

**Evolving epidemiology of human infections with avian influenza  
A(H7N9) virus across five epidemic waves in mainland China,  
2013–17: an epidemiological study of laboratory-confirmed case  
series**

Xiling Wang\*, Hui Jiang\*, Peng Wu\*, Timothy M. Uyeki\*, Luzhao Feng, Shengjie Lai,  
Lili Wang, Xiang Huo, Ke Xu, Enfu Chen, Xiaoxiao Wang, Jianfeng He, Min Kang,  
Renli Zhang, Jin Zhang, Jiabing Wu, Shixiong Hu, Hengjiao Zhang, Xiaoqing Liu,  
Weijie Fu, Jianming Ou, Shenggen Wu, Ying Qin, Zhijie Zhang, Yujing Shi, Juanjuan  
Zhang, Jean Artois, Vicky J. Fang, Huachen Zhu, Yi Guan, Marius Gilbert, Peter W.  
Horby, Gabriel M. Leung, George F. Gao, Benjamin J. Cowling†, Hongjie Yu†

**School of Public Health, Fudan University, Key Laboratory of Public Health  
Safety, Ministry of Education, Shanghai, China** (X Wang PhD, Z Zhang, PhD, J  
Zhang MSc, Prof H Yu PhD); **Key Laboratory of Surveillance and Early-  
warning on Infectious Disease, Division of Infectious Disease, Chinese  
Center for Disease Control and Prevention, Beijing, China** (H Jiang MD, L Feng  
PhD, S Lai MD, Y Qin PhD, Y Shi MD); **WHO Collaborating Centre for Infectious  
Disease Epidemiology and Control, School of Public Health, Li Ka Shing  
Faculty of Medicine, The University of Hong Kong, Hong Kong Special  
Administrative Region, China** (P Wu PhD, V Fang MPhil, H Zhu PhD, Prof Y Guan

PhD, Prof G Leung MD, Prof B Cowling PhD); **Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA** (T Uyeki MD); **Institute Pasteur of Shanghai, Chinese Academy of Sciences, Shanghai, China** (L Wang MSc); **Jiangsu Provincial Center for Disease Control and Prevention, Suzhou, China** (X Huo MD, K Xu MD); **Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China** (E Chen MD, X Wang MD); **Guangdong Provincial Center for Disease Control and Prevention, Guangzhou, China** (J He MD, M Kang MD); **Shenzhen Center for Disease Control and Prevention, Shenzhen, China** (R Zhang MD); **Anhui Provincial Center for Disease Control and Prevention, Hefei, China** (J Zhang MD, J Wu MD); **Hunan Provincial Center for Disease Control and Prevention, Changsha, China** (S Hu MD, H Zhang MD); **Jiangxi Provincial Center for Disease Control and Prevention, Nanchang, China** (X Liu MD, W Fu MD); **Fujian Provincial Center for Disease Control and Prevention, Fuzhou, China** (J Ou MD, S Wu MD); **Spatial Epidemiology Lab. (SpELL), 'Université Libre de Bruxelles', Brussels, Belgium** (J Artois PhD, M Gilbert PhD); **Centre of Influenza Research and State Key Laboratory of Emerging Infectious Diseases, School of Public Health, The University of Hong Kong, Hong Kong Special Administrative Region, China** (H Zhu PhD, Prof Y Guan PhD, Prof G F Gao PhD); **State Key Laboratory of Emerging Infectious Diseases (The University of Hong Kong-Shenzhen Branch),**

**Shenzhen Third People's Hospital, Shenzhen, China** (H Zhu PhD, Prof Y Guan PhD); **Shantou University-The University of Hong Kong Joint Institute of Virology, Shantou University, Shantou, China** (H Zhu PhD, Prof Y Guan PhD); **Fonds National de la Recherche Scientifique, Brussels, Belgium** (M Gilbert PhD); **Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK** (Prof P W Horby MBBS); **Chinese Center for Disease Control and Prevention, Beijing, China** (Prof G F Gao PhD)

\*Contributed equally to this work

†These authors are joint senior authors.

Corresponding author: Prof Hongjie Yu, School of Public Health, Fudan University, No. 130 Dongan Road, Shanghai 200032, China; email: cfetpyhj@vip.sina.com

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**Running head:** Epidemiology of A(H7N9) human cases in 2013–17

## SUMMARY

**Background:** Avian influenza A(H7N9) virus has caused human infections in China since 2013, and a large epidemic in 2016–17 has prompted concerns of whether the epidemiology has changed to suggest an increasing pandemic threat. Our study aimed to describe the epidemiological characteristics, clinical severity, and time-to-event distributions of A(H7N9) case-patients in the 2016–17 epidemic wave compared with previous waves.

**Methods:** We obtained information about all laboratory-confirmed human cases of A(H7N9) virus infection reported in mainland China as of 23 February 2017. We described the epidemiological characteristics across epidemic waves, and estimated the risk for death, mechanical ventilation, and admission to the intensive care unit for patients who required hospitalization for medical reasons. We estimated the incubation periods, and time delays from illness onset to hospital admission, illness onset to initiation of antiviral treatment, and hospital admission to death or discharge.

