Analysis of recent scientific information on avian influenza A(H7N9) virus

10 February 2017

Background

An increase in human infections with avian influenza A(H7N9) virus has been reported by China since October 2016[1]. This document presents recent scientific findings on A(H7N9) viruses.

Current information

Geographical distribution in animals:

A(H7N9) virus causes little or no illness in poultry and is therefore generally only detected through active virological surveillance. A number of surveillance systems routinely monitor for A(H7N9) activity in animals in China. From December 2016, the Chinese national animal influenza virus surveillance program of the Ministry of Agriculture detected influenza A(H7N9) virus in birds in Anhui, Guangdong and Zhejiang provinces[2]. Based on live poultry market (LPM) surveillance conducted by the Chinese provincial Health and Family Planning Commissions in December 2016, 9.4% of environmental samples were positive for A(H7N9) from LPMs in Guangdong and 15.8% of samples from LPMs in Jiangsu were positive for A(H7), of which most were positive for A(H7N9)[3,4].

The low pathogenicity of the virus in birds adds to the difficulty in identifying its international spread through infected birds. To date, A(H7N9) virus has not been reported in poultry populations outside China. Some countries adjacent to China have intensified their surveillance, and several countries have imposed a temporary ban on importing live birds from China[2].

Human infections:

Sudden increases in the number of human A(H7N9) cases reported during December and January have been observed in previous years[5].* Compared to earlier waves of infection, further geographic spread of the virus was observed in this fifth wave[6]. Of the cases where information on exposure history was known, as previous waves, most reported prior exposure to live poultry or potentially contaminated environments, including in LPMs[6].

Among cases reported in the fifth wave, three clusters were reported, comparable to findings in previous waves[1,6]. Limited human-to-human transmission could not be ruled out in these clusters. So far, there has been no indication of significant changes in the epidemiology of the human infections reported, no evidence of sustained human-to-human transmission and no significant changes in the clinical presentation or disease outcome[6].

Population immunity:

In the general population, three serological surveys using specimens collected in 2011 to 2013 reported zero or very low human population immunity against A(H7) viruses[7-9]. Studies of poultry workers with specimens collected in 2011 to 2013 reported between 0 and 7% seropositivity[7,8,10]. In

2015-2016, 15,191 serum samples from poultry workers were collected by 31 provincial Centers for Disease Control (CDCs) in Mainland China, and were tested for A(H7N9) antibody in the WHO Collaborating Centre for Reference and Research on Influenza (WHOCC) in Beijing (also as the Chinese National Influenza Center), of which 26 were positive (0.17%).

Disease severity:

In most cases, infection with A(H7N9) virus is characterized by high fever, cough, shortness of breath and rapidly progressing severe pneumonia. Complications include acute respiratory distress syndrome (ARDS), septic shock and multi-organ failure requiring intensive care[11]. Severe illness and fatal outcome have been more frequently observed in pregnant women[12], in older persons[6] and those with underlying chronic conditions[13]. Asymptomatic and mild infections with A(H7N9) virus have been detected, but the underlying rate of such infections is not well understood[14,15].

Virology:

The detailed virological surveillance data from the first 4 waves have been published[16,17]. For the fifth wave, since 1 October 2016, 83 full genome sequences were analysed: 2 environmental isolates from LPMs in Guangdong and 81 A(H7N9) viruses isolated from specimens collected from human cases by the WHOCC in Beijing. These human specimens were from Jiangsu (N=26), Zhejiang (N=21), Guangdong (N=13), Anhui (N=12), Fujian (N=5) and Hunan (N=4) provinces.

Phylogenetic analysis results show that all the internal genes continue to cluster with previously reported A(H7N9) and A(H9N2) viruses. And the haemagglutinin (HA) and neuraminidase (NA) genes are clustered and evolving in two lineages on the phylogenetic trees; the Yangtze River Delta lineage and the Pearl River Delta lineage (Annex 1 and Annex 2). In general, all of the viruses causing human infections remain similar to viruses analysed since 2013.

Key molecular makers associated with mammalian adaptation and pathogenicity are summarized below and detailed in Annex 3:

a. All viruses contained the 177V and 217L/I (H3 numbering 186V and 226L/I) in HA1, similar with the A(H7N9) viruses since 2013.
b. All viruses contained the 69-73 deletion in NA, same with the A(H7N9) viruses since 2013.
c. Of the 83 viruses, 59 carried 627K in PB2 and 10 carried 701N, and 78 viruses carried I368V in PB1, similar with the A(H7N9) viruses since 2013.

Analyses of these recently isolated viruses from Mainland China as well as Hong Kong Special Administrative Region (SAR) do not show evidence of any changes in known genetic markers of virulence or mammalian adaptation. In comparison to candidate vaccine viruses, amino acid substitutions in the HA of some viruses were identified in antigenic sites. Analysis is underway to determine if existing candidate vaccine viruses remain antigenically correspondent to fifth wave viruses.

