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Human infections by avian influenza virus H5N6: Increasing risk by dynamic reassortment?

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To the Editor,

Despite the increased surveillance and control by vaccination, avian influenza virus (AIV) remains enzootic in domestic poultry in China and in many Asian and countries (Guan et al. 2009; Huang et al. 2016), and infected poultry remains the source for human infections. As of 20 January 2016, the World Health Organization (WHO) has reported 846 laboratory-confirmed human infections with highly pathogenic avian influenza HPAI H5N1 across 16 countries resulting in 449 deaths since 2003 (http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_20_Jan_2016.pdf?ua=1), indicating that HPAI remains a significant public health threat (Peiris et al. 2007). In addition, increasing number of subtypes other than H5N1 and H9N2 had emerged, e.g., H5N2, H5N6, H5N8, and H7N9, a result of reassortment either among enzootic viruses in poultry, or with viruses carried by migratory birds. Conditions conducive to this "dynamic reassortment" (continuous reassortment/process involving) include poultry trade and mixing of host species in live poultry markets (LPM). A novel AIV H5N6, with the HA from a variant of the Asian HPAI H5 lineage, was first identified in Laos, Vietnam, and China in 2013 (Reassortant Highly Pathogenic Influenza A(H5N6) Virus in Laos; Mok et al. 2015). This virus has caused epizootics in poultry and at least nine human infections (Table S1),with the earlier three deaths reported in the southwest China while the most recent five cases all occurring in the Guangdong Province. Of concern, four additional human infections by AIV H5N6 were reported in January 2016 alone (http://www.who.int/csr/don/archive/country/chn/en/).

On genetic analysis of human isolates, generation of novel H5N6 viruses by "dynamic reassortment" is best illustrated in Fig. 1. As shown, H5N6 isolates from human cases in Sichuan was caused by a reassortant virus with the HA gene from a clade 2.3.4.4 Sichuan-like H5N1 virus (nomenclature according to (Smith et al., 2015)), and the NA and other internal genes from a H6N6 virus and a virus of clade 2.3.2.1 H5N1 virus, respectively. Likewise, the Guangzhou case was caused by a reassortant virus with the HA originated from a Guangdong-Jiangxi-like clade 2.3.4.4 H5N1 virus (Mok et al. 2015; Pan et al. 2016; Yang et al. 2015). The progenitor H5N1 viruses were from ducks. However, the two human cases in 2015 were caused by a new H5N6 reassortant, of which the HA and NA genes were from Guangzhou-like H5N6 virus, but the internal genes were from H7N9/H9N2 in chickens. (Data source: A/Yunnan/14563/2015 and A/Yunnan/14564/2015 (Xu et al. 2016); and Shenzhen http://www.szcdc.net/jkdt/zxdt/yqcl/201601/t20160103_3417204.htm). These clinical isolates have high sequence identity to viruses detected in poultry farm and in LPMs (Bi et al. 2015; Pan et al. 2016; Qi et al., 2014) (Xu et al. 2016)· (http://www.szcdc.net/jkdt/zxdt/yqcl/201601/t20160103_3417204.htm.). Clinical history suggests that LPMs were the source of some of these human H5N6 infections. This is not unexpected, as the most significant factor for transmission and dissemination of AIV in China is by live poultry trade and LPMs (Su et al. 2015; Su et al. 2014), posing a risk for the general public.

This dynamic reassortment provides a new venue to study the virulence of HPAI H5NX, and it should be a priority for further research. Of note, retention of internal genes from H7N9/H9N2 in human cases of H5N6, H7N9, and H10N8 infections has been observed (Liu et al. 2014; Su et al. 2015; Xu et al. 2016), but the contribution of these internal genes to virulence remains to be elucidated. In view of these emerging H5N6 cases and the continuing human infections by AIV H7N9, a better understanding of the circulation and evolution of AIV in southern China is urgently needed (http://www.flu.org.cn/en/news_detail?action=ql&uid=&pd=&newsId=18492). Of note, a recently report shows that a novel reassortant H5N6 virus isolated from a girl patient in Changsha, in February, 2014 was a ternary reassortant virus by A/duck/Sichuan/NCXN11/2014(H5N1), A/chicken/Jiangxi/12782/2014(H10N6) and a H5N2 virus isolated in duck from Jiangxi, China (Zhang et al. 2016). Dense surveillance of these reassortant H5N6 viruses in southern China should be considered for public health hidden danger. Similar to the prevention of coronavirus reassortant in China(Su et al. 2016), a re-evaluation of current protocol for controlling AIV spread, including surveillance, vaccination, and risk assessment, is warranted.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.meegid.2016.04.009.