**Findings:** A total of 1220 laboratory-confirmed human infections with A(H7N9) virus has been reported as of 23 February 2017 in mainland China, with 134, 306, 219, 114 and 447 cases for the spring of 2013, 2013–14, 2014–15, 2015–16 and 2016–17 epidemic waves. The 2016–17 A(H7N9) epidemic wave began earlier, spread to more counties in affected provinces and had more confirmed cases than previous epidemic waves. The proportion of cases in middle-aged adults increased steadily from 41% to 57% from the first wave to the 2016–17

epidemic wave. Proportions of cases in semi-urban and rural residents in the 2015–16 and 2016–17 epidemic waves (63% and 61%) were higher than those in the first three epidemic waves (38%, 56% and 55%). The clinical severity of hospitalized cases in 2016–17 was comparable to the previous epidemic waves.

**Interpretation:** Age distribution and case sources changed gradually across epidemic waves, while clinical severity has not changed substantially. Continued vigilance and sustained intensive control efforts are needed to minimize the risk of human infection with A(H7N9) virus.

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**Key words:** Avian influenza; H7N9; Epidemiology; Risk assessment

## INTRODUCTION

The emergence of novel avian influenza A(H7N9) virus in 2013 poses a pandemic threat to humans, which necessitates close monitoring of the virus and continuing assessment of pandemic risk.<sup>1</sup> Human cases of A(H7N9) virus infection have occurred during annual winter-spring epidemic waves in mainland China since 2013,<sup>1</sup> reaching 1,220 laboratory-confirmed cases and 494 deaths as of 23 February 2017. After peaking during 2013–14, the number of cases identified in subsequent epidemic waves was generally lower, until a surge in A(H7N9) cases was observed in December 2016, in the 5<sup>th</sup> epidemic wave of human infections.<sup>2</sup> The 5<sup>th</sup> epidemic wave that started on 1 October 2016 has included 447 laboratory-confirmed cases in mainland China (as of 23 February 2017), and is the largest epidemic wave to date. The earlier start and larger epidemic size in the 5<sup>th</sup> A(H7N9) epidemic wave has prompted concerns of whether the epidemiology has changed to suggest an increasing pandemic threat.<sup>2,3</sup>

Prior to 2016–17, the avian influenza A(H7N9) viruses circulating among poultry in China have been classified as low pathogenic, and infected poultry have been asymptomatic. Experimental studies have reported that some A(H7N9) virus strains have acquired tropism to bind to receptors that are present in the human upper respiratory tract that could facilitate increased transmissibility among

humans.<sup>4,5</sup> On 19 February 2017, the Chinese Center for Disease Control and Prevention (China CDC) reported that A(H7N9) virus with a four basic amino-acid insertion in a host protease cleavage site in the HA protein was identified in two patients with A(H7N9) virus infection in Guangdong province,<sup>6</sup> suggesting that some A(H7N9) virus strains have evolved to become highly pathogenic in poultry.

A(H7N9) virus has the highest risk score among the 12 novel influenza A viruses evaluated by the Influenza Risk Assessment Tool to date, and is characterized as posing moderate-high potential pandemic risk by the U.S. Centers for Disease Control and Prevention.<sup>3</sup> In addition to the on-going monitoring of virological and molecular characteristics of A(H7N9) viruses recovered from infected poultry and humans, continuous epidemiological investigations and clinical severity assessments of A(H7N9) case-patients are critical to inform public health for pandemic preparedness.<sup>7-12</sup> The present study aims to assess changes of basic epidemiology, clinical severity and key epidemiological parameters of time-to-event distributions of A(H7N9) case-patients in the 5<sup>th</sup> epidemic wave compared with previous epidemic waves in mainland China.

## **METHODS**

### ***Data***

We collected individual records of all laboratory-confirmed human cases of avian influenza A(H7N9) virus infection in mainland China from an integrated electronic database managed by China CDC and provincial CDCs. Every identified human case of A(H7N9) virus infection was required to be reported to China CDC within 24 hours via a national surveillance system for notifiable infectious diseases. Staff from the local CDCs were responsible for field investigations to collect data using a standardized form. Case definitions, exposure definitions, surveillance for identification of cases, and laboratory testing for A(H7N9) virus have been described in detail elsewhere.<sup>7,13,14</sup> We extracted data about patients' demographic, epidemiological and clinical characteristics, time-to-event dates, and health outcomes on 23 February 2017. Details about the extracted variables are described in the Appendix. We defined the 1<sup>st</sup> epidemic wave from 1 January 2013 to 30 September 2013, and subsequent epidemic waves from October 1 to September 30 of the following year.

### ***Statistical analysis***

In clinical severity analysis, we selected A(H7N9) case-patients who required hospitalization because of serious illness, thus excluding those clinically mild cases admitted into hospitals only for isolation purposes. Clinically mild cases



referred to case-patients with mild respiratory symptoms without complications, and would not be admitted into hospitals based on routine clinical practice.<sup>15-17</sup> Clinical severity measurements included risk for death, risk for death or use of mechanical ventilation, and risk for death or use of mechanical ventilation or ICU admission among hospitalized A(H7N9) case-patients. Clinical severity measurements were estimated using data from hospitalized A(H7N9) patients with definite health outcomes for the first four epidemic waves, while estimated under the competing risk framework considering right-censoring of outcomes for the 5<sup>th</sup> epidemic wave.

