Spatial and temporal clusters of avian influenza A (H7N9) virus in humans across five epidemics in mainland China: an epidemiological study of laboratory-confirmed cases

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Abstract

Background: Avian influenza A (H7N9) virus was first reported in mainland China in 2013, and alarming in 2016-17 due to the surge in reported cases across a wide geographic area. Our study aimed to identify and explore the spatial and temporal variation across five epidemics to reinforce the epidemic prevention and control.

Methods: We drew spatial and temporal information about all laboratory-confirmed human cases of A (H7N9) virus infection reported in mainland China covering 2013-17 from the open source. The autocorrelation analysis and intensity of cases were used to analyse the spatial cluster while circular distribution method was used to analyse the temporal cluster.

Results: Across the five epidemics, a total of 1553 laboratory-confirmed human infection with A (H7N9) virus were reported in mainland China. The global Moran’s I index values of five epidemic were 0.610, 0.132, 0.308, 0.306, 0.336 respectively, all of which were statistically significant. Yangtze River Delta region and the Pearl River Delta region had the highest intensity, and range enlarged from the east of China to inner provinces and even the west of China across the five epidemics. The temporal clusters of the five epidemics were statistically significant, and the peak period was from the end of January to April. The peak periods of the first and fifth epidemic were later than the mean peak period.

Conclusions: Spatial and temporal clusters of avian influenza A (H7N9) virus in humans indeed exist, moreover the regions existing clusters may enlarge across five epidemics. Yangtze River Delta region and the Pearl River Delta region have the spatial cluster and the peak period is from January to April. The government should facilitate the tangible improvement for the epidemic preparedness.

Author Summary

The avian influenza A (H7N9) virus infections in human since 2013 in mainland China are
gaining in importance in terms of mortality and morbidity, as well as the extent to which the disease spread. With respect to understanding the spatial and temporal variance across the five epidemics to improve the prevention and control measures in the high-risk regions, especially in the high-risk periods, we have evaluated the spatial and temporal cluster through autoregression and circular distribution methods. The heterogeneity of spatial and temporal features across five epidemics designating in this study highlights that special strategies should be formulated in different at-risk areas and periods.

**Background**

From 2013 until present, the avian influenza A (H7N9) virus infections in humans in mainland China are unprecedented both in terms of mortality and morbidity (1-3), with the risk of continues emerge and spread for the virological and molecular characteristics (4-9). The A (H7N9) virus has the highest risk score among the 12 novel influence A virus assessed by the Influenza Risk Assessment Tool (10). The risk assessment of A H7N9 is crucial to inform public health for pandemic preparedness, especially in the neglected locations (11).

Many researches have described the characteristics of the epidemics. Clinical features of human infections in China reported during the five epidemics were similar(1), and the spatial and temporal characteristics were not (12). From the fourth epidemic, infections presented in areas that had not reported infections before, in addition to the increasing duration of the epidemic each year (9). At the same time, the timing of onset dates differed across the epidemics, shifting gradually from February-April to December-March (8).

Surprisingly, although five epidemics have happened in China, the evidence of spatial and temporal features have been gained through description methods without statistical inference. Moreover, the inherent bias may be present due to the cases centralized at the
prefecture or province level. Continuous epidemiological investigations should be crucial to outline the epidemic trajectory and inform public health for pandemic preparedness (13-16). In comparison of the description of the epidemics on the province level, the present study aimed to assess spatial and temporal variation across five epidemics through appropriate statistical inference methods. The result was helpful to understand the regulation of the epidemics and enhance China’s public health emergency capacity.

Methods

Data sources

The data of confirmed A (H7N9) human cases across the five epidemics in mainland China were drawn from the EMPRES Global Animal Disease Information System (EMPRES-i) of the Food and Agricultural Organization (FAO) (empres-i.fao.org/eipws3g/bioclimatic). The cases only included Low pathogenic avian influenza (LPAI) H7N9. The first epidemic was defined as being from Jan 1, 2013, to Sept 30, 2013. And subsequent epidemics were defined from Oct 1 to Sept 30 of the following year. All data was drawn from publicly available data sources, supplied and analysed in an anonymous format, without access to personal identifying information. Therefore, our study was exempt from institutional review board assessment.

