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# Spatio-temporal distribution of outbreaks of highly pathogenic avian influenza virus subtype H5N1 in Vietnam, 2015 to 2018

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## Abstract

Despite strong commitments of the central and provincial veterinary authorities in Vietnam to control highly pathogenic avian influenza H5N1 (HPAI-H5N1) in poultry and to diminish the risk of human infection, outbreaks continue to occur in poultry. This study describes the spatio-temporal distribution

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of HPAI-H5N1 outbreaks in Vietnam for the period December 2014 to April 2018 using the space-time K-function and the space-time scan statistic.

The space-time K-function analyses showed statistically significant spatio-temporal clustering of HPAI-H5N1 outbreaks in poultry during the study period of up to 50 days and 60 kilometres. The space-time scan statistic test identified three statistically significant space-time clusters of HPAI-H5N1 in the south of the country where the incidence of HPAI-H5N1 outbreaks was greater than that expected if outbreaks were randomly distributed in space and time. The analyses indicated shortfalls in the effectiveness of control measures used to control HPAI-H5N1 throughout the study period. Development of a better understanding of the relative impact of HPAI-H5N1 control measures (depopulation of infected flocks, vaccination, movement restrictions) on space-time interaction would allow animal health authorities to focus their efforts on control measures shown to have the greatest relative effect.

## Keywords

disease outbreaks; epidemiology; influenza A virus, H5N1 subtype; spatio-temporal analysis; Vietnam

## Introduction

Although the number of reported HPAI subtype H5N1 outbreaks in Vietnam has decreased markedly since 2004 (FAO Vietnam, 2017), substantial losses to the domestic poultry sector continue to occur (World Organisation for Animal Health, 2018). In addition, 64 people have died as a result of infection with H5N1 influenza viruses in Vietnam and, although the last human case was reported in early 2014, the risk of human infection remains high (World Health Organization, 2018).

From 2004 to 2011, phylogenetic analyses of whole-genome sequences of subtype H5N1 viruses isolated from poultry outbreaks of avian influenza in Vietnam identified a total of 48 genotype constellations with circulation of at least 12 distinct hemagglutinin clades (Boender et al., 2007) and subclades (1, 1.1, 2.3.4 [1–3], 2.3.2.1 [a–c] 3, 5, 7.1, 7.2) (Creanga et al., 2013; Tung et al., 2013).

An active surveillance program for avian influenza in 394 live bird markets (LBMs) in the north, central and southern regions of Vietnam between September 2011 and June 2013 showed that the prevalence of HPAI H5N1-positive markets (that is, LBMs in which at least one bird was H5N1 positive at the time of sampling) was 26% (95% CI 22% to 31%). Phylogenetic analyses of the partial HA gene sequences from these samples identified viruses of clade 2.3.2.1a ($n$ = 44 isolates), clade 2.3.2.1b (3 isolates), clade 2.3.2.1c (90 isolates), clade 1.1.1 (12 isolates), clade 1.1.2 (32 isolates) and clade 7.2 (13 isolates) (Nguyen et al., 2014) consistent with the poultry outbreak clades identified by Creanga et al. (2013) and Tung et al. (2013).

Prior to mid-2014, these six H5N1 clades circulated in Vietnam, each with different disease dynamics, making epidemiological research impractical. In 2014, HPAI subtype H5N6 appeared and spread through Vietnam, initially causing high mortality rates in young ducks (World Organisation for Animal Health, 2014). In the same year, five clades of HPAI H5N1 ceased to be detected leaving HPAI H5N1 (clade 2.3.2.1c) and H5N6 (clade 2.3.4.4) the only subtypes endemic in Vietnam (Nguyen et al., 2017), both highly pathogenic for chickens and ducks. With only one clade of HPAI H5N1 and one clade of HPAI H5N6 circulation in Vietnam from late 2014 till early 2018, this epidemiological study became possible.

Although a considerable amount of work has been carried out to both describe the epidemiology of HPAI outbreaks in Vietnam (Minh et al., 2009) and to identify factors that render some flocks at greater risk of infection compared with others (Henning et al., 2009; Minh, Stevenson, Jewell, French, & Scheuer, 2010; Pfeiffer, Minh, Martin, Epprecht, & Otte, 2007) the epidemiology of HPAI in commercial and non-commercial poultry flocks in Vietnam remains relatively poorly understood. Reasons for knowledge gaps include: (1) an absence of up-to-date sampling frames providing details of commercial and non-commercial poultry enterprises throughout the country, making it difficult to design cross-sectional and prospective observational studies that allow inferences to be confidently extrapolated to the population level; (2) a high turnover of birds in individual poultry flocks, more so for broilers compared with layers; (3) complexity in the pattern of animal movement and dynamic value chains (Fournie et al., 2016); (4) constrains in disease detection and reporting (Delabouglise et al., 2016); and (5) as outlined above, complexity in the different virus subtypes and clades co-circulating in different regions of the country and in different poultry enterprise types.