Logistic regression models were used to assess potential factors associated with risk for death among hospitalized A(H7N9) case-patients, excluding patients in the 5<sup>th</sup> epidemic wave that had unresolved outcomes as of 23 February 2017. We considered risk factors of epidemic wave, age, sex, underlying chronic diseases, place of residence and time delay from illness onset to initiation of antiviral treatment, and we also stratified analyses by wave. We chose the 4<sup>th</sup> epidemic wave as the reference instead of the 1<sup>st</sup> epidemic wave because case-fatality risk was higher in case-patients admitted before the official announcement of the first confirmed human cases of influenza A(H7N9) than those admitted after the announcement in the 1<sup>st</sup> epidemic wave.<sup>9</sup> Moreover, we could compare the fatality risk in the 5<sup>th</sup> epidemic wave as compared to the previous 4<sup>th</sup> epidemic

wave. As highly pathogenic avian influenza<sup>6</sup> A(H7N9) virus formed a monophyletic subclade within lineage C and A(H7N9) lineage B viruses were only detected in Guangdong province,<sup>18,19</sup> we added a variable of province to examine whether the hospital-fatality risk differed for cases from Guangdong province and other provinces in the 5<sup>th</sup> epidemic wave. Adjusted odds ratios (aOR), together with 95% confidence intervals (CI), were used to assess the effects of the risk factors for mortality among hospitalized cases. To examine the linear trend of fatality risk over waves, we conducted a trend test by setting the wave factor as a continuous variable in the logistic regression model.

We used survival analysis to estimate epidemiologic parameters of time-to-event distributions for A(H7N9) cases.<sup>20</sup> The time-to-event distributions we assessed were presumed infection to illness onset (incubation period), illness onset to hospital admission, illness onset to initiation of antiviral treatment, hospital admission to death and hospital admission to discharge. Statistical analyses were described in detail in Appendix page 2–3.

Statistical analyses were conducted using R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria), and geographic distributions of A(H7N9) human cases were plotted using QGIS (QGIS Development Team, Open Source Geospatial Foundation Project).

### ***Ethical approval***

The collection of epidemiological and clinical data for laboratory-confirmed A(H7N9) human cases is a part of a continuing public health investigation of an emerging outbreak, ruled by The National Health and Family Planning Commission. Therefore, our study was exempt from institutional review board assessment.

### ***Role of the funding source***

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to publish. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## **RESULTS**

The first epidemic wave of human infections with A(H7N9) virus occurred in the spring of 2013 in mainland China, followed by four successive winter-spring epidemic waves from 2013–14, 2014–15, 2015–16 and 2016–17 with laboratory-confirmed cases of 134, 306, 219, 114 and 447, respectively (Table 1, Figure 1A). The number of A(H7N9) cases identified in the 5<sup>th</sup> epidemic wave was the highest among all epidemic waves and the epidemic wave is still on-

going (Figure 1A). The heatmap of wave-specific weekly proportion of laboratory-confirmed A(H7N9) case-patients shows that the 5<sup>th</sup> epidemic wave started earlier than previous epidemic waves (Figure 1B).

A total of 20/31 provinces have reported the identification of human cases of A(H7N9) virus infection, and cases were concentrated in the Yangtze River Delta in eastern China and Guangdong province in southern China (Figure 2 A–B; Appendix, page 4). Although Sichuan province was the only new province reporting laboratory-confirmed human case of A(H7N9) virus infection in the 5<sup>th</sup> epidemic wave, there were 144 newly affected counties (Figure 2C; Appendix, page 5–6). Zhejiang, Guangdong and Jiangsu were the three provinces with the highest cumulative case numbers of 294, 247 and 232, respectively.

The median age of laboratory-confirmed human infections with A(H7N9) virus in the 5<sup>th</sup> epidemic wave was 58 years, which was comparable to previous epidemic waves (Table 1). However, the proportion of cases under 16 years was reduced to 1% in the 5<sup>th</sup> epidemic wave with an increase in the proportion of cases aged 16–59 years (Table 1, Figure 3A). The difference in age distribution across epidemic waves was statistically significant (Table 1), although the 0–15 years age group was sparse and the 16–59 years age group was the only group with a consistent increasing proportion over the waves. Men consistently accounted for around

70% of all cases during the five epidemic waves (Table 1), while the age and sex distribution varied slightly across epidemic waves (Figure 3 B–G). Over half of the cases were finally admitted into a provincial hospital in the 1<sup>st</sup> epidemic wave, while cases were more likely to be admitted into prefecture level hospitals in subsequent epidemic waves (Table 1). Antiviral, antibiotic and corticosteroid treatments, oxygen treatment and mechanical ventilation were commonly administered for A(H7N9) case-patients, and less than 10% A(H7N9) case-patients received ECMO (Table 1). 34%–47% A(H7N9) case-patients died in the five epidemic waves (Table 1). Residence of A(H7N9) case-patients shifted gradually from urban to semi-urban and rural areas from the 1<sup>st</sup> to the 5<sup>th</sup> epidemic wave with a statistically significant difference in case residence across epidemic waves, although the situation varied by province (Table 1, Appendix page 7).

Around 70% of human cases of laboratory-confirmed A(H7N9) virus infection reported exposure to poultry within the 10 days before the onset of symptoms across five epidemic waves (Table 1). Visiting a live poultry market and exposure to backyard poultry were the two major sources of poultry exposure (Table 1). Although the chance of poultry exposure from visiting a live poultry market was lower for rural cases than urban and semi-urban cases, around 40% of rural A(H7N9) case-patients reported poultry exposure from visiting a live poultry

market (Table 1, Appendix page 7). For cases with occupational poultry exposures, semi-urban cases reported a higher proportion of exposure than urban and rural cases in the 1<sup>st</sup>, 2<sup>nd</sup>, 5<sup>th</sup> and total epidemic waves (Table 1, Appendix page 7).

