Risk signals of an influenza pandemic caused by highly pathogenic avian influenza subtype H5N1: Spatio-temporal perspectives

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ABSTRACT

Highly pathogenic avian influenza (HPAI) subtype H5N1 is a trans-boundary animal disease that has crossed the animal–human species barrier and over the past decade has had a considerable impact on the poultry industry, wild bird populations and on human health. Understanding the spatio-temporal patterns of H5N1 outbreaks can provide visual clues to the dynamics of disease spread and of areas at risk, and thus improve the cost-effectiveness of disease control and prevention. This study describes the characteristics and investigates the temporal, spatial and space–time dynamics of H5N1 outbreaks in domestic poultry between December 2003 and December 2009 using a global database.

The study found that the start date of the epidemic wave was postponed, the duration of the epidemic was prolonged and its magnitude reduced over time, but the disease transmission cycle was not efficiently interrupted. Two 'hot-spot' regions of H5N1 outbreaks were identified: well-documented locations in East and Southeast Asia, as well as a novel location at the boundaries of Europe and Africa, where enhanced surveillance should be conducted. The risk of a pandemic due to H5N1 remains high.

Introduction

The Asian avian influenza subtype H5N1 is a highly pathogenic strain of influenza A virus (HPAI H5N1). While initially causing numerous influenza outbreaks in domestic poultry and wild bird populations (Wallace et al., 2007; Ward et al., 2008), the virus crossed the species barrier to infect humans in 1997 (Wallace et al., 2007; Ward et al., 2008). Since 2003, a total of 549 cases of human infections have been reported in 15 countries and 320 (58.3%) people have died (WHO, 2011). Although measures such as restricting animal movements, quarantine, disinfection, preemptive animal culling, 'stamping-out' and vaccination have been used to control the disease, intermittent and sporadic outbreaks in poultry continue to be reported worldwide (Capua and Alexander, 2010).

Adaptive mutation or genetic re-assortment raise the possibility that the H5N1 virus could be transmitted between humans (Webster and Govorkova, 2006; Park and Glass, 2007; Pfeiffer et al., 2007), causing a human pandemic (Park and Glass, 2007). Close contact with sick or dead poultry is the strongest risk factor for human H5N1 infection (Mounts et al., 1999; Areechokchai et al., 2006; Dinh et al., 2006; Zhou et al., 2009). The control of the virus in poultry is therefore crucial to the prevention of human infection (Zhou et al., 2009; Yupiana et al., 2010) and to achieve this an understanding of the spatio-temporal patterns of virus spread during outbreaks in poultry is essential (Ward et al., 2008).

Spatial and temporal studies have been conducted previously in Bangladesh (Ahmed et al., 2010), China (Oyana et al., 2006), Thailand (Tiensin et al., 2009), Vietnam (Pfeiffer et al., 2007; Minh et al., 2009) and globally (Si et al., 2009), mainly using short-term data up to 2006 during which time the global HPAI H5N1 threat was most serious. A long-term survey is therefore necessary to gain a comprehensive profile on the outbreak dynamics of HPAI H5N1 since the spatio-temporal pattern may change, particularly following interventions.

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The objective of this study was to describe the epidemic characteristics of global HPAI H5N1 outbreaks and to depict the spatio-temporal pattern dynamics of these outbreaks in domestic poultry using a newly integrated global database covering the period December 2003–December 2009. An overview of the changing spatio-temporal pattern would provide valuable insights into the risk of an emerging pandemic strain of HPAI H5N1 and would facilitate strategic planning for disease preparedness and control.

Materials and methods

Data collection

Global HPAI H5N1 outbreak data in domestic poultry were collected from the World Organization for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO), and integrated into one dataset based on the administrative unit of sub-district for the study period from December 2003 to December 2009 (Zhang et al., 2010).

An outbreak was defined as 'the confirmed presence of disease, clinically expressed or not, in at least one individual in a defined location and during a specified period of time' (Toma et al., 1999). The spatio-temporal attributes of each outbreak were used, including outbreak date and the centroids of outbreak sub-districts. The global country map was obtained from the website of Global Administrative Areas[1] to facilitate the presentation of data and the interpretation of results.