Despite strong commitments of the central and provincial veterinary authorities to control HPAI in poultry and to diminish the risk of further human infection, HPAI outbreaks continue to occur in Vietnam (World Organisation for Animal Health, 2018). The aim of this study was to describe the spatio-temporal distribution of HPAI-H5N1 (clade 2.3.2.1c) and H5N6 (clade 2.3.4.4) outbreaks on farms in Vietnam for the period December 2014 to April 2018 and to use that information to identify the additional outbreak information that needs to be recorded to determine the relative effectiveness of outbreak control measures. The current control measures include culling of infected flocks, cleaning and disinfection of contaminated premises, vaccination of at-risk flocks and risk communication. A better understanding of those control measures that have the greatest impact on suppression of disease spread will allow resources to be more appropriately allocated by disease control authorities.

## Materials and methods

### Data collection and management

Details of HPAI-H5N1/H5N6 outbreaks that occurred in domestic poultry in Vietnam for the period 24 December 2014 to 30 April 2018 (inclusive) were obtained from the Department of Animal Health of the Ministry of Agriculture and Rural Development, Hanoi. An outbreak was defined as the presence of at least one laboratory-confirmed HPAI-H5N1/H5N6 infected bird (by either virus isolation or polymerase chain reaction, PCR) in either a commercial or non-commercial poultry flock (MARD, 2014). All outbreaks were reported through the passive surveillance system. In the usual situation the presence of illness or elevated mortality rates in a flock prompts a poultry flock owner to contact the local community animal health worker, who will contact a local government district veterinarian who then initiates a flock investigation. If HPAI is suspected, tissue (whole carcass) samples are submitted for confirmatory testing at one of the seven Regional Animal Health Office laboratories located throughout the country or at the National Centre for Veterinary Diagnostics in Hanoi.

Data from laboratory confirmed outbreaks of HPAI-H5N1/H5N6 for the period 24 December 2014 to 30 April 2018 included the address of the affected poultry flock, the date of on which the investigation was initiated, the species involved (chickens, ducks, or Muscovy ducks) and details of the specimens collected and tested to confirm the diagnosis. Because the address details provided for each affected poultry enterprise were not uniform in the level of detail sufficient to allow geocoding, the spatial resolution of the location of each outbreak was limited to the commune level. Communes are the smallest administrative unit in Vietnam with a median area of 15 $km^2$. Digital maps of the primary (provincial), secondary (district) and tertiary (commune) boundaries of Viet Nam were obtained from http://www.diva-gis.org/datadown. Longitude and latitude coordinates of the centroid of each of the 11,162 communes of Viet Nam were calculated using the Geographic Information System Quantum GIS (QGIS Development Team, 2018). Centroid coordinates of each commune were re-projected to the

Universal Transverse Mercator projection zone 48N (European Petroleum Survey Group: 3857) using the contributed rgdal package (Bivand, Keitt, & Rowlingson 2018) in R (R Core Team, 2018) version 3.5.1.

**Data analysis**

A total of 138 poultry flock outbreaks of HPAI-H5N1 were reported (passive surveillance) during the period 24 December 2014 to 30 April 2018. No HPAI-H5N1 infection was detected in poultry flocks through active surveillance. The analysis of flock outbreaks caused by HPAI-H5N6 (n = 55) did not result in any significant findings and was not further discussed. HPAI-H5N1 detected in individual birds in LBMs during the same time period were not included in the analyses presented in this paper (as described till December 2015 by Mellor et al. (2018)), as the origin of these infected birds could not be determined.

Two separate analyses were carried out to describe the spatio-temporal characteristics of HPAI-H5N1 outbreaks on poultry farms in Vietnam throughout the study period. The first involved calculation of the space-time K-function (Diggle, Chetwynd, Häggkvist, & Morris, 1995) in an effort to identify the general property of space-time interaction in the HPAI-H5N1 outbreak data. This answered the question: if an outbreak of HPAI-H5N1 occurred in a given location at a given time, how likely was it that additional cases of HPAI-H5N1 were detected within a given Euclidean distance and time from the date of detection of that outbreak? In veterinary epidemiology the space-time K-function has been used to describe the presence of space-time interaction (colloquially termed ‘contagiousness’) in the outbreak of foot-and-mouth disease that occurred in the United Kingdom in 2001 (Wilesmith, Stevenson, King, & Morris, 2003), bovine tuberculosis in New Zealand (Porphyre, McKenzie, & Stevenson, 2007) and outbreaks of HPAI-H5N8 in France in 2016-2017 (Guinat et al., 2018).