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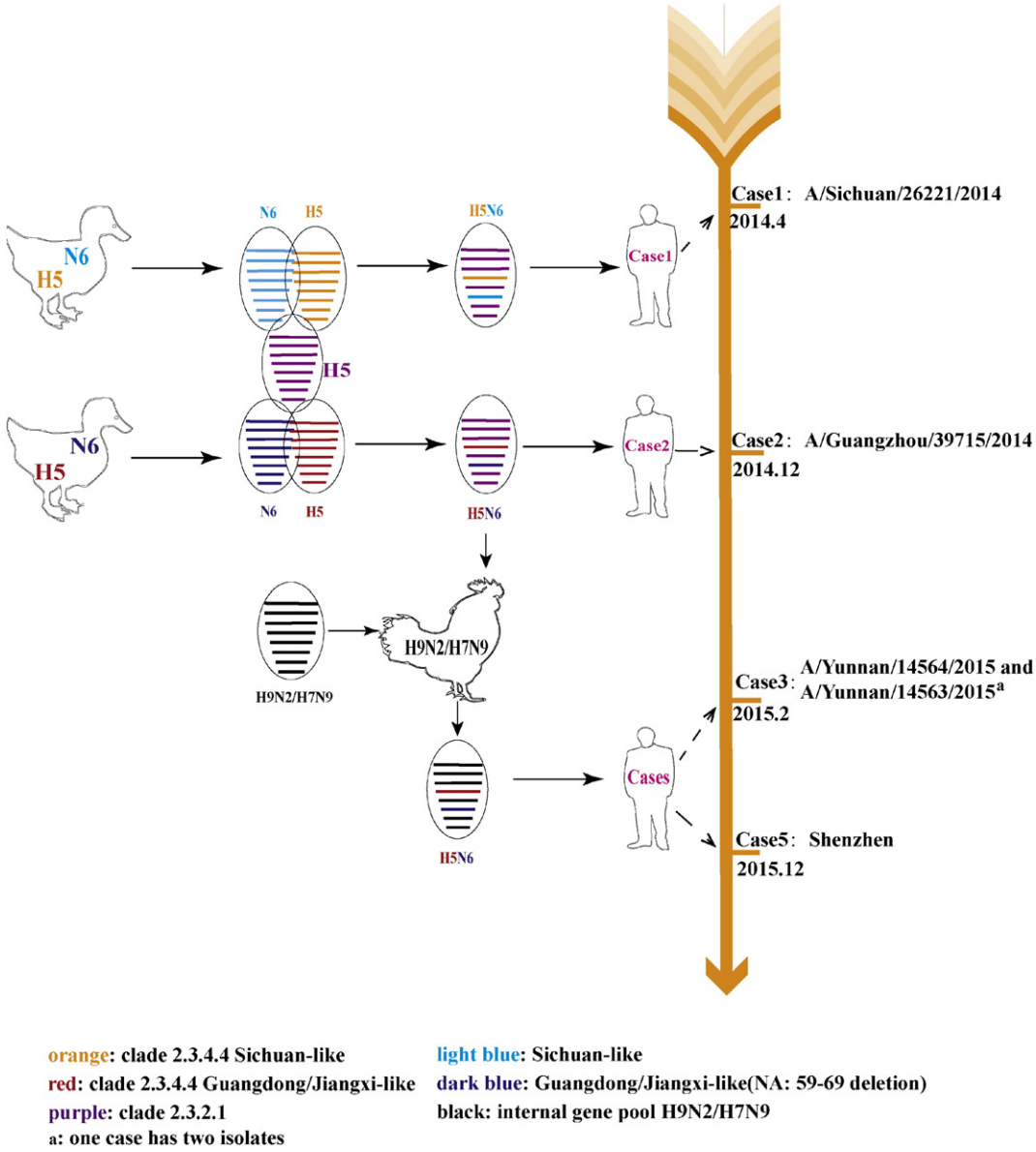

Fig. 1. Schematic for the emergence of novel reassortants H5N6 in humans in China. Horizontal color bars represent the eight segmented viral genes. Top to bottom: PB2, PB1, PA, HA, NP, NA, M, and NS. Different colors represent different genetic origins. A timeline of emergence of H5N6 human cases in China is represented as a vertical line/arrow on the right.

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Gang Xing[1]
Jinyan Gu[1]
Jiangsu Engineering Laboratory of Animal Immunology, Institute of Immunology, Nanjing Agricultural University, Nanjing, Jiangsu, PR China

[1] These authors are co-first authors.

Liping Yan[1]
Jiangsu Engineering Laboratory of Animal Immunology, Institute of Immunology, Nanjing Agricultural University, Nanjing, Jiangsu, PR China
Key Laboratory of Animal Virology of Ministry of Agriculture, Zhejiang University, Hangzhou, PR China
Collaborative Innovation Center and State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University, Hangzhou, PR China

Jing Lei
Jiangsu Engineering Laboratory of Animal Immunology, Institute of Immunology, Nanjing Agricultural University, Nanjing, Jiangsu, PR China

Alexander Lai
Division of Mathematics and Sciences/Biology, College of Arts and Sciences, Kentucky State University, KY, United States
Corresponding author.
E-mail address: Alexander.Lai@kys.edu.

Shuo Su
Jiangsu Engineering Laboratory of Animal Immunology, Institute of Immunology, Nanjing Agricultural University, Nanjing, Jiangsu, PR China
Jiangsu collaborative Innovation Center of Meat Production and Processing, Quality and Safety Control, PR China

Jiyong Zhou
Jiangsu Engineering Laboratory of Animal Immunology, Institute of Immunology, Nanjing Agricultural University, Nanjing, Jiangsu, PR China
Key Laboratory of Animal Virology of Ministry of Agriculture, Zhejiang University, Hangzhou, PR China
Collaborative Innovation Center and State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University, Hangzhou, PR China
Jiangsu collaborative Innovation Center of Meat Production and Processing, Quality and Safety Control, PR China
Corresponding author at: Jiangsu Engineering Laboratory of Animal Immunology, Institute of Immunology, Nanjing Agricultural University, Nanjing, Jiangsu, PR China.
E-mail address: jyzhou@njau.edu.cn.

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