

Turning Points and Climatic Impacts on the Multi-wave H7N9 Outbreaks in Guangdong Province, China

Piaopiao Zhou¹^a, Wenwen Li²^b, Xingfeng Huang³^c, Yuting Wang³^d and Tian Tang^{4,5,*}^e

¹Zhong De College, Zhengzhou Institute of Engineering and Technology, Zhengzhou, China

²Department of Public Basic Education, Henan vocational university of science and technology, Zhoukou, China

³School of Mathematics and Computer Science, Guilin University of Electronic Technology, Guilin, China

⁴National Demonstration Center for Experimental Electronic Circuit Education, Guilin University of Electronic Technology, Guilin, China

⁵Guangxi Key Laboratory of Cryptography and Information Security, Guilin University of Electronic Technology, Guilin, China

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Abstract: The constant emergence of avian influenza A (H7N9) epidemics posed a huge threat to public health in China recently. Based on the data of the human reported cases and climate from October 2013 to May 2017, we employed Richard model, generalized linear model (GLM) and generalized additive model (GAM) to infer the H7N9 transmission potentials in Guangdong Province, which is one of the important H7N9 epicenter. The results indicated that the turning points occurred around mid-January, one week after closing live poultry markets. It was further found that temperature and relative humidity are negatively proportional to the number of H7N9 cases with the lags of 1-3 and 1-5 weeks, respectively. The number of H7N9 cases has a non-linear relationship with rainfall and air pressure. These discoveries can provide practical information for risk assessment and intervention implementation against H7N9 transmissi.


1 INTRODUCTION


Human infections of influenza A (H7N9) virus were first identified in eastern China in March 2013 (Zhou 2015). Thereafter, five waves of human influenza A (H7N9) epidemic (including 1533 human cases with 592 deaths) have been reported in China. Guangdong Province is one of the high-risk areas, where a total of 258 cases have been reported as of December 2017. Current frequent emergence and rapid expansion of avian influenza A (H7N9) virus pose a huge threat to public health in China.


More and more studies have been conducted on the epidemiology and transmission dynamics of H7N9 in recent years. Previous studies have found that human H7N9 infections were associated with the exposure of live poultry markets (PLMs) (Zhou 2015,


Chen 2016, Chen 2013, Bao 2013, Li 2014, Han 2013, Wu 2013), hence LPMs can support the maintenance, amplification and dissemination of H7N9 virus (Chen 2016, Chen 2013, Bao 2013, Peiris 2014, Sims 2012). In view of this, closing LPMs has become the most commonly implemented measures to control H7N9 transmission. Some studies evaluated the effects of LPM closure on H7N9-incidence in humans and found that closing LPMs in different cities of China can reduced the risk of human infections by 73%-99% (Fourni'e 2014, Vittoria 2016, Yu 2014, Peiris 2016, Wu 2016, Yuan 2015, Wu 2017, Adam 2015). On the other hand, several studies were conducted to infer the associations between H7N9 infection with climate and environment, but the results exhibited geographic heterogeneity. For example, Liu et al. found that

^a <https://orcid.org/0000-0003-2583-2252>

^b <https://orcid.org/0000-0001-8373-0647>

^c <https://orcid.org/0000-0003-2391-2494>

^d <https://orcid.org/0000-0001-9051-0810>

^e <https://orcid.org/0000-0003-2291-3997>

temperature and absolute humidity were negatively associated with H7N9 infection in five Chinese regions during 2013-2016 (Tao 2018), similar results was observed in (Li 2015). Yi et al. indicated that minimum and maximum temperature but not humidity and daily temperature differences contributed to human H7N9 infections in China during 2013/14 seasons (Zhang 2015). Hu et al. claimed that H7N9 incidence rate in Shanghai during the spring of 2013 was linked with fortnightly mean temperature and fortnightly mean rainfall (Hu 2015). However, to our knowledge, we have not found related studies on the turning point and transmissibility of human H7N9 infection in Guangdong, as well as the climatic effects.

To fill the knowledge gap, in this paper, we went a further step to explore the transmission dynamics and the risk factors contributed to H7N9 transmission in Guangdong Province during 2013-2017. We first established a Richard model to fit the weekly H7N9 cases to detect the turning point for the outbreak. Turning points have epidemiological implications, which is the threshold between acceleration and deceleration. Identifying the turning points can help us to examine the impact of intervention measures relating to the turning point. We then used a generalized linear model (GLM) and generalized additive model (GAM) to explore the associations between the climates and human H7N9 infection, which enable us to clarify the long-term effects of climate on human H7N9 infections.

