Modelling the Avian Influenza H5N1 Virus Infection in Human and Analyzing its Evolution in China

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1. Introduction

Since the first human case of H5N1 avian influenza infection was found in Hong Kong 1997 (Ku and Chan 1999), the cumulative number of confirmed human cases of H5N1 infection reported to the World Health Organization (WHO 2012) to date is 596 in the world and which of 42 HPAI H5N1 human cases in China with 60% mortality. More than 80% of the total HPAI H5N1 human cases have been reported in avian influenza endemic areas, indicating hotspots for bird-to-human transmission (Watanabe et al. 2012). Further, the HA genes of 15 human isolates from Southern China are closely related to each other and to H5N1 poultry viruses isolated in the same geographic location at the same time, suggesting infected domestic poultry as the source of human infections (Shu et al. 2006, Wang et al. 2008). By contrast, the HA gene of one human isolate from the Xinjiang Autonomous Region in Northern China is more closely related to Qinghai Lake-like migratory birds viruses (Neumann et al. 2010). Therefore, many experts expect the occurrence of a pandemic due to a mutant avian influenza virus which can be easily transmitted among humans (Iwami et al. 2009). It is important and urgent to study the infection of HPAI H5N1 virus in human to refine the understanding of HPAI H5N1 virus evolution for better control and prevention of HPAI H5N1 virus transmission.

2. Methods

2.1 Population density surface in China

In this research, the total population number for each province of China 2008 was calculated based on the data of population distribution from LandScan within each of the province boundary in China. And then according to the natural human population growth rate for each province from China Statistics Yearbook of 2004-2010, the total population number for each province in the year of 2004-2007, 2009 was computed respectively. Finally, the total population number for each province in the year of 2004-2007, 2009 was allocated to each cell (size: 10 km × 10 km) and population density surfaces for

China 2004-2007, 2009 were made.

2.2 HPAI H5N1 HA gene sequence data allocation

Allocating HPAI H5N1 hemagglutinin (HA) gene sequence data to the HPAI H5N1 outbreak location was based on whether they had same species, same (outbreak or isolation) location, and same (outbreak or isolation) time basically. If one HPAI H5N1 outbreak didn't have its corresponding gene data in the same province, those with same species and same time in the nearest province would be allocated. In particular, allocating the gene data to the HPAI H5N1 outbreaks in wild birds was according to whether they were along the same bird migration flyways as well.

2.3 Patch-based SEIR CA epidemic model

Here the patch-based SEIR model has been combined with CA model to represent the avian influenza transmitting spatially. The patch-based SEIR model should be written as (Driessche 2008) :

$$\begin{aligned} S_i^{'} &= N_i - \beta S_i \\ E_i^{'} &= \beta S_i - \varepsilon E_i \\ I_i^{'} &= \varepsilon E_i - \gamma I_i \\ R_i^{'} &= \gamma I_i \end{aligned} \tag{1}$$

where S_i, E_i, I_i, R_i denote respectively the number of susceptible, exposed, infective and recovered individuals in the patch i for $i = 1,\ldots,n$; $S_i^{'}, E_i^{'}, I_i^{'}, R_i^{'}$ is the susceptible, exposed, infectious and recovered population of patch i respectively after some t; β is the contact rate including a mass-action transmission in the patch i and contact between any two patches; $1/\varepsilon$ is the average latent period, $1/\gamma$ is the average infectious period; the total population of patch i is N_i, and $N_i = S_i + E_i + I_i + R_i$.

The CA epidemic model used here was adapted the one, which had been used by Sirakoulis et al. (2000), Zhang and Atkinson (2008). Its transition from an exposed state to an infected state is achieved according to:

$$P_{p,i}^{t+1} = P_{p,i}^{t} + E_{p,i}^{t}(k(P_{p-1,i}^{t}, P_{p,i-1}^{t}, P_{p,i+1}^{t}, P_{p+1,i}^{t}) + l(P_{p-1,i-1}^{t}, P_{p-1,i+1}^{t}, P_{p+1,i-1}^{t}, P_{p+1,i+1}^{t})) \tag{2}$$

where $E_{p,i}^{t}$ is the proportion of the population that is exposed in the patch (p,i), $P_{p,i}^{t+1}$ represents the proportion of the individuals in the patch (p,i) infected by the avian influenza virus after some t. The effect of the adjacent nearest neighbours is multiplied by k, whereas the effect of the diagonal adjacent neighbours is multiplied by l.

2.4 Multiple sequence alignment and phylogenetic tree reconstruction

In order to define a quantitative measure of more sequences similarity, multiple sequence alignment had been done before reconstructing the phylogenetic trees here. And three methods had been used to reconstruct phylogenetic trees in this research, including distance methods, parsimony methods, and likelihood methods (Nei and Kumar 2000).

3. Results

3.1 Results of population density surfaces in China

Not only the total population number of China during 2004-2009 was growing steadily, but also its corresponding population density was getting higher and higher. The high population density areas nearly didn't change much during this period, which were distributed mainly in the middle, south and northeast of China sporadically. However, comparing to the population distribution in 2004, the population distribution in 2009 was expanding to north and west.

3.2 Results of avian influenza H5N1 virus infection in human in China

The plots on the results of average avian influenza H5N1 human cases number during any six days after infection in humans occurring in the years 2004-2009 had a similar form, the average human cases number increasing rapidly from the first day and arriving at the high-point in the second day, and then it began to drop, from the third day the line of average human cases number didn't change much and it kept level nearly.

3.3 Evolutionary analysis of avian influenza H5N1 virus in China

From the perspective of geographic distribution, most sublineages in the reconstructed phylogenetic trees comprise sequences from geographic adjacent areas. The three HPAI H5N1 virus strains very close to the strain of A/goose/Guangdong/1/1996 are in three quite different geographic areas, northeast, northwest and middle part of China.

4. Conclusion

This paper has completed two works. One was to apply a patch-based SEIR CA epidemic model to simulate the HPAI H5N1 transmission among poultry and humans and to explore the effects of human population density distribution on the human cases number of HPAI H5N1. Here, taking China as the study area, the results showed that different human population density distribution in China 2004-2009 had a small effect on the number of human cases in HPAI H5N1.

The other was to analyze the evolution of HPAI H5N1 virus in poultry and wild birds that can infect humans. The HPAI H5N1 virus infecting humans had the characteristics of geographic adjacent distribution in evolutionary relationship. This strengthens the viewpoint that the sublineage of A/goose/Guangdong/1/1996 continued to be prevalent in China 2004-2009. Besides, the evolutionary distance based on nucleotide substitutions and amino acid substitutions for the HPAI H5N1 virus strains infecting humans in China 2004-2009 went up steadily as a whole. It indicates that the HPAI H5N1 virus strains infecting humans was evolving continually by some rule.

5. References

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