Method of analysis

Daily, weekly and monthly epidemic curves of global HPAI H5N1 outbreaks were constructed to display outbreak magnitude and temporal trend using R 2.11 software (R Development Core Team, 2010). During an epidemic wave (EW), the number of disease outbreaks peaked rapidly and then decreased gradually until the epidemic was over (Zhang et al., 2010), and the number of outbreaks was calculated for each EW. Secondly, spatially adaptive kernel density estimation with variable smoothing parameters (Davies and Hazelton, 2010) was applied to describe the EW specific spatial patterns. Compared to traditional kernel density estimation with fixed bandwidth, this approach assigned a smaller bandwidth for closely clustered and a larger bandwidth for sparsely distributed outbreaks, thus preserving details in areas of concentrated outbreaks by reduced smoothing and by avoiding the allocation of undue importance to those areas with scattered outbreaks. Appendix A (Supplementary material) briefly summarises the adaptive kernel density estimation with variable smoothing parameters).

Retrospective space–time permutation scan statistics were applied to identify the spatio-temporal clusters for each EW by testing whether outbreaks were correlated in space and time using SaTScan 8.2.1 software (Kulldorff et al., 2005; Onozuka and Hagihara, 2008; Kulldorff, 2009). The scanning window was a cylinder with the spatial and temporal dimension as circular base and height, respectively. The temporal scanning window was set to <50% of the study period in each EW and a maximum of 50% of outbreaks were allowed in the spatial scanning window. The likelihood ratio statistic was used to evaluate the possibility of a true spatio-temporal cluster in a window. The window with maximum likelihood ratio statistic was considered the primary cluster while the remainder were considered secondary clusters. Their statistical significance was tested through Monte Carlo simulations of 999 replications. The time units of day, week and month were used, respectively. ArcGIS 9.3.1 software was used to overlay results from different methods in a map for visual comparisons (ESRI, Redlands).

Results

Epidemic waves of global HPAI H5N1 outbreaks

Six EWs (EW1–6) of global HPAI H5N1 outbreaks were identified over the study period (Fig. 1): EW1 began in December 2003, peaked in January 2004 and ended in June 2004 (10th December 2003–30th June 2004); EW2 began in July 2004, peaked in October 2004 and ended in May 2005 (1st July 2004–31st May 2005); EW3 began in June 2005, peaked in March 2006 and ended in October 2006 (1st June 2005–31st October 2006); EW4 began in November 2006, peaked in February 2007 and ended in September 2007 (1st November 2006–30th September 2007); EW5 began in October 2007, peaked in January 2008 and ended in October 2008 (1st October 2007–31st October 2008); EW6 began in

November 2008, peaked in February 2009 and ended in December 2009 (1st November 2008–31st December 2009).

Table 1 illustrates the numbers of outbreaks for each of the six EWs by region. In the first two EWs, H5N1 outbreaks were confined in Asia, but had spread to Europe and Africa by EW3, and continued to appear in Asia and Africa in EW6 although the number of outbreaks was greatly reduced by this time.

Spatial pattern of outbreak density

The spatial distribution of H5N1 outbreaks was confined to East and Southeast Asia in EW1 and 2, but had spread widely within Europe and Africa by EW3. A historic 'hot-spot' region in East and Southeast Asia was found to have a higher outbreak density in all EWs, but its location and size varied. A novel hot-spot at the junction of Europe and Africa emerged from EW3 and continued to EW6 with little change in either location or size (Fig. 2).

Spatio-temporal clusters

The primary spatio-temporal cluster was consistently detected in the historic 'hot-spot' region across all six EWs, but the location and size varied with EW. The secondary clusters varied in number and location over space and time. In the first two EWs, all secondary clusters were located in the historic hot-spot region, but from EW3 these were constantly identified in Europe and Africa, especially the newly emerged hot-spot. The primary cluster occurred within the first 3 weeks in EW1, but not in later EWs, while the secondary clusters appeared both in the early and late periods of each EW (Fig. 2). The results from outbreak day, week and month were very similar, and therefore only week-based results are reported.

Other data on identified clusters are detailed in Appendices B–F (Supplementary material). Appendices B and C illustrate spatial patterns and spatio-temporal clusters of day- and month-based global outbreaks over the six EWs, respectively. Outbreaks are represented by light green dots, and outbreak density from adaptive kernel density estimation in monochromatic grey – the higher the density, the darker the colour, and significant spatio-temporal clusters detected by space–time permutation scan statistics showing the most likely cluster (red circle) and secondary clusters (blue dashed circles). Appendices D–F detail the significant clusters of week-, day- and month-based global outbreaks detected by space–time permutation scan statistics over the six EWs, respectively.

Discussion

Spatio-temporal analyses of global HPAI H5N1 outbreaks can provide clues that increase our understanding of the dynamics of disease spread and can assist in identifying targeted areas where more investigations are needed. Such insights enhance the cost-effectiveness of planning and the implementation of disease control measures (Oyana et al., 2006; Ahmed et al., 2010). Although global efforts have been made to control or eradicate HPAI H5N1 in poultry, and to restrict the infection to East and Southeast Asia (Ferguson et al., 2005; Longini et al., 2005), consistently reappearing hot-spots remain indicating that the virus could evolve into a strain with human pandemic potential.

