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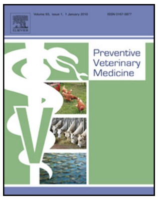

Spatiotemporal pattern and risk factors of the reported novel avian-origin influenza A(H7N9) cases in China

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ABSTRACT

A total of 134 laboratory-confirmed human cases of the novel avian-origin influenza A(H7N9) were reported in China between February to July 2013. To illustrate the spatiotemporal patterns of H7N9 outbreaks in humans and investigate the risk factors associated with their distribution, we mapped the distribution of affected human cases and carried out directional distribution analysis and a direction test. We also collected data on anthropogenic, vegetation, climatic, and topographic factors, and used multiple logistic regression to examine the contribution of each factor. Two different spatiotemporal patterns were found: clustered and regular directional distributions in four distinct temporal phases in the Yangtze River Delta, and sporadic but spread in three direction across the provinces adjacent to the Yangtze River Delta. Mean monthly precipitation, mean monthly temperature, normalized difference vegetation index, and poultry consumption were significantly associated with the occurrence of human H7N9 infection. The model generated a map showing the high-risk areas for human H7N9 infection for mainland China. These findings provide an empirical basis for identifying priority areas for implementing preventive intervention to reduce the number of future human infections.

1. Introduction

The novel avian-origin influenza A(H7N9) virus was first isolated from humans in Shanghai and Anhui Province in China in March 2013 (Shi et al., 2013). As of July 2013, 134 laboratory-confirmed infection human cases had been detected in 10 provinces, two municipalities, and Taipei City. A total of 44 deaths have been reported (WHO, 2013b). This virus has generated global interest because it is a potential pandemic threat to humans. Experts investigated the origins and genomic evolution of the virus, and concluded that it is of avian origin and mainly transmitted by transmitted by contact with poultry (Chen et al., 2013; He et al., 2013; Gao et al., 2013; Shi et al., 2013). H7N9 virus is most likely spread by infected birds, especially poultry, and environmental contamination. However, limited information is available on the patterns of spread of the emerging avian influenza A(H7N9) virus in China, and the underlying environmental risk factors affecting epidemic

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transmission. The lack of such knowledge has made it difficult to refine prevention and control strategies. The virus has not been reported to cause severe disease in poultry and birds (WHO, 2013c), and the absence of this useful warning signal limits the ability to easily detect the virus.

Spatiotemporal studies focused on the quantification of the spread and distribution of emerging infectious diseases can provide additional insights and knowledge to better understand the patterns and risk factors for avian influenza epidemics (Oyana et al., 2006; Sinha and Mark, 2005; Zhang et al., 2008). Although human cases have occurred sporadically (He et al., 2013; WHO, 2013a), spatiotemporal patterns may exist in disease occurrence. Analysis of the spatiotemporal process of the disease may also be complementary to molecular genomic and clinical studies.

This study aimed to analyze spatiotemporal processes and track possible outbreak routes according to the chronological order of onset dates of human cases. It also aimed to investigate the association between infected cases and environmental factors, and map predicted risks based on a multiple logistic regression model to aid targeted epidemiological investigation, prevention, and control work.

2. Materials and methods

2.1. Data collection and processing

Data on reported influenza A(H7N9) cases were collected from three main sources, namely, (1) the Epidemics Bulletin published on the website of the China National Health and Family Planning Commission (http://www.chinapop.gov.cn/), (2) Chinese Center for Disease Control and Prevention (http://www.chinacdc.cn/), and (3) World Health Organization (WHO, 2013b). For inconsistencies in the onset date of the illness and similar situations during HPAI H5N1 data collection (inconsistencies in the outbreak date or location) (Martin et al., 2011), we compared the reported cases from these official websites with published studies (He et al., 2013; Guan et al., 2013), interviewed local people through the network (Sina Weibo, http://www.weibo.com/), and consulted experts to obtain accurate case information. Onset dates were known for 80% (108/134) of the reported cases. Twenty-two cases had no available onset data, but had diagnosis data that could be obtained using the average time (days) from the onset of the illness until diagnosis. The remaining four cases were retrospectively confirmed in Shanghai without demographic information (Guan et al., 2013). All the cases were geocoded according to the reported address where the cases were infected (instead of their ancestral home). Patient mobility was not considered. The administrative center of each prefecture or town was used to represent the case location if an accurate address was unavailable. If one administrative district had multiple cases, the points around the administrative district center would be representative.

2.2. Spatiotemporal pattern analysis

A total of 134 confirmed human cases of the novel influenza A(H7N9) virus in China were detected from 19 February 2013 to 27 July 2013. In the following two months, no new cases were identified by laboratory confirmation. This result indicates the temporary end of this outbreak, and affords opportunity to consider the spatiotemporal emergence patterns. We performed directional distribution and spread sequence analyses to investigate the spatiotemporal pattern.

Directional distribution analysis using the standard deviational ellipse has been widely used in outbreak studies to model the spread of disease over time (Gesler, 1986; Ward et al., 2008a; Farnsworth and Ward, 2009). The method measures whether a distribution of features exhibits a directional trend by calculating the standard distance of a set of points separately in the x- and y-directions, and creates elliptical polygons to provide information on the central tendency, dispersion, and directional trends. The attributed values for these output ellipse polygons include X and Y coordinates for the mean center, two standard distances (long and short axes), and ellipse orientation. The ellipse allows us to determine whether the distribution of points is elongated and has a particular orientation. We used the ellipse to measure the directional trend, and provide information about the dispersion of human cases during different time periods. One standard deviation was used to represent the distribution that covers approximately 68% of all input human cases (Ward and Carpenter, 2000; Osmani et al., 2014).

A direction test (Jacquez and Oden, 1994) was used to determine whether the human cases tend to be in a systematic, directional spread. A chain of infection is constructed by first sequencing the cases by time of occurrence. The test statistic includes the average direction of spread (average angle) and the angular concentration. Angles are taken as counter clockwise degrees from horizontal, with East corresponding to 0 and North to 90. Concentration is in the range of 0–1, with 1 indicating an angular variance of 0, equal a random spread of cases. We specified the time connection matrix as *relative* (each outbreak connected to all of the outbreaks that followed it) (Osmani et al., 2014). The first patient's onset date in the prefecture level division (the secondary administrative region of the People's Republic of China, named for the administrative unit above the county and under the provincial level) was assumed as the time that the A(H7N9) virus first appeared in this area. We observed these first cases to determine whether they present a spread route trend according to the time sequence. The significance of the test statistic was estimated by use of Monte Carlo simulation (ClusterSeer v. 2.5. Biomedware Inc., MI, 2011).

All spatial analyses mentioned were carried out in ArcGIS 10.1 (ESRI Inc., Redlands, CA, USA).

2.3. Risk factor analysis

The primary risk factors considered in this analysis included anthropogenic, vegetation, climatic, and topographic variables. First, we considered the anthropogenic variables, including human population density and consumption of poultry. Second, we investigated the distance to nearest roads, railways, and bodies of water; main migration routes of migratory birds based on a previous