2 MATERIALS AND METHODS

2.1 Study Site

Guangdong Province was selected as the study area because it was one of the hardest-hit areas by H7N9 in China. This province is situated in the southern China, with an area of 179,800 square kilometers and about 100.7 million inhabitants. The climate is subtropical humid, with short, mild, dry winters and long, hot, wet summers. The annual mean temperature is 21.8 centigrades and the annual accumulate precipitation is 1,789 mm.

2.2 Data

Human H7N9 cases from October 2013 to April 2017 in Guangdong was used in this study. The data was ex-tracted from the Center for Health Protection of HongKong (<https://www.chp.gov.hk/sc/resources/29/332.html>),

regarding to the number of reported apparent and confirmed human cases per week. The temperature and relative humidity during the study period were downloaded from Guangdong Meteorological Service (<http://www.grmc.gov.cn/>).

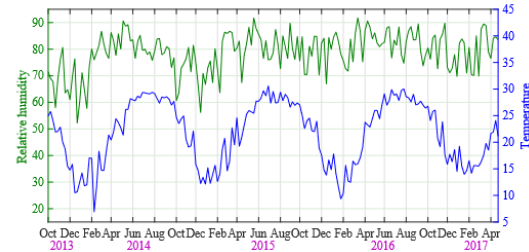


Figure 1: Time series of weekly relative humidity and average temperature during October 2013 and April 2017.

2.3 Richards Model

The Richards model was widely used to analyze the development trend and transmission potentials of infectious diseases (Hsieh 2018, Hsieh 2009, Hsieh 2006), which is written as

$$I(t) = K / [1 + e^{-r(t-t_m)}]^{1/\alpha} \quad (1)$$

where $I(t)$ is the cumulative number of notification cases at time t , k is the maximum case number over the course of the outbreak, r is the per capita growth rate of the infected population, and α is the deviation exponent of, t_m is related to the turning point t_i of the epidemic (or the inflection point of the cumulative case curve) by the simple formula $t_m = t_i + (\ln \alpha) / r$. This parameter has important epidemiological significance, which indicates the beginning of a popular phase (from deceleration to acceleration) or end (from acceleration to deceleration) (Hsieh 2018, Hsieh 2009, Hsieh 2006).

The Richards model is a phenomenological model allowed to describe the evolution of the cumulative case number (Hsieh 2018, Hsieh 2009, Hsieh 2006). By using standard software with nonlinear least-squares (NLS) approximation tool, the parameters K , r , α and t_m was estimated by fitting the Richards model to the epidemic curve in each epidemic season (October to next April).

2.4 Generalized Linear Model

Generalized linear models (GLM) have been proved to be an effective approach allowed to analyze the associations between disease outbreaks and the predictor variables. GLM is designed to model response variables that may follow a general

distribution, which is viewed as a unification of linear and nonlinear regression models. It includes three components: (1) a response variable distribution, (2) a linear predictor that involves a number of independent variables, and (3) a link function that connects the predictor with the response variable (Joseph 2006). Here, we used GLM to infer the effects of climate on H7N9 emergence. It is assumed that human reported cases follow Poisson distribution, in that the infection of H7N9 is a small probability event. We specified the expected number of human H7N9 cases as follows:

$$\ln y_t = \beta_0 + \beta_1 RH_{t-\tau_1} + \beta_2 TEM_{t-\tau_2} \quad (2)$$

where RH and TEM represent the relative humidity and temperature, respectively; and τ_1 and τ_2 are the time lag of variables. The statistical analyses were performed using the statistical software R.

2.5 Generalized Additive Model

Generalized additive model (GAM) is a nonparametric extension of Generalized linear model which can effectively address the complex nonlinear relationship between independent variables and dependent variables. GAM is characterized by smooth function fitting for some or all independent variables to reduce errors caused by linear model assumptions and hence the requirements for model samples are more relaxed. We applied GAM to infer the impact of climate on the emergence of H7N9 virus. Its basic form is as follows:

$$g(E(Y)) = a + \sum_{i=1}^k S_i(X_i, df) \quad (3)$$

where $S(\cdot)$ represent the spline function of the independent variable that has nonlinear relationship with the dependent variable. Statistical software R was also used for analysis.

3 RESULTS

Between October 2013 and June 2017, a total of 258 cases of human infection were reported in Guangdong Province (Fig. 2). The incidence rate is 0.00024%, and the mortality rate is 38.76%. The epidemic curve exhibited a strong seasonal cycle, as human infections usually occurred in the winter/spring and reached a peak in January.

The 2013/14 epidemic season possessed the most number of human infections (109 cases), followed by 2014/15 season (72 cases) and 2013/14 season (63 cases). The H7N9 epidemic in 2015/16 season is

relatively soft with 12 reported cases. In response to the outbreak, many LPMs were closed by local government. Such intervention was usually implemented in January.