Clinical severity for hospitalized A(H7N9) case-patients increased from the 1<sup>st</sup> to subsequent epidemic waves (Figure 4A). A linear increase in fatality risk was observed from the younger age groups to older age groups (Figure 4B). Case-patients aged over 60 years consistently had higher risks for death, death/mechanical ventilation, death/mechanical ventilation/ICU admission than case-patients aged below 60 years (Figure 4 C–E). After adjusting for age, sex, underlying medical conditions, case residence and delay from illness onset to antiviral treatment, the aOR for fatality risk increased by epidemic waves except for the 4<sup>th</sup> epidemic wave (Table 2), and trend test for wave was statistically significant ( $P=0.0342$ ). Case-patients with older age had higher risk for death, and the aORs increased from 0.70 (95% CI, 0.03–6.38) for 0–15 years, 1 for 16–59 years (reference group), 1.84 (95% CI, 1.28–2.65) for 60–74 years to 2.28 (95% CI, 1.43–3.68) for  $\geq 75$  years, and trend test for age was statistically significant ( $P<0.0001$ ). Case-patients with underlying medical conditions or that received antiviral treatment  $>48$  hours after symptom onset consistently had higher risks for death, although the aORs were not statistically significant (Table

2). In the 5<sup>th</sup> epidemic wave, case-patients from Guangdong province had a slightly lower risk for death, but this was not statistically significant (Table 2). The median days from illness onset to initiation of antiviral treatment were 5·5, 6·2, 5·4, 4·4 and 4·8 days from wave 1 to wave 5, respectively (Appendix, page 8).

## **DISCUSSION**

Our study presented the temporal pattern and spatial dissemination of A(H7N9) epidemics in China, and provided a comprehensive description of the epidemiology of laboratory-confirmed cases of A(H7N9) virus infection, and assessed the clinical severity of A(H7N9) case-patients during the 5<sup>th</sup> epidemic wave. The 5<sup>th</sup> epidemic wave occurred earlier, spread to more counties in affected provinces and infected more people compared to previous epidemic waves.

Although there was only one additional province (Sichuan province) reporting human infections with A(H7N9) virus in the 5<sup>th</sup> epidemic wave as of February 2017, an analysis at the county level suggested much wider geographic spread with many newly affected counties, and the 5<sup>th</sup> epidemic wave is on-going.

Human infections with A(H7N9) virus shifted gradually from urban to semi-urban and rural areas, although the shift differed by provinces.

The earlier occurrence of the 5<sup>th</sup> epidemic wave may be associated with changes in environmental factors such as weather conditions, and more research is

needed to elucidate the mechanisms for seasonality. The geographic expansion of human infections with A(H7N9) virus suggests that A(H7N9) viruses circulating among poultry have spread more widely in China since the emergence of human cases in 2013. The majority of human infections with A(H7N9) virus to date have been with a low pathogenic avian influenza (LPAI) A virus until recently as some virus strains have evolved to be highly pathogenic in the 5<sup>th</sup> epidemic wave. Since LPAI A(H7N9) virus does not cause illness in infected poultry, prevention and containment can be very challenging. LPAI A(H7N9) virus may be undetected in poultry farms, and wholesale and retail markets, unless active surveillance is conducted.<sup>21</sup> Moreover, as increasing numbers of live poultry markets were closed in counties where laboratory-confirmed A(H7N9) cases were reported, it might have resulted in movement of ready-for-market poultry infected with LPAI A(H7N9) virus to wider geographic areas without or with less strict implementation of market closure, including previously unaffected counties. Hence, we suspect that LPAI A(H7N9) virus could spread silently along the poultry trade and transportation routes although we do not have data on trans-regional poultry trade in China.

Laboratory-confirmed cases with A(H7N9) virus infection reported similar frequencies of exposure to sick/dead poultry across the five epidemic waves. However, the exposure pattern may change in the future depending upon the



proportion of low and highly pathogenic avian influenza A(H7N9) viruses circulating among poultry in China. On-going assessment of poultry exposures is essential to study the changes in exposure risk, especially to sick/dead poultry. Although the pattern of poultry exposures for reported human infections with A(H7N9) virus has not changed substantially, the prevalence of poultry infected with A(H7N9) viruses is probably higher than before, as more human infections were reported during the 5<sup>th</sup> epidemic wave.

Although the risk for death showed an increasing trend across waves, no statistically significant risk difference was observed when comparing the 5<sup>th</sup> epidemic wave to the 4<sup>th</sup> epidemic wave. Avian influenza A(H7N9) viruses have undergone some genetic changes,<sup>6</sup> but our findings suggest that the clinical severity of A(H7N9) case-patients in the 5<sup>th</sup> epidemic wave remained similar to the previous epidemic wave. However, if we set the 1<sup>st</sup> epidemic wave as the reference group, we could observe the adjusted ORs from the logistic regression model were statistically significant for the 2<sup>nd</sup>, 3<sup>rd</sup> and 5<sup>th</sup> epidemic waves. The increased clinical severity after the first epidemic wave could result from case ascertainment bias.<sup>8,9</sup> After announcement of the first human case of A(H7N9) virus infection in the 1<sup>st</sup> epidemic wave, both the government and the public were extremely concerned about this novel avian influenza A virus. For example, people became more worried than usual if they developed influenza-like illness

(ILI), especially in urban areas.<sup>22</sup> Laboratory testing for A(H7N9) virus was conducted intensively among suspected cases in the 1<sup>st</sup> epidemic wave. It is possible that after 2013, an improved public perception of a lower risk of A(H7N9) virus infection may have changed people's health seeking behavior. We found that the initiation of antiviral treatment within 48 hours after illness onset was associated with a lower risk for death than the delayed treatment beyond 48 hours since symptom onset. Although antiviral treatment started slightly earlier for A(H7N9) case-patients identified in the latest two epidemic waves than the first three epidemic waves, a reduced fatality risk was not observed in the hospitalized patients detected in recent waves.