Data analysis

Overview

To explore the variance of spatial and temporal clusters of avian influenza A (H7N9) infections in humans, we used global Moran’s I statistic to evaluate the spatial clusters, and circular distribution method to evaluate the temporal clusters. All statistical computations were performed using R software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). All codes used in the analysis are available on request from the corresponding author.
Spatial cluster analysis

We used spatial autocorrelation analysis and intensity of cases to analyse the spatial clusters. Global Moran’s $I$ statistic is usually used in spatial autocorrelation analysis (17). The value of $I$ is between -1 and 1. $I > 0$ is positive spatial correlation and means aggregation distribution; $I = 0$ means random distribution; $I < 0$ is negative spatial correlation and means discrete distribution. Intensity is the average density of points (expected number of points per unit area) (18). In general, the intensity of point will vary from place to place, so the intensity may be inhomogeneous. The kernel smoothing intensity function can be estimated nonparametrically in this study.

Temporal cluster analysis

Seasonal analysis is an important part of epidemiology. Circular distribution method is a statistical method that transforms the data with periodic changes into linear data through the transformation of trigonometric function (19, 20). It can evaluate whether there is temporal cluster and even provide the precise kurtosis time. The central tendency is expressed by the mean angle, while the discrete tendency is expressed by the standard deviation. Table 1 expressed the conversion.

Discussion

Our study presented the temporal and spatial features of avian influenza A (H7N9) virus in humans across the five epidemic in mainland China through the statistical inferences of the clusters. We demonstrated there were aggregation distributions in the east of China initially, followed by the inner and west of China presented cluster in the fourth and fifth epidemics. Moreover, the peak periods shifted gradually from the first until the fifth epidemic. The results were similar with Dong’s description results (21). The Yangtze River Delta region and the Pearl River Delta region were higher intensity
regions, especially the Yangtze River Delta region. The fourth epidemic has begun to expand to the central China, and the fifth epidemic has expanded to the northern and western regions. There was contest that geographical expansion of A (H7N9) virus implied the human-human epidemic trajectory. However, the evidence was not sufficient. The H7N9 virus may spread silently due to most of them belonging to Low pathogenic avian influenza (LPAI) (22). Guangdong and Shaanxi province have reported High pathogenic avian influenza (HPAI), and the H7N9 virus infecting humans in Shaanxi province derived, directly or indirectly, from strains circulating in local farms and Live poultry markets (LPMs) (23). H7N9 virus infecting humans came from avian origins, and mutated into the novel LPAI H7N9 breaking human-animal interface without disease in poultry (24). During the fifth wave, the low pathogenic phenotype in poultry converted into the high pathogenic phenotype with the four amino acids inserting into the HA cleavage site (25). Local density of LPMs was the most important predictor of H7N9 infection risk (22, 26-28). LPMs, keeping the avian in crowded conditions which may facilitate avian influenza virus genetic reassortment, have been considered as the reservoir and amplifier for avian influenza viruses (29). Higher density of markets may exacerbate the risk and explain the strong spatial correlation with H7N9 infection (26). In accordance with the researches, exposure to LPMs was the major epidemic trajectory. Although spatial clusters virtually existed, there has been no evidence of sustained human-to-human transmission so far. The peak incidence was concentrated in February and March, accounting for March in first epidemic, February in the following epidemics. The result wasn’t consistent with prior reports. Lei (2) and et al indicated that the fifth epidemic began earlier and increased rapidly through the description of the epidemics. However, the peak period was not earlier than before via statistical inference in our study. Li (30) and et al found temperature and rainfall played important roles in the risk of human H7N9 infection, the same as research
of Hu (31) and et al. Since migratory aquatic birds transmit H7N9 virus to domestic ducks and then to chickens (32), the transmission process needs adequate meteorological condition, such as the temperature and relative humidity (21). During the H7N9 outbreaks, temperature ranging from approximately 9℃ to 19℃ favored the survival of H7N9 viruses (31, 33). The seasonality of A (H7N9) virus in humans was related with the meteorological condition, and the at-risk period may shift gradually across China.