HPAI H5N1 commonly caused outbreaks in winter and early spring (i.e. from October to March), suggesting this was a higher risk period (Park and Glass, 2007; Si et al., 2009). This may be related to increased virus survival at low temperature (Shortridge et al., 1998). Six EWs divided by different time scales of day, week and month showed similar patterns, which may indicate that HPAI
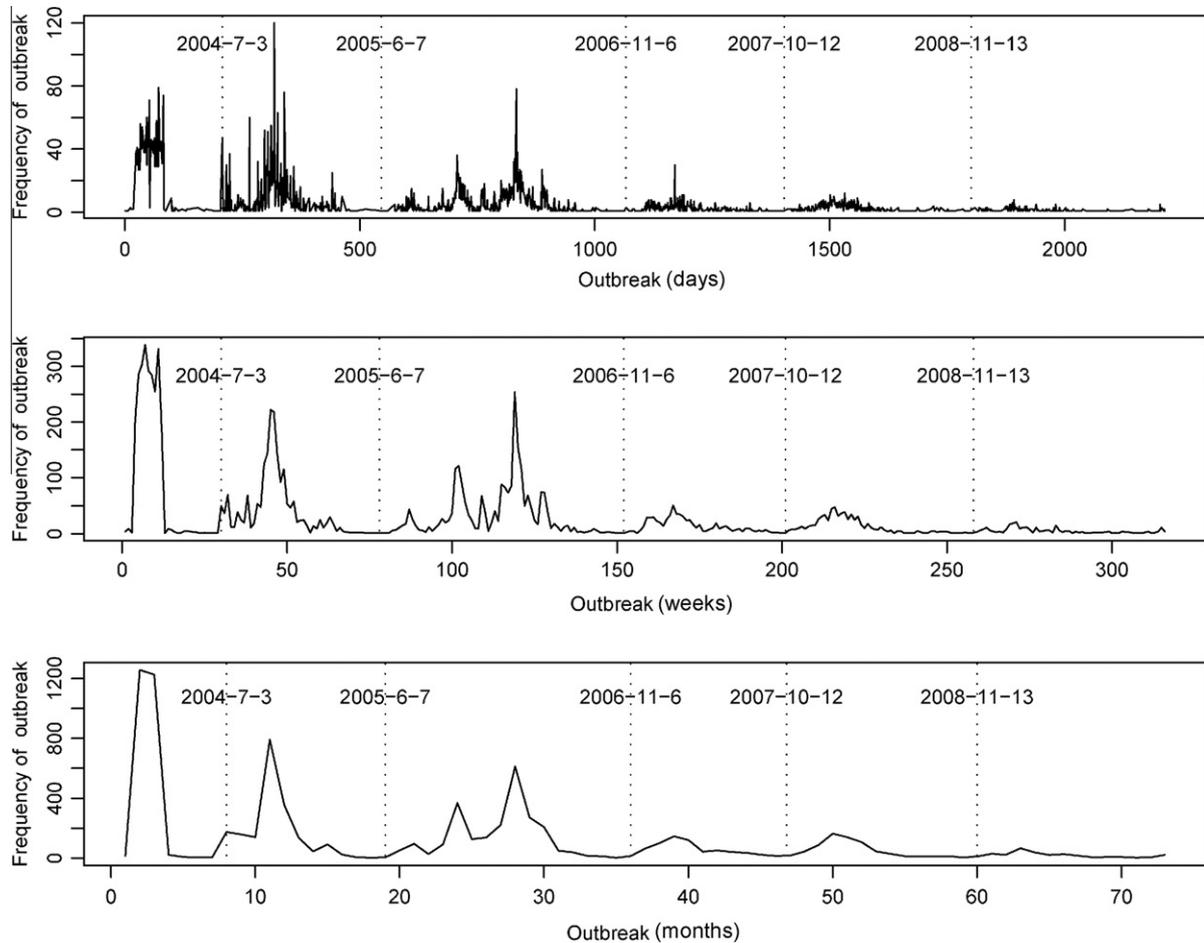
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[1] See: http://www.gadm.org/world.

Fig. 1. Epidemic curves of global outbreaks of highly pathogenic avian influenza subtype H5N1 between December 2003 and December 2009, illustrating daily, weekly, and monthly numbers of outbreaks as a function of time. Vertical lines delineate the six epidemic waves.

Table 1
Number of outbreaks during each of the six epidemic waves in each region.