Although clusters of human cases have been reported, with epidemiological evidence suggesting some instances of limited human-to-human transmission,<sup>14</sup> there has been no evidence of sustained human-to-human A(H7N9) virus transmission to date. Poultry-to-human transmission remains the major transmission route, and high proportions of laboratory-confirmed cases of A(H7N9) virus infection reported poultry exposure by visiting live poultry markets. Environmental surveillance conducted in Zhejiang province during 2015–16 revealed that 17·3% of the environmental samples collected from live poultry markets were contaminated by H7 subtype viruses.<sup>23</sup> Closure of live poultry markets has been demonstrated to be highly effective in reducing the risk

of human infection with A(H7N9) virus by reducing poultry exposures.<sup>24,25</sup>

Although some cities have temporarily or permanently closed live poultry markets, there are still reported A(H7N9) cases from these cities. Although closure of large live poultry markets may have been implemented in central urban areas, it is possible that smaller live poultry markets in semi-urban and rural areas may still be operating. Epidemiological investigations revealed that more than 40% of semi-urban and rural cases reported that they had visited a live poultry market before illness onset. Closure of live poultry markets in many areas may have been implemented too late in the 5<sup>th</sup> epidemic wave, and only after many A(H7N9) cases had been identified. Regular closure of live poultry markets before the annual winter A(H7N9) epidemic period could be a more effective prevention measure than closure after A(H7N9) cases have been identified.<sup>21</sup> The expansion of areas with permanent closure of live poultry markets might also help to further reduce A(H7N9) cases in the future.

Zhejiang, Jiangsu and Guangdong were the three provinces with the highest cumulative numbers of reported human infections with A(H7N9) virus since early 2013. We observed a weak association between the incidence of A(H7N9) human infections and chicken/duck density,<sup>26</sup> which may be confounded by chicken breeds. Yellow chicken is produced and consumed much more commonly than white chicken in the southern part of the country. Further investigation of

factors associated with the persistence of A(H7N9) virus among poultry in these three provinces is necessary to inform prevention and control measures to reduce the risk of human cases. Risk mapping of A(H7N9) virus in the Yangtze River Delta and Pearl River Delta may provide evidence for making future preventive strategies.

Sentinel surveillance for ILI contributes to identification of clinically mild A(H7N9) cases. The ILI surveillance network consists of 554 sentinel hospitals across 31 provinces, covering 2.5% of all hospitals in China. For each sentinel hospital, 10–15 respiratory specimens were collected each week by convenience samples of patients with ILI symptoms. Considering the sampling method currently used for sentinel surveillance, a large number of undetected A(H7N9) cases with mild symptoms could be occurring.<sup>15</sup> Identification of clinically mild cases through ILI surveillance reveals the “iceberg under the sea”, with implications for the estimation of the infection-fatality risk (which may be much lower than the hospitalization-fatality risk estimated in our study) and the total number of A(H7N9) virus infections that have occurred.<sup>15,27</sup> However, the true denominator of human A(H7N9) virus infections to date, including asymptomatic and clinically mild illness in China, to better inform severity assessments, is unknown.

Our study had several limitations. First, our study analyzed only laboratory-confirmed human infections with A(H7N9) virus that were hospitalized and excluded clinically mild cases. Therefore, the full clinical spectrum of human infection with A(H7N9) virus was not assessed. Second, our estimates for clinical severity could be biased if there were undetected hospitalized patients with A(H7N9) virus infection that were not suspected by clinicians and therefore not tested for A(H7N9) virus infection, or due to lack of access to laboratory testing in some areas. Third, it is possible that the cases or their family members may not have accurately recalled and reported exposure to poultry or to live poultry markets, which might affect estimation of the incubation period. Fourth, some cases did not have an exact date of hospital admission reported in the China CDC A(H7N9) case database, which could result in a slightly biased estimation of the clinical severity.

In conclusion, the 5<sup>th</sup> epidemic wave of human cases of A(H7N9) virus infection occurred earlier, spread to more areas and infected more people compared to previous epidemic waves. Cases shifted from the elderly to middle-aged adults and from urban locations to semi-urban and rural areas. The clinical severity remains unchanged to date. Continuous monitoring and regular assessments of the epidemiology characteristics and clinical severity of human infections with avian influenza A(H7N9) virus are necessary for pandemic risk assessment.

## **Contributors**

HY conceived, designed, and supervised the study. HJ, LF, LW, XH, KX, EC, XW, JH, MK, RZ, JZ, JW, SH, HZ, XL, WF, JO and SW collected data. YQ, YS, JZ and XW cleaned data. XW, PW and VF analyzed the data. JZ, SL and ZZ mapped the case geographic distribution. XW, PW, BC, TU and HY wrote the drafts of the manuscript. HY, BC, TU, JA and MG interpreted the findings. HZ, YG, GG, PWH and GL commented on and revised drafts of the manuscript. All authors read and approved the final manuscript.

## **Conflicts of interest**

BJC has received research funding from Sanofi Pasteur. The authors report no other potential conflicts of interest.

