Editorial

Avian influenza A (H7N9) virus infections in humans across five epidemics in mainland China, 2013–2017

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Human infections due to a novel avian influenza A (H7N9) virus were first confirmed in Mar 2013 in China in three urban residents hospitalized with severe pneumonia in Shanghai and Anhui (1). The incubation period of human infection with the A (H7N9) virus ranges from 1 to 10 days, with an average of 5 days. The median duration from exposure to poultry to onset of illness was 6 days, while the median duration from illness onset to hospitalization, progression to acute respiratory distress syndrome (ARDS), commencement of antiviral therapy, and death were 4, 7, 6, and 21 days respectively (2). Preexisting comorbid conditions occurred in >60% of these cases. The major presenting symptoms included fever, cough, fatigue, and dyspnea, while lymphopenia and thrombocytopenia were common laboratory findings. Cytokine dysregulations have been noted in patients hospitalized with A (H7N9) infection and the excessive cytokine responses were associated with the clinical severity of A (H7N9) infection (3,4).

Since 2013, there have been five seasonal epidemics, with an upsurge in the number of humans infected with A (H7N9) virus since Oct 2016 in mainland China, raising the concern that the virus might have become more virulent and augmenting the risk of a pandemic (5). Human cases of A (H7N9) infection have been confirmed in Hong Kong (n=21), Taiwan (n=5), Macau (n=2), Canada (n=2) and Malaysia (n=1) in travellers who developed symptoms after returning from the mainland of China to their home cities (6). The estimated hospitalization fatality risk (HFR) among patients hospitalized with A (H7N9) infection in the second epidemic was 48% (95% credibility interval: 42–54%) versus 36% in the first epidemic wave. In the second epidemic, the estimated HFR was 36% (95% CI, 28–45%) among patients below 60 years of age but increased to 59% (95% CI, 51–67%) among those aged at least 60 years (7).

Based on analysis of a large electronic database managed jointly by the China Center for Disease Control and Prevention (CDC) and the provincial CDCs, Wang *et al*. (8) have described in more details the epidemiological data, clinical severity of illness, and time-to-event distributions of patients infected with A (H7N9) in the fifth [2016–2017] epidemic in comparison to previous epidemics. Between 19 Feb 2013 and 23 Feb 2017, 1,220 cases of human infections with A (H7N9) virus were confirmed in mainland China. There were 134 cases in the first epidemic (spring of 2013), 306 in the second epidemic [2013–2014], 219 in the third wave [2014–2015], 114 in the fourth epidemic [2015–2016], and 447 in the fifth epidemic [2016–2017] respectively. The fifth epidemic had started much earlier in time, spread to more counties/districts in the affected provinces, with many more confirmed human cases than the first four epidemics. There was also an increase in the percentage of middle-aged adults infected with A (H7N9) virus from 41% (55 of

134) to 57% (254 of 447) from the first to the fifth epidemic respectively. Residence of patients infected with A (H7N9) virus seemed to have shifted gradually from urban to semi-urban and rural areas from the first to the fifth epidemic, as reflected by the higher percentages of human infections in semi-urban and rural areas in the fourth and fifth epidemics [63% (72 of 114) and 61% (274 of 447), respectively] in comparison to those in the first three epidemics [39% (52 of 134), 55% (169 of 306), and 56% (122 of 219), respectively]. Despite the sharp rise in the number of human cases, the clinical severity of patients hospitalized in the fifth epidemic was similar to that in the first four epidemics while the poultry exposure history has not changed substantially (8).

A more recent review has shown that between 31 Mar 2013 and 07 Aug 2017, there were 1,557 human cases of A (H7N9) infection with 605 deaths (9). Similar to the first four epidemics, 70% of human infections during the fifth epidemic occurred in men, with median age of 57 years (range, 4–93 years), and the majority (90%) had a history of recent poultry exposure and resulted in severe respiratory failure. Among the 759 human cases reported as of 07 Aug 2017 in the fifth epidemic, 14 clusters of 2–3 persons with A (H7N9) infection were reported to the WHO versus an average of 9 clusters in each of the previous epidemics (9). While most human cases confirmed since 2013 were caused by low pathogenic avian influenza (LPAI) A (H7N9) virus infection, 27 cases of highly pathogenic avian influenza (HPAI) A (H7N9) virus infection have been confirmed in three provinces in southern China during the fifth epidemic. Preliminary analysis indicated that HPAI A (H7N9) human cases were more likely to occur in rural areas, have exposure to sick or dead poultry, and hospitalized earlier than LPAI A (H7N9) cases (10).