Epidemic wave	Asia	Europe	Africa	Total
1	2540	0	0	2540
2	1927	0	0	1927
3	1000	455	883	2338
4	286	31	340	657
5	484	26	172	682
6	150	0	133	283
Total	6387	512	1528	8427

H5N1 has a strong epidemic characteristic with high contagion. The six EWs were also of prolonged duration (7, 11, 17, 11, 13 and 14 months, respectively), and the starting dates of these waves were also postponed from June/July to October/November. Together, these findings suggest the disease control procedures were somewhat effective (Minh et al., 2009), and that the disease transmission cycle was not interrupted.

Although the number of HPAI H5N1 outbreaks largely decreased over time, their spatial distribution was still extensive, suggesting that the potential risk of spatial spread has not been correspondingly decreased. Two hot-spot regions were detected, namely, the well-recognized region in East and Southeast Asia where the virus is endemic in wild birds and intermittently infects poultry (Paul et al., 2010), and the newly emerged 'hot-spot' located at the border between Europe and Africa, which, to date, has been largely ignored. This region covers the Black and Mediterranean Seas and neighbouring regions such as Egypt, Greece and Turkey, where the risk of HPAI H5N1 outbreaks has historically been high.

Given that this novel hot-spot began to appear in EW3 and persisted up until EW6, it is easy to understand why it has not been reported in previous short-term studies that mainly covered the period EW1–3. This newly identified hot-spot is extremely important in terms of our overall understanding of global HPAI H5N1 outbreaks in that (1) the virus sub-type in this region belongs to Clade 2.2 that is of high virulence and caused the most widespread outbreaks in 2006 (Webster and Govorkova, 2006); (2) extensive wetlands in this region have formed significant breeding and congregation sites for migratory and other wild birds and for domestic poultry, increasing the risk of contact (Ward et al., 2008) and facilitating virus evolution; and the existence of two bird migratory routes across this region (the Black Sea–Mediterranean and the East Africa–West Asia flyways), which link Asia, Europe and Africa.

The potential risk that migratory birds spread the disease is very high (Si et al., 2009), and it is imperative that enhanced surveillance in this region is conducted to reduce the risk of generating a future potentially pandemic strain. Furthermore, bio-security measures should be in place to protect domestic poultry and a regional disease control strategy should be enacted to limit the spread of the virus once a flock has become infected.

In the present study, we used spatio-temporal permutation scan statistics to pinpoint the space–time cluster's precise locations. This approach requires minimal assumptions about outbreak date, location and size, and also takes into account natural, spatial,
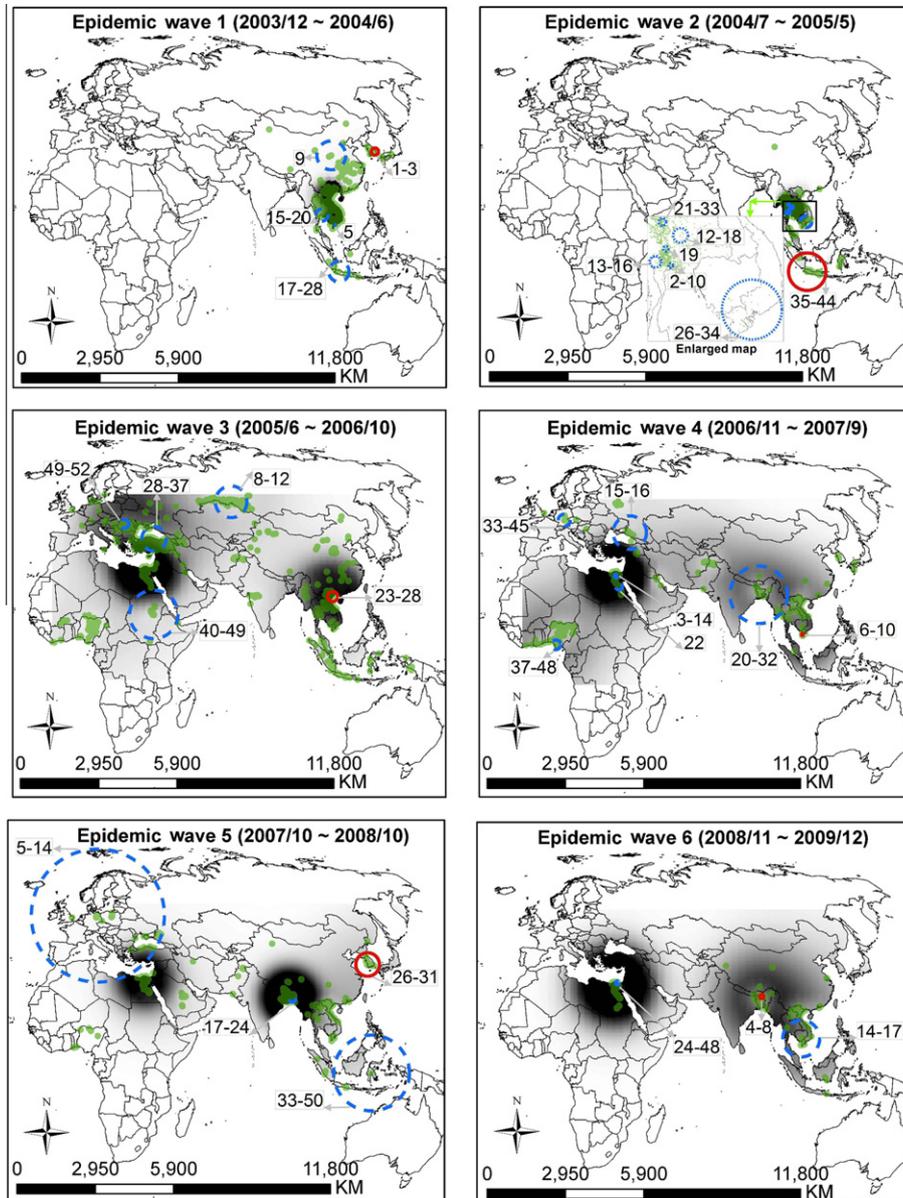
Fig. 2. Spatial patterns and spatio-temporal clusters of week-based global outbreaks of highly pathogenic avian influenza subtype H5N1 over six epidemic waves. Outbreaks represented by light green dots and outbreak density from adaptive kernel density estimation highlighted in monochromatic grey (the higher the density, the darker the colour). Significant spatio-temporal clusters detected from the space–time permutation scan statistics are illustrated by the most likely cluster (red circle) and by a secondary cluster (blue-dashed circles). The week-based time-frame for each cluster is also shown.