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**Table 1. Characteristics of laboratory-confirmed cases of A(H7N9) virus infection by epidemic waves, Mainland China, 2013–2017.**

Characteristic	No. (%) cases						Chi-square statistics	P value
	Wave 1, Jan 2013–Sep 2013, n=134	Wave 2, Oct 2013–Sep 2014, n=306	Wave 3, Oct 2014–Sep 2015, n=219	Wave 4, Oct 2015–Sep 2016, n=114	Wave 5, Oct 2016–Feb 2017, n=447	All waves, Jan 2013–Feb 2017, n=1220		
Median age (range)	61 (2–91)	57 (2–88)	56 (1–89)	58 (13–92)	58 (4–93)	58 (1–93)		
Age group, y							36.05	<0.0001
0–15	7 (5)	19 (6)	17 (8)	2 (2)	3 (1)	48 (4)		
16–59	55 (41)	151 (49)	116 (53)	61 (54)	254 (57)	637 (52)		
≥60	72 (54)	136 (44)	86 (39)	51 (45)	190 (43)	535 (44)		
Male	94 (70)	212 (69)	156 (71)	77 (68)	317 (71)	856 (70)	0.73	0.9478
Presence of at least one underlying medical conditions							8.57	0.0728
Yes	59 (44)	109 (36)	82 (37)	55 (48)	153 (34)	458 (38)		
No	59 (44)	171 (56)	117 (53)	54 (47)	236 (53)	637 (52)		
Unknown	16 (12)	26 (8)	20 (9)	5 (4)	58 (13)	125 (10)		
Final admitted hospital level							64.32	<0.0001
Provincial level	78 (58)	55 (18)	48 (22)	14 (12)	72 (16)	267 (22)		
Prefecture level	35 (26)	136 (44)	101 (46)	41 (36)	145 (32)	458 (38)		
County/township level	16 (12)	37 (12)	21 (10)	11 (10)	38 (9)	123 (10)		
Unknown	5 (4)	78 (25)	49 (22)	48 (42)	192 (43)	372 (30)		
Residence							27.90	0.0005
Urban	81 (60)	135 (44)	97 (44)	41 (36)	169 (38)	523 (43)		
Semi-urban	30 (22)	97 (32)	73 (33)	42 (37)	140 (31)	382 (31)		
Rural	22 (16)	72 (24)	49 (22)	30 (26)	134 (30)	307 (25)		
Unknown	1 (1)	2 (1)	0 (0)	1 (1)	4 (1)	8 (1)		
Poultry exposure								
Any exposure to poultry							1.85	0.7633
Yes	107 (80)	209 (68)	151 (69)	83 (73)	337 (75)	887 (73)		

No	25 (19)	46 (15)	42 (19)	23 (20)	74 (17)	210 (17)		
Unknown	2 (1)	51 (17)	26 (12)	8 (7)	36 (8)	123 (10)		
Visited live poultry market							7.21	0.1254
Yes	75 (56)	165 (54)	127 (58)	59 (52)	269 (60)	695 (57)		
No	58 (43)	100 (33)	65 (30)	48 (42)	142 (32)	413 (34)		
Unknown	1 (1)	41 (13)	27 (12)	7 (6)	36 (8)	112 (9)		
Exposure to backyard poultry							41.46	<0.0001
Yes	54 (40)	51 (17)	28 (13)	30 (26)	107 (24)	270 (22)		
No	63 (47)	175 (57)	170 (78)	74 (65)	311 (70)	793 (65)		
Unknown	17 (13)	80 (26)	21 (10)	10 (9)	29 (6)	157 (13)		
Exposure to sick or dead poultry							15.91	0.0031
Yes	5 (4)	3 (1)	11 (5)	10 (9)	28 (6)	57 (5)		
No	124 (93)	276 (90)	181 (83)	99 (87)	392 (88)	1072 (88)		
Unknown	5 (4)	27 (9)	27 (12)	5 (4)	27 (6)	91 (7)		
Occupational exposure to poultry							8.43	0.0770
Yes	8 (6)	22 (7)	24 (11)	12 (11)	25 (6)	91 (7)		
No	126 (94)	279 (91)	189 (86)	102 (89)	417 (93)	1113 (91)		
Unknown	0 (0)	5 (2)	6 (3)	0 (0)	5 (1)	16 (1)		
<hr/>								
Poultry exposure by residence								
Any exposure to poultry								
Yes_Urban	61 (75)	82 (61)	65 (67)	29 (71)	126 (75)	363 (68)	0.27	0.9916
Yes_Semi-urban	25 (83)	69 (71)	49 (67)	28 (67)	106 (76)	277 (71)	3.15	0.5323
Yes_Rural	20 (91)	56 (78)	37 (76)	25 (83)	103 (77)	241 (77)	3.90	0.4192
Visited live poultry market								
Yes_Urban	50 (62)	74 (55)	62 (64)	26 (63)	117 (69)	329 (62)	5.57	0.2333
Yes_Semi-urban	16 (53)	51 (53)	41 (56)	19 (45)	86 (61)	213 (55)	5.98	0.4578
Yes_Rural	8 (36)	39 (54)	24 (49)	14 (47)	64 (48)	149 (47)	3.63	0.0001
Exposure to backyard poultry								
Yes_Urban	21 (26)	11 (8)	5 (5)	4 (10)	21 (12)	62 (12)	22.84	<0.0001
Yes_Semi-urban	15 (50)	18 (19)	9 (12)	10 (24)	26 (19)	78 (20)	19.34	0.0007
Yes_Rural	17 (77)	22 (31)	14 (29)	15 (50)	60 (45)	128 (41)	16.73	0.0022

