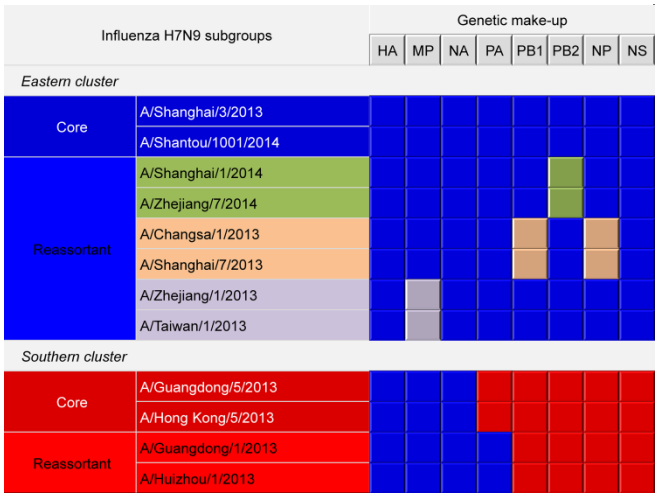
Figure 1. Timeline of H7N9 cases in China. Number of laboratory-confirmed H7N9 cases reported by month in China (A) and specifically in the province of Guangdong, China (B), based on data obtained from the Centre for Health Protection in Hong Kong, China. Data from the Centre for Health Protection is current as of February 16th, 2015.



circulation among market birds in outbreak regions [5, 6] and frequent history of previous poultry contact among hospitalized H7N9 patients [4, 7] suggested zoonotic transmission of the H7N9 virus. In response to the link between poultry contact and zoonotic transmission, Chinese authorities enforced widespread poultry market closures. The closures coincided with a decrease in new cases during the first wave [3, 8].

The second wave of H7N9 human cases began in the fall of 2013 and diminished during the spring 2014, resulting in 266 cases during this period. This wave emerged in two principle locations, the Guangdong province of southern China and the Zhejiang province of eastern China [2, 9, 10]. The peak of the second wave coincided with the Chinese spring festival celebration of the lunar new year. The clinical and epidemiologic features of human H7N9 infection may have changed during this second wave. In addition to a geographic shift to southern China [2, 9], the second H7N9 outbreak was associated with increased hospitalized patient fatality rates [10, 11], including among individuals under 60 years of age [11]. Novel H7N9 variants were also detected in a number of cases in Guangdong, China [12-14]. New H7N9 variants contained internal gene segments PB1, PB2, NP, and NS, which were closely related to locally circulating H9N2 strains [12, 13], revealing the potential for human infection with novel H7N9 reassortants circulating within the avian reservoir. Figure 2 shows a summary of H7N9 genotypic variants in eastern and southern China.

Figure 2. Genetic make-up of the human isolates of influenza H7N9 during the two first waves of the disease. The Eastern and Southern clusters are two differenciated groups of H7N9 that originated from separate sets of circulating avian influenza strains but share nearly identical versions of the HA, MP and NA genes. The genetic variability of influenza H7N9 is mostly due to gene reassortments that resulted in the emergence of several sub-groups. For each sub-group of reassortant viruses, two representative strains are shown.



The initial H7N9 isolates of the first wave arose from a triple reassortment event in poultry between enzootic H9N2 viruses and H7 and N9 viruses introduced from wild birds [1, 5, 15, 16]. H9N2 viruses are endemic in the Chinese poultry population [16] and provide the opportunity for continual H7N9 reassortment and evolution, as evidenced by the new H7N9 variants detected in Guangdong during the second wave [12, 13]. The dynamic nature of the H7N9 virus population has been further emphasized by phylogenetic analyses which have identified considerable genetic diversity among H7N9 viruses and ongoing internal gene segment exchange with enzootic H9N2 viruses [17, 18]. Internal genes including PB2 and NP have been identified as important determinants of avian virus pathogenicity and fitness in mammalian hosts [19-22] and ongoing H7N9 evolution in the avian reservoir may have contributed to changes in H7N9 epidemiology during the second wave. Continued reassortment in the avian reservoir could also allow for the emergence of novel H7N9 strains in subsequent outbreaks with increased pathogenicity or capacity for human-to-human transmission. Rapid analysis of epidemiological data and sequence variants of human H7N9 isolates from the third wave will enable early warnings of increased pathogenicity or increased propensity for human-to-human transmission.