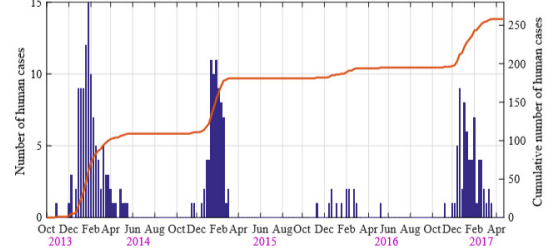


Figure 2: Time series of weekly human H7N9 cases reported during October 2013 and April 2017. The blue bar and the yellow curve correspond to the new and the cumulative cases, respectively.

Fitting the cumulative number of human H7N9 case to the previously described Richards model procedure, we obtained the parameter estimates of the four waves (Table 1), with the corresponding theoretical epidemic curve (3). It is found that the model performed well in terms of fitting the real-world observations. We found that the four turning points occurred on January 17, 2014, January 16, 2015, February 3, 2016 and December 30, 2016, which corresponded to the timing of closing live poultry markets. It should be noted that after the periods of the turning points, the outbreak started to ease, reversing the initial exponential growth.

Table 1: Estimation results of the Richards model parameters with the 95% CI for the four H7N9 waves in Guangdong Province during 2013-2017.

| Time period | t_i | r | K | a |
|-----------------|-------|------|--------|------|
| 2013.10-2014.04 | 16.50 | 0.32 | 104.51 | 0.81 |
| 2014.10-2015.04 | 16.47 | 0.65 | 72.31 | 1.41 |
| 2015.10-2016.04 | 19.33 | 0.75 | 13.14 | 3.85 |
| 2016.10-2017.04 | 13.75 | 0.28 | 64.05 | 0.07 |

Based on the GLM analysis, we found that the average temperature and the relative humidity were entered into the model, where the detailed information of coefficients is presented in Table 4 and 2. The results indicated that the relative humidity and the average temperature have significant influence on the human H7N9 infections, where human cases are most negatively correlated with the changes of relative humidity and average temperature at lags of 1-5 and 1-3 weeks, respectively.

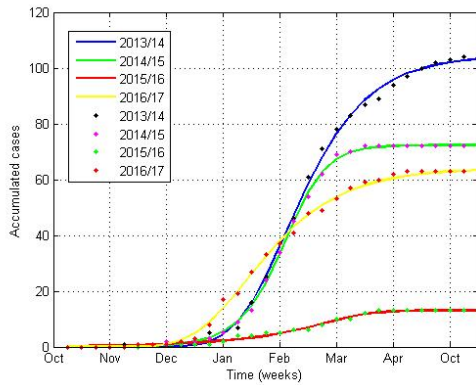


Figure 3: Fitting the cumulative H7N9 infections in Guangdong during the four epidemic seasons by using the Richards model.

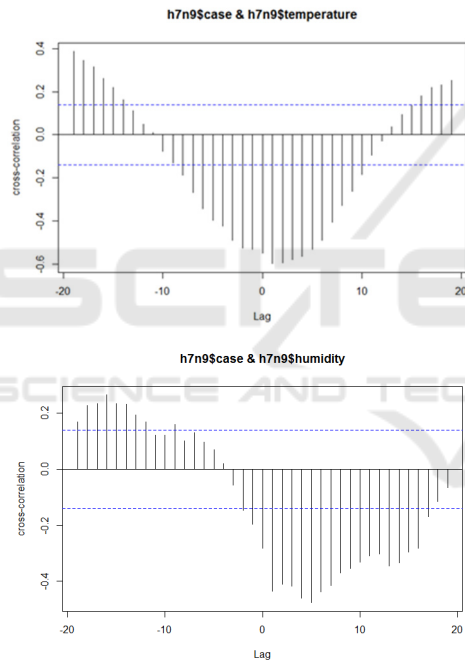


Figure 4: The correlation between the number of H7N9 cases and temperature, as well as relative humidity.

Table 2: Results from the generalized linear model.

| | Estimate | Std.error | Z-Value | Pr(> Z) |
|-----------|----------|-----------|---------|----------|
| Intercept | 6.8612 | 0.4791 | 14.32 | < 2e-16 |
| RH | -0.0391 | 0.0073 | -5.35 | 8.8e-08 |
| TEM | -0.2022 | 0.0148 | -13.70 | < 2e-16 |

The correlation coefficients between human infections and meteorological factors are shown in Table 3. It is found that infection is negatively and strongly relevant to average, highest and lowest temperature, with correlation coefficient around -

0.66. Infection is also positively associated with average air pressure, with correlation coefficient as 0.45. Yet the linear relation between infection and humidity, wind speed, rainfall, sunlight is not significant, which indicates that it may exist nonlinear connection between them.