Exposure to sick or dead poultry								
Yes_Urban	0 (0)	1 (1)	2 (2)	2 (5)	2 (1)	7 (1)	5.36	0.2521
Yes_Semi-urban	2 (7)	2 (2)	4 (5)	1 (2)	5 (4)	14 (4)	2.57	0.6323
Yes_Rural	3 (14)	0 (0)	5 (10)	7 (23)	21 (16)	36 (11)	16.16	0.0028
Occupational exposure to poultry								
Yes_Urban	2 (2)	6 (4)	7 (7)	2 (5)	5 (3)	22 (4)	3.75	0.4405
Yes_Semi-urban	5 (17)	10 (10)	7 (10)	5 (12)	13 (9)	40 (10)	1.49	0.0144
Yes_Rural	1 (5)	5 (7)	10 (20)	5 (17)	7 (5)	28 (9)	12.43	<0.0001
Treatment								
Antiviral							4.63	0.3269
Yes	79 (59)	247 (81)	178 (81)	94 (82)	310 (69)	908 (74)		
No	5 (4)	15 (5)	13 (6)	7 (6)	10 (2)	50 (4)		
Unknown	50 (37)	44 (14)	28 (13)	13 (11)	127 (28)	262 (21)		
Antibiotic							9.10	0.0588
Yes	103 (77)	269 (88)	188 (86)	102 (89)	318 (71)	980 (80)		
No	4 (3)	16 (5)	8 (4)	3 (3)	4 (1)	35 (3)		
Unknown	27 (20)	21 (7)	23 (11)	9 (8)	125 (28)	205 (17)		
Corticosteroid							19.95	0.0005
Yes	38 (28)	138 (45)	118 (54)	70 (61)	203 (45)	567 (46)		
No	38 (28)	87 (28)	56 (26)	17 (15)	94 (21)	292 (24)		
Unknown	58 (43)	81 (26)	45 (21)	27 (24)	150 (34)	361 (30)		
Oxygen							26.11	<0.0001
Yes	120 (90)	251 (82)	158 (72)	101 (89)	291 (65)	921 (75)		
No	11 (8)	33 (11)	30 (14)	2 (2)	15 (3)	91 (7)		
Unknown	3 (2)	22 (7)	31 (14)	11 (10)	141 (32)	208 (17)		
Mechanical ventilation							3.34	0.5028
Yes	73 (54)	133 (43)	111 (51)	62 (54)	185 (41)	564 (46)		
No	47 (35)	113 (37)	75 (34)	40 (35)	118 (26)	393 (32)		

ECMO	Unknown	14 (10)	60 (20)	33 (15)	12 (11)	144 (32)	263 (22)	12.38	0.0147
	Yes	14 (10)	8 (3)	11 (5)	4 (4)	25 (6)	62 (5)		
	No	103 (77)	237 (77)	168 (77)	95 (83)	278 (62)	881 (72)		
ICU	Unknown	17 (13)	61 (20)	40 (18)	15 (13)	144 (32)	277 (23)	8.97	0.0618
	Yes	89 (66)	153 (50)	129 (59)	71 (62)	234 (52)	676 (55)		
	No	34 (25)	84 (27)	53 (24)	29 (25)	73 (16)	273 (22)		
	Unknown	11 (8)	69 (23)	37 (17)	14 (12)	140 (31)	271 (22)		
Outcome								8.40	0.0780
	Death	45 (34)	131 (43)	102 (47)	47 (41)	169 (38)	494 (40)		
	Recover	89 (66)	175 (57)	117 (53)	64 (56)	188 (42)	633 (52)		
	Unknown/Unresolved <sup>a</sup>	0 (0)	0 (0)	0 (0)	3 (3)	90 (20)	93 (8)		

<sup>a</sup> The health outcomes for cases in wave 4 were unknown because of loss to follow up, while the health outcomes for cases in wave 5 were unresolved as they were still in hospital when we retrieved the data.

Abbreviations: ECMO, extra-corporeal membrane oxygenation; ICU, intensive care unit.

**Table 2. Comparison of risk for death among hospitalized patients with laboratory-confirmed A(H7N9) virus infection by epidemic waves, mainland China, 2013–2017.**