The major and original source of A (H7N9) outbreaks is the Yangtze River Delta region, located in eastern China. Based on evolutionary analysis of the *HA* gene sequences of A (H7N9) viruses from the first three epidemic waves, the Pearl River Delta region has been identified as another source of A (H7N9) outbreak. There have been repeated introductions of A (H7N9) viruses from these two sources to the other areas and the persistent circulation of A (H7N9) viruses in poultry has led to continuous epidemic waves. The AnH1 genotype was predominant during the first epidemic wave, but was replaced by JS537, JS18828, and AnH1887 genotypes during the second and third epidemic waves (11). Among 166 A (H7N9) virus *HA* gene sequences from the fifth epidemic, 159 were from the Yangtze River Delta lineage versus 7 from the Pearl River Delta lineage. Three patients in the fifth epidemic were confirmed to be infected with HPAI A (H7N9) viruses with severe clinical symptoms and the viruses belonged to the Yangtze River Delta lineage. Four amino acids insertion (Lys, Arg, Thr, Ala) at the *HA* cleavage site facilitated the A (H7N9) HPAI virus in displaying a trypsin-independent infectivity (12). Although maintaining dual receptor-binding preference, their *HA* antigenicity was distinct from LPAI A (H7N9). Furthermore, NA R292K conferred a multidrug resistance phenotype (13).

A (H7N9) virus has been detected and isolated in birds, their secretions and in live poultry market (LPM) environments while closure of LPMs was effective in reducing the human risks of A (H7N9) infection. It has been estimated that closure of LPM could decrease the mean number of A (H7N9) virus infections in humans daily in the four most affected cities by 97% to 99% (14). Closure of LPMs in the mainland of China is however difficult to maintain due to the local cultural preference for live poultry.

Most of the human cases of A (H7N9) infection are sporadic but there have been a number of family clusters in which human-to-human H7N9 virus transmission is likely to have occurred on a limited and non-sustained scale (2,15). Visiting LPMs even without direct poultry contact, chronic obstructive pulmonary disease, immune-suppressive medications (16), and raising backyard poultry at home are risk factors for primary infection (17). Limited human to human transmission in the hospital settings, together with risk factors such as an overcrowded ward environment and performance of aerosol-generating procedures, has been reported (18,19). Administration of systemic corticosteroids and double-dose neuraminidase inhibitors (NAIs) became the norm for patients hospitalized for A (H7N9) infection (8,20). Predictors of death included complications such as ARDS, heart failure and septic shock, administration of systemic corticosteroids, and disease duration (20). When managing patients with acute respiratory infection (ARI), the WHO infection prevention and control (IPC) guidelines for ARI patient care that are applicable to H7N9 patients include early recognition and isolation of patients, application of routine IPC standard precautions for all patients, airborne precautions for high risk aerosol-generating procedures, and other strategies in healthcare facilities such as early recognition and source control, environmental/engineering controls, administrative controls, and appropriate personal protective equipment (21).

NAIs are the main class of licensed therapeutic agents for treatment of A (H7N9) influenza virus infections in

humans. However, the emergence of NAI-resistant variants of A (H7N9) viruses with an NA R292K mutation has posed some difficulty on clinical treatment. In two patients who had received systemic corticosteroid treatment for ARDS despite treatment with NAI, an Arg292Lys mutation in the virus *NA* gene, known to confer resistance to both zanamivir and oseltamivir, was identified. In one of the two patients, wild-type sequence Arg292 was observed 2 days after commencement of NAI treatment, and the resistant mutant Lys292 dominated 9 days after commencement of NAI treatment (22). In another patient with a persistently high viral load despite oseltamivir treatment, an R292K variant of the Anhui (22) lineage was isolated, with a high level of resistance conferred by the R292K mutation to oseltamivir carboxylate and moderate resistance to peramivir and zanamivir. Other classes of antivirals, such as favipiravir, ribavirin and NT-300, efficiently inhibited both the variant and the wild-type in cell-based assays. A combination of NAIs and other classes of antiviral agents did not show any synergistic effect against the R292K variant. However, a combination of two different classes of antiviral agents (favipiravir and ribavirin) demonstrated significant synergism against the mutant virus. In experimentally infected mice, the variant showed delayed onset of symptoms, a decreased viral load, and reduced fatality in comparisons with the wild-type (23). The study findings have suggested that other classes of antiviral agents should be evaluated individually or in combination in animal models and as clinical trials for A (H7N9) patients who have persistently high viral loads despite treatment with NAI (23).

Among all the influenza viruses assessed by the CDC's Influenza Risk Assessment Tool, avian influenza A (H7N9) virus has the highest potential for pandemic risk (24). The emerging A (H7N9) viruses clearly highlight the importance of early analysis and public sharing of sequence data in order to facilitate pandemic preparedness efforts (9). Enormous efforts are needed to prevent and control the spread of A (H7N9) viruses (both LPAI and HPAI) in the poultry population, through continuous surveillance of poultry, the environment, and humans for the presence of A (H7N9) viruses in both urban and rural China, in addition to antiviral surveillance. It is important to avoid the use of high dose systemic corticosteroids which was associated with prolonged viral shedding and increased risk of death (25). Development of H7N9 vaccines is critical in controlling the virus in the poultry population while long-term closure of LPMs is another important public health measure that should be considered if the HPAI viruses continue to emerge in the poultry population (26).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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