Antiviral susceptibility:

Genetic analysis of 83 recent A(H7N9) viruses showed that one virus contained 243T (N2 numbering 246T) and two contained 289K (N2 numbering 292K) mutations in the NA gene, indicating reduced sensitivity to NA inhibitors. All of the other 80 viruses did not contain any of the amino acid substitutions that are known to confer reduced inhibition by the NA inhibitor class of antivirals. Testing of some viruses is underway to assess *in vitro* susceptibility to the NA inhibitor class of antivirals. As observed for A(H7N9) viruses from previous waves of human infection, all 83 viruses carried the S31N mutation on the M2 protein indicating resistance to amantadine and rimantadine.

Transmission in animal models:

Transmission studies of A(H7N9) viruses from 2013 using ferret models indicate that the virus can transmit efficiently through direct contact but inefficiently through respiratory droplets[18-25]. The virus can replicate in swine respiratory tract tissue[26], highlighting the need to screen for further mammalian adaptation. Further studies with more recent A(H7N9) viruses are needed to monitor for any changes in transmissibility.

Conclusions

Based on information reported, there is no evidence of sustained human-to-human transmission, and there are no significant changes in A(H7N9) virus properties or the epidemiology of human infections. As long as humans are exposed to infected animals and their environments, further human cases can be expected.

WHO, through its Global Influenza Surveillance and Response System (GISRS), in collaboration with the OIE FAO Network of Experts on Animal Influenza (OFFLU) and national authorities, will continue monitoring the A(H7N9) virus situation.

As traditionally the consumption of poultry among the general population increases during the Chinese New Year celebrations, the movement, trade and slaughter of poultry during this period may subsequently increase human exposure to the A(H7N9) virus[6]. Countries are encouraged to continue strengthening influenza surveillance, including surveillance for severe acute respiratory infections (SARI) and influenza-like illness (ILI), carefully review any unusual epidemiological patterns, immediately alert WHO Global Influenza Programme (GIP) and WHOCCs of GISRS of unsubtypable influenza viruses, ensure reporting under the International Health Regulations (IHR, 2005), and continue national influenza pandemic preparedness actions.

- Annex 1: Phylogenetic tree for haemagglutinin gene
  pdf, 364kb
- Annex 2: Phylogenetic tree for neuraminidase gene
  pdf, 360kb
- Annex 3: Table of molecular markers for mammalian adaptation and pathogenicity of avian influenza A(H7N9) viruses
  pdf, 236kb

---

*These increases in cases have been referred to as waves. WHO defines these waves as beginning on 1 October until 30 September of the following year. Thus, currently, the increase in human cases is referred to as the fifth wave (1 October 2016 through 30 September 2017).

1. World Health Organization. Human infection with avian influenza A(H7N9) virus – China. Available from: www.who.int/emergencies/disease-outbreak-news/item/18-january-2017-ah7n9-china-enon/17-january-2017-ah7n9-china/en/
2. Food and Agriculture Organization. H7N9 situation update 24 January 2017. Available from: www.fao.org/ag/againfo/programmes/en/empres/H7N9/situation_update.html
3. Health and Family Planning Commission of Guangdong Province. Available from: www.gdwst.gov.cn/a/zwxw/2017011717051.html
4. Jiangsu Provincial Commission of Health and Family Planning. Available from: www.jswst.gov.cn/wsxx/nrglIndex.action?catalogID=4028816b2ba99317012ba99950740003&type=2&messageID=ff80808159433fad015981a71c580427