Characteristic	All waves		Wave 1		Wave 2		Wave 3		Wave 4		Wave 5	
	aOR (95% CI)	<i>P</i> value	aOR (95% CI)	<i>P</i> value	aOR (95% CI)	<i>P</i> value	aOR (95% CI)	<i>P</i> value	aOR (95% CI)	<i>P</i> value	aOR (95% CI)	<i>P</i> value
Age group, y												
0-59	1.00		1.00		1.00		1.00		1.00		1.00	
≥60	1.96 (1.42,2.72)	<0.0001	2.29 (0.71,8.05)	0.1735	2.55 (1.31,5.11)	0.0066	1.29 (0.64,2.62)	0.4673	5.79 (1.97,19.0)	0.0021	1.61 (0.91,2.88)	0.0995
Sex												
Female	1.00		1.00		1.00		1.00		1.00		1.00	
Male	0.88 (0.63,1.24)	0.4859	0.43 (0.12,1.42)	0.1722	0.80 (0.38,1.65)	0.5608	0.76 (0.35,1.63)	0.4963	1.53 (0.48,4.94)	0.4634	0.88 (0.48,1.58)	0.6772
Underlying medical conditions												
No	1.00		1.00		1.00		1.00		1.00		1.00	
Yes	1.32 (0.96,1.83)	0.0812	0.99 (0.30,3.29)	0.9867	0.88 (0.45,1.71)	0.7245	1.33 (0.67,2.66)	0.4116	1.31 (0.44,3.83)	0.6095	1.72 (0.98,3.07)	0.0595
Residence												
Urban	1.00		1.00		1.00		1.00		1.00		1.00	
Semi-urban	0.95 (0.65,1.38)	0.7942	1.17 (0.23,5.53)	0.8416	1.19 (0.53,2.73)	0.6609	1.33 (0.62,2.85)	0.4562	0.15 (0.04,0.51)	0.0034	1.22 (0.63,2.37)	0.5409
Rural	1.02 (0.69,1.52)	0.9023	0.30 (0.01,2.28)	0.3118	1.43 (0.64,3.26)	0.3816	1.06 (0.45,2.49)	0.8766	0.19 (0.04,0.71)	0.0173	1.56 (0.79,3.12)	0.1998
Onset to antiviral treatment, d												
0-2	1.00		1.00		1.00		1.00		1.00		1.00	
≥3	1.52 (0.91,2.57)	0.1074	1.38 (0.19,12.4)	0.7476	1.68 (0.37,7.72)	0.4855	1.66 (0.53,5.46)	0.3807	1.79 (0.41,8.49)	0.4401	1.39 (0.62,3.15)	0.4146
Province												
Province other than Guangdong											1.00	
Guangdong											0.86 (0.41,1.81)	0.7048
Wave												



1	0.53 (0.26,1.07)	0.0822
2	1.25 (0.72,2.16)	0.4240
3	1.36 (0.78,2.38)	0.2667
4	1.00	
5	1.48 (0.88,2.50)	0.1380

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Abbreviation: aOR, adjusted odds ratio.

## **Panel**

### **Evidence before this study**

Avian influenza A(H7N9) virus merged in 2013 and posed a pandemic threat to human population. Human cases of avian influenza A(H7N9) virus infection have occurred during annual winter-spring epidemic waves in mainland China since 2013. A sudden increase in human infections with avian influenza A(H7N9) virus was observed in December 2016 in mainland China, prompting concerns of whether the epidemiology had changed to suggest an increasing pandemic threat. On 13 March 2017, we searched the PubMed for the terms “H7N9” and “epidemiolog\*” in title/abstract, restricting the publication date after 1 October 2016. We identified 12 English language publications, but none described the 5<sup>th</sup> A(H7N9) epidemic wave after reviewing the title and abstract. We have been continuously tracking the publications of A(H7N9) epidemiology characteristics and clinical assessment since 1 October 2016. We knew of an article published in the Western Pacific Surveillance Response Journal that described the epidemic curve of human infections with A(H7N9) virus up to December 2016 in China. However, human infections had not reached the peak when that paper was published. We also knew of a recent article published in the Morbidity and Mortality Weekly Report reporting human cases infected with A(H7N9) virus until February 2017, but no epidemiological characteristics were reported. No

study assessing the clinical severity of A(H7N9) virus infection for the 5<sup>th</sup> epidemic wave was identified.

### **Added value of this study**

Our study presented the temporal pattern and spatial dissemination of A(H7N9) epidemics across epidemic waves. The 5<sup>th</sup> epidemic wave started earlier, spread to more counties in affected provinces and infected more people compared to previous waves. Detailed epidemiological data for the laboratory-confirmed human infections with A(H7N9) virus in the 5<sup>th</sup> epidemic wave were provided and compared with previous epidemic waves. Residence of A(H7N9) case-patients shifted gradually from urban to semi-urban and rural areas from the 1<sup>st</sup> to the 5<sup>th</sup> epidemic, although the situation varied by province. The poultry exposure risk has not changed substantially. The clinical severity of human infections with A(H7N9) virus among hospitalized cases remained similar to previous three epidemic waves.

### **Implications of all the available evidence**

This is the first study that provided detailed epidemiological characteristics and assessed the clinical severity for hospitalized cases of human infections with A(H7N9) virus in the 5<sup>th</sup> epidemic wave. Regular closure of live poultry market before annual winter A(H7N9) epidemics and expansion of areas with

permanent closure of live poultry markets are recommended. Continued vigilance and sustained intensive control efforts are needed to minimize the risk of human infection with A(H7N9) virus.

## Figure Legends

**Figure 1: Temporal pattern of laboratory-confirmed cases of A(H7N9) virus infection, Mainland China, 2013–2017.** A) Epidemic curve of cases by week; B) Heatmap of weekly proportion of laboratory-confirmed cases by waves.

**Figure 2: Geographic distribution of laboratory-confirmed cases of A(H7N9) virus infection in Mainland China, 2013–2017.** A) All waves; B) Wave 5; C) Counties affected by A(H7N9) across 5 epidemic waves.

**Figure 3: Age and sex distributions of laboratory-confirmed cases of A(H7N9) virus infection by five epidemic waves, Mainland China, 2013–2017.** A) Age distribution; B–G) Age and sex distribution in wave 1–5 and all waves.

**Figure 4: Clinical severity profile for hospitalized laboratory-confirmed cases of A(H7N9) virus infection.** A) Risk for deaths, death/mechanical ventilation, death/mechanical ventilation/ICU admissions by waves; B) Risk for deaths, death/mechanical ventilation, death/mechanical ventilation/ICU admissions by age groups; C) Risk for deaths by waves and age groups; D) Risk for deaths/mechanical ventilation by waves and age groups; E) Risk for deaths/mechanical ventilation/ICU admissions by waves and age groups. (ICU,

intensive care unit)