In response to the epidemic situation, a series of measures and interventions have already been implemented by the national and local authorities. To a certain extent, LPM closures were effective in the control of human risk of avian influenza A (H7N9) virus infection (34, 35), which was only a temporary measure for not eliminating the source of the infection (34). Inter-departmental alliances and effective implementation of evidence-based disease management were crucial to form One Health in China to control the number of human infections (36). It is necessary to facilitate the capacity to rapidly detect and contain public health threats at their source via risk communication (37).

Our study had the limitation. Our study analysed only laboratory-confirmed human infections with A (H7N9) virus and excluded the clinically mild cases without confirmed test. Dennis (38) and et al found there was “clinical iceberg” phenomenon in influenza A (H7N9) in humans. Therefore, the full spectrum of human infection was unknown. Large population-based serological studies would be permitted to assess the number of infected cases.

Conclusions

This analysis provided the statistical inference of spatial and temporal cluster of A (H7N9) epidemic in humans, and presented the aggregation distribution and peak periods. Yangtze River Delta region and the Pearl River Delta region had the spatial cluster and the peak period was from January to April. The spatial scope has begun to expand since the
fourth epidemic and temporal heterogeneity varied slightly. With the evaluation, it is necessary to improve the comprehensive collaboration of inter-departmental alliances to monitor continuously, assess risk regularly and communicate epidemic risk.

Declarations

Acknowledgments

We thank Y Chen for assistance in data collections.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributors

S Li and L Chen supervised the study and helped revise drafts of the manuscript. X Shan conceived, designed the study and collected the data, finalized the analysis, wrote the drafts of the manuscript. Y Wang designed the study. R Song, W Wen, H Liao collected the data and analyzed the data. All authors read and approved the final manuscript.

Ethics approval

All data were obtained from publicly available data sources, supplied and analysed in an anonymous format, without access to personal identifying information. Therefore, our study was exempt from institutional review board assessment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests. The study is supported by the Science and Technology Project of the Health Planning Committee of Sichuan (18PJ576). The funders play no role in the study.
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Tables

Table 1. Month conversion of circular distribution method

| Month | Days of each month (days) | Mid-point days (days) | Median angle (degree) | Median angle (radian) |
|-------|---------------------------|-----------------------|-----------------------|-----------------------|
| 1     | 1-31                      | 15.5                  | 15.288                | 0.267                 |
| 2     | 32-59                     | 45.0                  | 44.384                | 0.775                 |
| 3     | 60-90                     | 74.5                  | 73.479                | 1.283                 |
| 4     | 91-120                    | 105.0                 | 103.562               | 1.808                 |
| 5     | 121-151                   | 135.5                 | 133.644               | 2.333                 |
| 6     | 152-181                   | 166.0                 | 163.726               | 2.857                 |
| 7     | 182-212                   | 196.5                 | 193.808               | 3.383                 |
| 8     | 213-243                   | 227.5                 | 224.383               | 3.916                 |
| 9     | 244-273                   | 258.0                 | 254.465               | 4.441                 |
| 10    | 274-304                   | 288.5                 | 284.548               | 4.966                 |
| 11    | 305-334                   | 319.0                 | 314.630               | 5.491                 |
| 12    | 335-365                   | 349.5                 | 344.712               | 6.016                 |

Note: The days of a year are distributed to a circular equally.

