Some Perspectives Regarding Risk Factors for A(H7N9) Influenza Virus Infection in Humans

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(See the Major Article by Liu et al on pages 787–94.)

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As of 20 May 2014, 439 confirmed cases of human A(H7N9) virus infection were reported to the World Health Organization (WHO) [1]. All cases, including those that were detected in Chinese Taipei, Hong Kong Special Administrative Region, and Kuala Lumpur, Malaysia, were presumably infected in mainland China. The cases have occurred in 2 waves: an initial wave (n = 133) during February–May 2013 and a second wave starting in October 2013. This virus has persisted in poultry with a seasonal pattern similar to that of other influenza viruses, circulating at higher levels in cold weather and at lower levels in warmer seasons.

Although complete epidemiologic and virologic analysis of the second wave is yet to be published, risk assessment–related information shared between China and WHO appears to indicate that the host and virus characteristics have not changed substantially between the 2 waves [2]. Most of these infections are believed to result from exposure to infected poultry or contaminated environments. Although some mild illnesses in human A(H7N9) cases have been detected, particularly among younger individuals, most patients have had severe respiratory illness, with about one-third of cases resulting in death. There were no significant increases of clusters during the second wave, and clusters remain limited in size. Epidemiological patterns for A(H7N9) cases from the first wave likely remain valid [3]. Because influenza viruses constantly change, the pandemic potential of this virus persists. As the extent of transmission in poultry is unknown, a surge of sporadic cases of A(H7N9) associated with poultry exposure can be anticipated next winter in eastern China.

Few epidemiologic studies have been published to evaluate risk factors for A(H7N9) virus infection in humans. The article published by Liu et al in this issue of Clinical Infectious Diseases [4] is the first large-scale study of risk factors in which data were collected by different investigating teams from several provinces; a total of 89 cases that occurred in 8 provinces over most of the first-wave time period (March–June 2013) were matched with 339 controls by age, sex, and place of residence. The authors confirmed previous findings that exposure to poultry—particularly from live bird markets (LBMs)—was the main source of infection in humans. Comorbidities were also confirmed to increase the risk of severe disease. Significant comorbidities or medical conditions included chronic obstructive pulmonary disease (COPD), obesity, and use of immunosuppressive medications.

Case-control methods are ideal and commonly used when investigating risk factors for emerging diseases. Timely conducting of this study and sharing of preliminary findings [5] have been indispensable for effective control of infection spread and assessment of risk. However, these findings remain relatively limited in scope. As the spectrum of the H7N9 virus infection remains to be determined, the study’s findings may only apply to risk factors for severe morbidity. Above all, specific details of the mode of transmission are yet to be explored. The understanding of what constitutes a sufficient exposure to avian influenza should also be addressed. Exploration of these detailed risk factors is important when adjusting meaningful biosecurity measures in LBMs, for example. Additional case-control designs could be encouraged. For example, comparison between cases and controls who visit LBMs, particularly the same LBM, could be a systematic adjunct of outbreak investigations of any emerging avian influenza virus infection in humans. Potential risk
Factors to be collected should help refine definitions of direct and indirect contacts to evaluate different pathways of exposure at the animal–human interface, their length and intensity, and host susceptibility (eg, genetic and immunologic factors). Such specific detailed information should be collected in a way that minimizes recall biases—for example, strengthening capacity to administer a standardized questionnaire in a timely manner.

The authors have highlighted the challenges that are inherent to the case-control approach, particularly at the height of an emergency response over a large geographic area. A long delay between periods of interest and interviews coupled with frenzied media attention increases recall biases that are commonly found in case-control studies. In the current study, additional biases are difficult to reduce—for example, coordinating several investigation teams where data quality is difficult to ensure. A lesson learned is the importance of preparation. Preparedness plans that contain procedures for outbreak investigations and response should incorporate other key elements including the development of a package that encompasses several case-control design and respective study template data collection instruments. Given the frequent occurrence of new avian influenza viruses in humans recently—that is, sporadic cases of A(H9N2), A(H10N8), or A(H5N6)—the need for such readiness and preparation is compelling.

Environmental contamination of retail markets may be widespread. Surveillance in Guangzhou city, for instance, appears to indicate high polymerase chain reaction positivity rates of environmental samples tested for A(H7N9) [6]. Many people who work or visit LBMs are exposed to contaminated environments, so it is uncertain why human cases have been concentrated in elderly individuals and, in particular, older men. Given the age- and sex-matching approach of Liu et al’s study, this question remains. The interesting analysis of the controls ruled out differences in the exposure to LBMs by age and sex. This finding was consistent with a recent survey using a larger population in southern China [7]. Similarly, healthcare access bias in relation to sex disparities would not explain the age and sex distribution of the reported cases as such disparities appear limited in China, particularly in urban areas [8].

Identified risk factors alongside aging add to several lines of evidence suggesting that impaired immunity could be a common denominator to explain the epidemiologic features of A(H7N9) patients. Weakened immune system increases risk of infection with A(H7N9). Yet aging, as well as obesity and COPD, are known to be independently associated with weakened immunity [9, 10]. These patterns are also observed in seasonal influenza, which is known to significantly contribute to mortality with underlying respiratory and circulatory causes and diabetes in the United States. Also in the United States, men had higher rates than women of seasonal influenza–associated mortality with underlying respiratory system diseases, COPD, or myocardial infarctions [11]. Interestingly, in China, among all chronic conditions, COPD or other chronic respiratory conditions appeared to be more frequent in males [12].

The importance of LBMs is undeniable for the dynamics of transmission of A(H7N9) and other avian influenza viruses in China. Market closure is thought to effectively interrupt bird-to-human transmission during the epidemic period. Nevertheless, compliance with the highest biosecurity and market management standards in LBMs is essential, although, as seen in 2014, its implementation and enforcement is challenging. It is reported that China’s poultry industry has had approximately $3.3 billion in losses due to the decline in consumer demand in 2014 [13]. These losses have led to major complaints from the poultry industry. The Chinese authorities may aim at a win-win opportunity to urge and engage the industry to promote and self-enforce high standards of poultry market management to safeguard their business and mitigate a possible third wave of A(H7N9) epidemic next winter. Insufficient market management would result in market closure during outbreaks, and alternative market channel options may develop, including illegal trading between provinces and with neighboring countries [14]. These countries may not be as well-equipped as China to conduct surveillance and undertake effective control. Introduction of a low-pathogenic virus in a low-income country could spread more efficiently than A(H5N1) in a backyard poultry network and may subsequently increase the risk of infection to humans.

Control of the virus that focuses mainly on LBMs is not sufficient of itself. These viruses in LBMs are likely to originate in farms, contaminating the entire transport chain; however, infected farms are difficult to detect because A(H7N9) causes inapparent infection in chickens, and its detection relies on effective laboratory-based surveillance. Of note, the first positive farm for A(H7N9) (in Zhubai, Guangdong province) was only notified in March 2014. Thus, the poultry trading business may need major rethinking to encompass food safety measures, applying traceability “from farm to fork.”

**Note**

**Potential conflicts of interest.** Author certifies no potential conflicts of interest.

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**References**


6. Guangzhou City Government. 60% of markets have been found positive for A(H7N9) virus; 82 poultry markets are closed. Available at: http://www.guangzhou.gov.cn/node_2190/node_2215/2014/04/29/1398738181427373.shtml. Accessed 29 April 2014.