The space-time K-function requires calculation of $K(s,t)$ defined as the cumulative expected number of HPAI-H5N1 outbreaks within distance $s$ and time $t$ of an arbitrarily selected HPAI-H5N1 outbreak event divided by outbreak intensity $\lambda$ (the mean number of outbreak events per unit space and per unit time). In this context the observed space-time K-function, $K(s,t)$, is comprised of two components: the independent effect of space $K_S(s)$ and time $K_T(t)$, $K_S(s)K_T(t)$, and the interaction between space and time, $D(s,t)$. Because $D(s,t)$ cannot be observed directly, it is estimated as the difference between $K_S$ $(s,t)$ and $K_S(s)K_T(ts)$:

$$D(s,t) = K(s,t) - K_S(s)K_T(t) \qquad \text{Equation 1}$$

Thus $D(s,t)$ provides an estimate of the cumulative number of HPAI-H5N1 outbreaks expected within distance $s$ and time $t$ of an arbitrarily selected outbreak attributable to the interaction between space and time, scaled by $\lambda$. To facilitate inference $D_0$ is calculated as:

$$D_0(s,t) = \frac{D(s,t)}{K_S(s)K_T(t)} \qquad \text{Equation 2}$$

which estimates, for distance $s$ and time $t$, the proportional increase in disease risk attributable to space-time interaction (Diggle et al., 1995).

Acknowledging that outbreak location details were recorded at the commune level and to minimise the possibility that we might bias the distance component of $D_0$ by assuming that all outbreaks occurred in the centre of each commune, a series of 100 Monte Carlo simulations were carried out in which the location of each outbreak was randomly assigned to a point location with the boundaries of its respective commune. For each of the 100 simulations $D(s,t)$ was calculated and summed. The summed values of $D(s,t)$ were then ranked and the $D_0(s,t)$ matrices corresponding to the 5th percentile, 50th and 95th percentiles of the $D(s,t)$ sums were selected for reporting.

For each of the three $D_0(s,t)$ matrices selected for reporting, the significance of space-time clustering was assessed by conducting 99 Monte Carlo simulations in which each of the $n$ = 138 HPAI-H5N1 outbreak locations were randomly labelled with the observed 138 time 'markers'. For each of the 99 Monte Carlo simulations, the sum of $D(s,t)$ over all $s$ and $t$ was calculated, as before. The sum of $D(s,t)$ for the observed data was then ranked among the empirical frequency of the 99 $D(s,t)$ sums. If the observed value of $D(s,t)$ ranked $k$th largest (or smallest) the one-sided attained significance level was $k/100$ (Wilesmith et al., 2003).

Our second analysis used Kulldorff's space-time scan statistic (Kulldorff, 1997) to identify the geographical locations and time frames of spatio-temporal clusters of HPAI-H5N1 that occurred during the study period. With the space-time scan statistic, the number of observed HPAI-H5N1 outbreaks in a given area and time frame is compared to what would have been expected if the spatial and temporal locations of outbreaks were independent of each other. That is, a spatio-temporal cluster of HPAI-H5N1 outbreaks was said to exist in a given area if that area had a higher proportion of its cases in that time period compared to the remaining geographical areas. The geographic location of spatio-temporal clusters of HPAI-H5N1 outbreaks were determined using the space-time permutation model of the spatial scan statistic implemented in SaTScan version 9.6 (Kulldorff, Heffernan, Hartman, Assunção, & Mostashari, 2005; Park et al., 2016). The analysis was conducted across the duration of the study period, from 24 December 2014 to 30 April 2018. Because inference was at the national level the location of HPAI-H5N1 outbreaks was assumed to be the centroid of each affected flock's commune. Most likely clusters were reported at a significance level of 5% based on 999 Monte Carlo replications, without geographical overlap, using a maximum circular spatio-temporal window set to 25% of the total number of cases ($n$ = 35) and 10% of the study period (approximately three months).

## Results

### Descriptive analysis

Throughout the study period a total of 138 HPAI-H5N1 outbreaks were reported in poultry flocks in 34 of the 63 provinces (67 of the 713 districts) of Vietnam. Figure 1 is a map of Vietnam showing the centroid coordinates of the 113 communes that were identified as HPAI-H5N1 positive for the period 21 December 2014 to 8 April 2018.

The number of outbreaks reported per commune ranged from one to six, with 13% (15 of 113) of the total number of HPAI-H5N1 positive communes reporting more than one outbreak. The incidence of HPAI-H5N1 outbreaks varied over time (Figure 2) with five outbreaks or less reported per month for the period December 2014 to December 2016. In February 2017 a total of 19 outbreaks were reported from different parts of the country. The relatively large number of outbreaks in February 2017 could be the result of intensified poultry trade and movements prior and during the festive lunar New Year. These seasonal peaks have been reported earlier (Minh,  et al., 2009). From June 2017 the frequency of outbreaks reported per month decreased to less than five per month.