Table 3: The correlation between the number of H7N9 cases and climatic impacts

| Climatic factor | R-Value | P-Value |
|---------------------------|---------|---------|
| Average temperature | -0.66 | 0 |
| Highest temperature | -0.62 | 0 |
| lowest temperature | -0.66 | 0 |
| rainfall | -0.29 | 0 |
| Average relative humidity | -0.33 | 0 |
| Average wind speed | 0.18 | 0.09 |
| Average air pressure | 0.45 | 0 |
| Average sunlight | -0.15 | 0.21 |

Based on GAM analysis, the results showed that there was a complex nonlinear relationship between climate factors and the incidence of H7N9. As shown in Figure 5, the number of H7N9 cases gradually decreased with the increase of temperature. When the average temperature reached 20°C, the number of cases was almost zero. When the rainfall was more than 200mm, the number of cases increased with increasing rainfall. The risk of H7N9 infection peaks when relative humidity reaches 80 percent. When the air pressure is close to 1005hPa, it is most favorable for human infections of H7N9 virus.

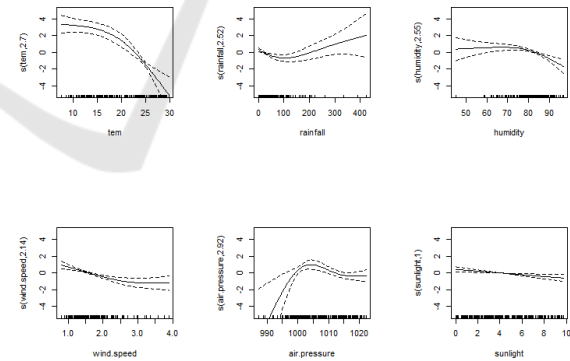


Figure 5: Effect chart of relationship between climatic factors and the number of H7N9 cases.

4 DISCUSSION

The recent emergence of avian influenza A (H7N9) virus has becoming a big public health issue in China. Exploring the risk factors and evaluating the intervention strategies are the priority for controlling

and preventing H7N9 epidemics. In this study, we used a Richards model, generalized linear model and generalized additive model to investigate the associations between incidence decline and LPM closure, and to infer the effects of climatic factors on H7N9 transmission. Two insights arising from our results could provide meaningful clues for policymakers to implement effective interventions on H7N9 infection.

First, we found that the turning points of the four epidemic waves occurred exactly at one week after closing LPMs. Before the turning points, human cases had the potential to increase exponentially. After that, the numbers began to decelerate. During 2013/14 and 2014/15 epidemic seasons in Guangdong, human infections were sporadically reported in December. The local governments successively closed LPMs in early January. In these cases, we found that the turning points occurred in mid-January. The H7N9 epidemic in 2015/16 season is less serious, and only a few LPMs were closed in January 2016. We found that the turning point was relatively late, occurring on February 3. H7N9 outbreak in 2016/17 season was much earlier, where human cases were recorded from mid-December. The Guangdong government responded very quickly and instructed the local authorities to close LPMs. Consequently, we found that the turning point occurred in late December. In short, we found that the turning points occurring after about one week of LPM closure. Such time lag could be related to the latent period of H7N9 virus in human and poultry. Our results indicated that closing LPMs can effectively reduce human H7N9 infections, which is consistent with previous findings (Yu 2014, Wu 2014, Adam 2015, Zhu 2021).

Second, we found that the change in human H7N9 infections appears to be most closely correlated with change in temperature at lags of 1-3 weeks, meanwhile the changes in relative humidity seems to be most correlated with change in H7N9 case number at lag of 1-5 weeks. Our findings are consistent with previous analysis, where they claimed that temperature and humidity are the dominant variables for H7N9 transmission (Tao 2018, Li 2015, Zhang 2015, Hu 2015). This can be explained by changes in virus activity under different climate conditions. Low temperature and humidity favoured the survival and transmission of H7N9 viruses during its outbreak, and can also directly/indirectly affect people's behaviour, making them more vulnerable to H7N9 viruses (Tao 2018, Hu 2015). Further understanding of the impact of socio-ecological factors on the incidence of H7N9 with the development of early warning system can be

useful and important in the control and prevention of H7N9.

In summary, we have detected the turning points of the four H7N9 epidemic waves, and clarified the potential relationship between human cases and temperature as well as relative humidity. Our results indicated that closing LPMs can significantly reduce human infections, and LPM closure and climatic factors played a role in the seasonality of H7N9 transmission.

In addition to climate, human activities and contact with live poultry could be the important factors contributed in the spread of H7N9. Government regulation toward live poultry market can modify the transmission pattern of H7N9. These factors should be considered in future studies for guiding H7N9 control.

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