temporal, and space–time variations (Onozuka and Hagihara, 2008). The most likely clusters were all located in the historic hot-spot region in six EWs, while secondary clusters had spread to the new hot-spot and were continuously identified. On spatial analysis the hot-spot represents the accumulative risks largely from the internal hosts of HPAI H5N1 (e.g. domestic ducks) which were similar across space and time.

Meanwhile, clusters from spatio-temporal analysis can be regarded as instant risks from externally imported hosts (e.g. infected migratory birds) that are relatively unstable and influenced by various factors such as temperature. Both types of risk have appeared in the novel hot-spot, further highlighting its importance. Taken together, these findings suggest that the current highest risk region remains the established historic hot-spot, but another high risk region has emerged and its level of risk has been rising. This novel hot-spot offers added opportunities for the virus to mutate, which increases the risk of a pandemic. Surveillance and

regional disease control preparedness should be strengthened accordingly.

There are two potential limitations in this study. One is that our analysis did not include the at-risk poultry population in each outbreak because the global HPAI H5N1 outbreak data were either not available or imprecise. Therefore, our results do not reflect the absolute risk of infection, but rather the *degree* of infectivity risk. Besides, the mortality rate due to HPAI H5N1 infection approaches 100% in poultry (Alexander, 2000), and 'stamping-out' is always conducted immediately after a positive case is found (Loth et al., 2010). As a result, the at-risk poultry population may vary greatly because of possible delayed diagnoses, resulting in traditional measures of risk remaining un-quantifiable. In our analysis, we treated each sub-district as an infected unit if it had experienced a H5N1 outbreak, regardless of the size of its poultry population.

A further limitation was the fact that since the study was based on both passive and active surveillance data, under-reporting of

outbreaks was inevitable (Ahmed et al., 2010), and the details of some outbreaks were confidential (J. Pinto, personal communication). The incompleteness of the data-set may have resulted in errors following analysis, although the overall spatio-temporal patterns appear correct (Farnsworth et al., 2010; Zhang et al., 2010). Despite these limitations, the existence of the new hot-spot appears well founded.

Conclusions

Two important findings have emerged from this long-term investigation of the spatio-temporal distribution of global HPAI H5N1 outbreaks. Firstly, the initiation of the EW was postponed, the epidemic duration was prolonged and the magnitude of the wave decreased over time as a possible consequence of the disease control measures implemented. Secondly, two disease hot-spots have been identified where enhanced surveillance is recommended. Although the EWs lessened in magnitude with time, the sustainability of the infection in two major regions indicates that the risk of a pandemic from HPAI H5N1 remains high.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tvjl.2011.08.012.

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