Table 1. Summary of H7N9 cluster reports to date

Cluster Number	Date[a]	Location	Number of Cases	Index Patient		Contact Patients		References
				Gender, Age	Poultry Exposure[b]	Gender, Age	Poultry Exposure[b]	
1	11 February 2013	Shanghai	3	Male, 57	Yes, < 2 weeks	Male, 69 Male, 87	None Reported None Reported	Li Q et al. (2014) N Engl J Med 370:520–32 [3] Jie Z et al. (2013) Am J Respir Crit Care Med 188: 114-115 (23)
2	8 March 2013	Jiangsu	2	Male, 60	Yes, < 1 week	Female, 32	None Reported	Li Q et al. (2014) N Engl J Med 370:520–32 [3] Qi X et al. (2013) BMJ 347:f4752 (24)
3	27 March 2013	Shanghai	2	Female, 51	Yes, < 1 week	Male, 56	None Reported	Li Q et al. (2014) N Engl J Med 370:520–32 [3] Hu J et al. (2014) Euro Surveill 19 (25)
4	16 April 2013	Shandong	2	Male, 36	Unclear	Male, 4	Unclear	Li Q et al. (2014) N Engl J Med 370:520–32 [3] Liu T et al. (2014) BMC Infect Dis 14: 98 [26]
5	21 November 2013	Zhejiang	2	Male, 57	Yes, < 1 week	Male, 31	None Reported	Gao HN et al. (2014) Int J Infect Dis 29:254-8 [27]
6	3 January 2014	Guangdong	2	Male, 29	Yes, < 1 week	Female, 5	Yes, < 2 weeks	Yi L et al. (2015) J Clin Microbiol 53: 22-28 [9] Xiao XC et al. (2014) Euro Surveill 19 [28]
8	13 January 2014	Zhejiang	3	Male, 49	Yes, < 1 week	Female, 24 Female, 43	Yes, < 1 week Yes, < 1 week	Ding H et al. (2014) BMC Infect Dis 14: 698 [29]
9	26 January 2014	Guangdong	2	Male, 37	Yes, < 1 week	Female, 2	Unclear	Yi L et al. (2015) J Clin Microbiol 53: 22-28 [9]
10	28 January 2014	Guangdong	2	Male, 5	Yes, < 1 week	Female, 4	Yes, < 1 week	Yi L et al. (2015) J Clin Microbiol 53: 22-28 [9]
11	23 February 2014	Zhejiang	2	Female, 1.9	Yes, < 1 week	Female, 7	Yes, < 1 week	Mao H et al. (2015) J Clin Virol 63:18-24 [30]
12	16 February 2015	Guangdong	2 [c,d,e]	Not known	Not known	Male, 33 yrs Male, 59 yrs	Not known	

3 additional family clusters have been reported between 20 December 2014 and 27 January 2015, per the World Health Organization (http://who.int/csr/don/8-february-2015-avian-influenza/en/), last accessed 13 February 2015

[a]: First day symptoms were recorded
[b]: If poultry exposure reported, time of last exposure before symptoms indicated
[c]: These 2 cases were confirmed by Guangdong CDC, China
[d]: One suspected H7N9 case is also included in this cluster
[e]: Two confirmed and one suspected H7N9 cases were consented and their clinical and epidemiological information was obtained by H7N9 influenza study group at the Division of Immunology, IIII.

The Guangdong province located in southern China accounts for about 10% of China's domestic poultry industry with trade of more than 950 million birds in the year 2014 (Department of Agriculture for Guangdong Province, http://www.gdagri.gov.cn/zxpt/nyyw/201502/t20150203_462034.html). It is, therefore, not surprising that this province would be the crucible for the generation of novel strains of H7N9 reassortants observed in the second wave and the site of the largest number of cases in the third wave. Through 16 February of this year, 588 human cases of H7N9 have been reported in China, and it would appear that live poultry sold in wet markets are a major source of human exposure to the H7N9 virus. The large number of human cases has now prompted the government to issue a restriction on the sales of live poultry with the hope of diminishing the number of human infections resulting from zoonotic transmission (Guangdong Provincial Center for Disease Control and Prevention, http://www.cdcp.org.cn/gdsjbyfkzzx/mtbd/201502/ea8dc04bbec74309ac9ea0d3dc8b39d2.shtml).

Even though the vast number of H7N9 human infections has been associated with contact with live poultry, a growing number of clusters of human infections has been associated with contact with infected humans, indicating that human-to-human transmission occurs often enough to merit the vigilant use of personal protective equipment and practices by health care workers. Table 1 summarizes the number of reported human clusters. It would appear that in almost all clusters the index case was the result of exposure to poultry, presumably infected with H7N9 (Table 1). Secondary infections developed in care givers and family members exposed to the infected individual (Table 1). Sustained H7N9 human-to-human transmission has not been documented to date in any of these reports. A recent cluster of infections in a hospital setting in Shantou, China, is worth discussing (Table 1). Two attending physicians in a respiratory unit at a local hospital developed pneumonia-like symptoms on the same day in early February. One of them was subsequently diagnosed with H7N9 and developed ARDS. The other physician did not develop ARDS and had a milder course of illness. Repeated testing for H7N9 remains equivocal and sero conversion will be used to determine H7N9 infection status of this patient. Both patients had no known recent exposure to live poultry. A third patient who also spent time in the same respiratory unit in early February has tested positive for H7N9 and had no known recent exposure to live poultry. The identification of an index case of H7N9 in the respiratory unit has not been established and the relationship of these cases with each other is currently under investigation. This cluster of infections suggests that new H7N9 variants may pose a risk for health care workers and care givers and special precautions should be employed when treating suspected and confirmed H7N9 patients during the third wave.

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