Table 2. Five epidemics of avian influenza A (H7N9) virus in humans in 2013-17 (%
| Province     | First epidemic (2013.1-2013.9) | Second epidemic (2013.10-2014.9) | Third epidemic (2014.10-2015.9) | Fourth epidemic (2015.10-2016.9) |
|--------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Zhejiang     | 45(13.89)                     | 93(28.70)                       | 46(14.20)                       | 36(11.11)                       |
| Guangdong    | 1(0.39)                       | 105(40.70)                      | 73(28.68)                       | 15(5.81)                        |
| Jiangsu      | 28(11.72)                     | 27(11.30)                       | 23(9.62)                        | 26(10.88)                       |
| Anhui        | 5(4.55)                       | 14(12.73)                       | 14(13.64)                       | 5(4.55)                         |
| Fujian       | 5(4.67)                       | 17(15.89)                       | 41(38.32)                       | 10(9.35)                        |
| Hunan        | 2(2.11)                       | 22(23.16)                       | 2(2.11)                         | 8(8.42)                         |
| Shanghai     | 33(60.00)                     | 8(14.55)                        | 6(10.91)                        | 2(3.64)                         |
| Jiangxi      | 6(11.32)                      | 2(3.77)                         | 3(5.66)                         | 3(5.66)                         |
| Sichuan      | 0(0)                          | 0(0)                            | 0(0)                            | 0(0)                            |
| Beijing      | 2(5.88)                       | 3(8.82)                         | 2(5.88)                         | 3(8.82)                         |
| Guangxi      | 0(0)                          | 3(9.38)                         | 0(0)                            | 0(0)                            |
| Hebei        | 1(3.13)                       | 0(0)                            | 0(0)                            | 3(9.38)                         |
| Henan        | 4(12.50)                      | 0(0)                            | 0(0)                            | 1(3.13)                         |
| Hubei        | 0(0)                          | 0(0)                            | 1(3.13)                         | 1(3.13)                         |
| Shandong     | 2(7.14)                       | 3(10.71)                        | 1(3.57)                         | 3(10.71)                        |
| Guizhou      | 0(0)                          | 1(5.00)                         | 1(5.00)                         | 0(0)                            |
| Xinjiang     | 0(0)                          | 2(15.38)                        | 8(61.54)                        | 0(0)                            |
| Chongqing    | 0(0)                          | 0(0)                            | 0(0)                            | 0(0)                            |
| Shaanxi      | 0(0)                          | 0(0)                            | 0(0)                            | 0(0)                            |
| Liaoning     | 0(0)                          | 0(0)                            | 0(0)                            | 1(16.67)                        |
| Yunnan       | 0(0)                          | 0(0)                            | 0(0)                            | 0(0)                            |
| Gansu        | 0(0)                          | 0(0)                            | 0(0)                            | 0(0)                            |
| Tianjin      | 0(0)                          | 0(0)                            | 0(0)                            | 2(40.00)                        |
| Jilin        | 0(0)                          | 2(66.67)                        | 0(0)                            | 0(0)                            |
| Shanxi       | 0(0)                          | 0(0)                            | 0(0)                            | 0(0)                            |
| Xizang       | 0(0)                          | 0(0)                            | 0(0)                            | 0(0)                            |
| Inner Mongolia | 0(0)                       | 0(0)                            | 0(0)                            | 0(0)                            |
| **Total**    | 134(8.63)                     | 302(19.46)                      | 221(14.43)                      | 119(7.67)                       |

Table 3. Global autocorrelation analysis on distribution of avian influenza A (H7N9) in humans across five epidemics in mainland China
| Year | Number of cases | $E(I)$  | $\text{Var}(I)$  | Z Score | P-value |
|------|----------------|---------|------------------|---------|---------|
| 2013 | 145            | 0.840*  | 1.930            | 19 March| 13 February–22 April |
| 2014 | 314            | 0.779*  | 1.742            | 6 February | 27 December–19 March |
| 2015 | 208            | 0.743*  | 1.742            | 11 February | 29 December–29 March |
| 2016 | 130            | 0.554*  | 1.742            | 26 February | 25 December–30 April |
| 2017 | 756            | 0.700*  | 1.742            | 27 February | 9 January–16 April |
| Total| 1553           | 0.688*  | 1.742            | 25 February | 5 January–16 April |

Note: $E(I)$ was Moran's $I$ expectation, $\text{Var}(I)$ was variation of Moran's $I$. 

Table 4. The peak period of avian influenza A (H7N9) in humans in 2013–17.
The intensity of A (H7N9) avian influenza in humans across five epidemics. Note: A~E showed the intensity of five epidemics. The intensity was represented on a
continuous scale of low (blue) to high (yellow). Data sources used in the maps including: confirmed A (H7N9) human cases data was collated from EMPRES-i of FAO (empres-i.fao.org/eipws3g/bioclimatic); the base maps were obtained from the GADM database (https://gadm.org/download_country_v3.html). Maps were built using R software version 3.4.3. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.