5. World Health Organization. Monthly Risk Assessment Summary : Influenza at the Human-Animal Interface. Available from: https://www.who.int/teams/global-influenza-programme/avian-influenza/monthly-risk-assessment-summary
6. Zhou L, Ren R, Yang L, Bao C, Jiabing W, Wang D, et al. Sudden increase in human infection with avian influenza A(H7N9) virus in China, September-December 2016. Western Pac Surveill Response J. 2017;9(1). Available from: ojs.wpro.who.int/ojs/index.php/wpsar/article/view/521/733
7. Wang X, Fang S, Lu X, Xu C, Cowling BJ, Tang X, et al. Seroprevalence to avian influenza A(H7N9) virus among poultry workers and the general population in southern China: a longitudinal study. Clin Infect Dis. 2014;59(6):e76-83. Available from: doi.org/10.1093/cid/ciu399
8. Yang S, Chen Y, Cui D, Yao H, Lou J, Huo Z, et al. Avian-origin influenza A(H7N9) infection in influenza A(H7N9)-affected areas of China: a serological study. J Infect Dis. 2014;209(2):265-9. Available from: doi.org/10.1093/infdis/jit430
9. Wang W, Peng H, Tao Q, Zhao X, Tang H, Tang Z, et al. Serologic assay for avian-origin influenza A (H7N9) virus in adults of Shanghai, Guangzhou and Yunnan, China. J Clin Virol. 2014;60(3):305-8. Available from: dx.doi.org/10.1016/j.jcv.2014.04.006
10. Bai T, Zhou J, Shu Y. Serologic study for influenza A (H7N9) among high-risk groups in China. N Engl J Med. 2013;368(24):2339-40. Available from: DOI: 10.1056/NEJMc1305865
11. Yang Y, Guo F, Zhao W, Gu Q, Huang M, Cao Q, et al. Novel avian-origin influenza A (H7N9) in critically ill patients in China. Crit Care Med. 2015;43(2):339-45. Available from: DOI: 10.1097/CCM.0000000000000695
12. Liu S, Sha J, Yu Z, Hu Y, Chan TC, Wang X, et al. Avian influenza virus in pregnancy. Rev Med Virol. 2016;26(4):268-84. Available from: DOI: 10.1002/rmv.1884
13. Liu B, Havers F, Chen E, Yuan Z, Yuan H, Ou J, et al. Risk factors for influenza A(H7N9) disease--China, 2013. Clin Infect Dis. 2014;59(6):787-94. Available from: dx.doi.org/10.1093/cid/ciu423
14. Yu H, Wu JT, Cowling BJ, Liao Q, Fang VJ, Zhou S, et al. Effect of closure of live poultry markets on poultry-to-person transmission of avian influenza A H7N9 virus: an ecological study. Lancet. 2014;383(9916):541-8. Available from: dx.doi.org/10.1016/S0140-6736(13)61904-2
15. Lin YP, Yang ZF, Liang Y, Li ZT, Bond HS, Chua H, et al. Population seroprevalence of antibody to influenza A(H7N9) virus, Guangzhou, China. BMC Infect Dis. 2016;16(1):632. Available from: dx.doi.org/10.1186/s12879-016-1983-3
16. Wang, D., L. Yang, W. Zhu, Y. Zhang, S. Zou, H. Bo, et al. Two Outbreak Sources of Influenza A (H7N9) Viruses Have Been Established in China. J Virol. 2016;90(12): 5561-5573. Available from: dx.doi.org/10.1128/JVI.03173-15
17. Xiang N, Li X, Ren R, et al. Assessing Change in Avian Influenza A(H7N9) Virus Infections During the Fourth Epidemic — China, September 2015–August 2016. MMWR Morb Mortal Wkly Rep 2016;65:1390–1394. Available from: dx.doi.org/10.15585/mmwr.mm6549a2
18. Belser JA, Gustin KM, Pearce MB, Maines TR, Zeng H, Pappas C, et al. Pathogenesis and transmission of avian influenza A (H7N9) virus in ferrets and mice. Nature. 2013;501(7468):556-9. Available from: dx.doi.org/10.1038/nature12391
19. Zhu H, Wang D, Kelvin DJ, Li L, Zheng Z, Yoon SW, et al. Infectivity, transmission, and pathology of human-isolated H7N9 influenza virus in ferrets and pigs. Science. 2013;341(6142):183-6. Available from: dx.doi.org/10.1126/science.1239844
20. Zhang Q, Shi J, Deng G, Guo J, Zeng X, He X, et al. H7N9 influenza viruses are transmissible in ferrets by respiratory droplet. Science. 2013;341(6144):410-4. Available from: dx.doi.org/10.1126/science.1240532
21. Watanabe T, Kiso M, Fukuyama S, Nakajima N, Imai M, Yamada S, et al. Characterization of H7N9 influenza A viruses isolated from humans. Nature. 2013;501(7468):551-5. Available from: dx.doi.org/10.1038/nature12392
22. Luk GS, Leung CY, Sia SF, Choy KT, Zhou J, Ho CC, et al. Transmission of H7N9 Influenza Viruses with a Polymorphism at PB2 Residue 627 in Chickens and Ferrets. J Virol. 2015;89(19):9939-51. Available from: dx.doi.org/10.1128/JVI.01444-15
23. Belser JA, Creager HM, Sun X, Gustin KM, Jones T, Shieh WJ, et al. Mammalian Pathogenesis and Transmission of H7N9 Influenza Viruses from Three Waves, 2013-2015. J Virol. 2016;90(9):4647-57. Available from: dx.doi.org/10.1128/JVI.00134-16
24. Richard M, Schrauwen EJ, de Graaf M, Bestebroer TM, Spronken MI, van Boheemen S, et al. Limited airborne transmission of H7N9 influenza A virus between ferrets. Nature. 2013;501(7468):560-3. Available from: dx.doi.org/10.1038/nature12476

25. Xu L, Bao L, Deng W, Dong L, Zhu H, Chen T, et al. Novel avian-origin human influenza A(H7N9) can be transmitted between ferrets via respiratory droplets. J Infect Dis. 2014;209(4):551-6. Available from: doi.org/10.1093/infdis/jit474
26. Jones, JC, Baranovich T, Zaraket H, Guan Y, Shu Y, Webby RJ, and Webster RG. Human H7N9 influenza A viruses replicate in swine respiratory tissue explants. J.Virol. 2013; 87:12496-12498. Available from: dx.doi.org/10.1128%2FJVI.02499-13