The majority of outbreaks were in chicken flocks (59%, 82 of 138), followed by duck (30%, 42 of 138) and then multispecies flocks (i.e. flocks comprised of chickens, ducks and geese 10%, 14 of 138). Of the 138 outbreaks, 121 (88%) occurred in commercial flocks while the remaining 17 occurred in non-commercial flocks comprised of less than 100 birds. The HPAI-H5N1 positive commercial flocks were comprised of a median of 650 birds (range 100 to 42,000 birds).

### Spatio-temporal analyses

The space-time K-function analyses showed that there was significant spatio-temporal clustering of HPAI-H5N1 outbreaks in poultry during the study period with Monte Carlo p-values of 0.03, 0.03, and 0.02 for the 5th percentile, 50th, and 95th percentile $D_0(s,t)$ matrices, respectively. Figure 3 is a perspective plot showing $D_0(s,t)$ as a function distance (in kilometres) and time (in days) for the 50th percentile $D_0(s,t)$ matrix. For the 50th percentile $D_0(s,t)$ matrix, $D_0$ was greater than unity for a period of up to 50 days and 60 kilometres from an arbitrarily selected HPAI-H5N1 case flock. This indicated that the observed number of outbreaks which were located within 60 km around a given outbreak and, which occurred within 50 days after the date of conformation of this given outbreak, was greater than the number of outbreaks that would have been observed in the absence of space–time interaction (i.e. random distribution in space and time). Figure 3 also shows that the likelihood of additional cases decreased rapidly ($D_0(s,t)$) after 20 days and over 20 km.

The space-time permutation model of the space-time scan statistic test identified three statistically significant space-time clusters of HPAI-H5N1 in the south of the country where the incidence of HPAI-H5N1 outbreaks was greater than that expected if outbreaks were randomly distributed in space and time (Table 1 and Figure 4). Clusters 1 (5 outbreaks) and 3 (3 outbreaks) were temporarily and geographically distinct comprised of an 8- or 9-day time interval and a radius of 5 kilometres or within the same commune, respectively. Cluster 2 (3 outbreaks) was larger, covering an area greater than 500 km$^2$ and persisted for 26 days (Table 1 and Figure 4). No clusters were detected in the north of the country as the outbreaks there were spatial and temporal randomly dispersed.

## Discussion

Our space-time K-function analyses identified intense space-time interaction {as indicated by $D(s,t)$ values that were greater than $K_S(s)K_T(t)$} over distances of up to 60 kilometres and time frames of up to 50 days from an arbitrarily selected HPAI-H5N1 outbreak. Figure 3 shows that there was a high risk of HPAI-H5N1 disease transmission early in the incursion up to 60 kilometers and the risk of local spread of HPAI-H5N1 outbreaks on farms remained high for up to 50 days. These findings are consistent with previous evidence showing higher transmission rates of HPAI in the vicinity of infected poultry holdings (Boender et al., 2007; Guinat et al., 2018). We note that preventive or control measures applied in response to detection of infected flocks (e.g. movement restrictions, preventive vaccination or vaccination as a control measure of farms in the neighborhood (ring vaccination) and/or depopulation, cleaning and disinfection of infected farms) act to suppress, or ideally eliminate, space-time interaction of infection risk and, as a result, the magnitude of $D_0(s,t)$ at given scales of distance and time will decrease over calendar time if control measures are effective (Guinat et al., 2018; Wilesmith et al., 2003).

HPAI-H5N1 was endemic in Vietnam throughout the study period and, for this reason, animal health authorities throughout the country had well-established protocols for outbreak control. The presence of significant space-time interaction in the data (Figure 3) and the three clusters identified by the space-time scan statistic (Table 1 and Figure 4) points to shortfalls in the effectiveness of the disease control measures. Unfortunately, it is not possible to determine from the data if these shortfalls were related to measures applied to suppress local spread (e.g. prompt depopulation of infected flocks, effective cleaning and disinfection, movement restriction on and off the farm of people, animals and materials and vaccination of at-risk properties) or measures to suppress long distance spread (e.g. movement restrictions). The relatively long distance (60 kilometres) and time frame (up to 50 days) over which $D(s,t)$ was greater than $K_S(s)K_T(t)$ is substantially greater than the 8 kilometres and 13 days reported by Guinat et al. (2018) in their analyses of the spread of HPAI-H5N8 in France in 2016-2017, which would imply that there were shortfalls in both.

This study provides insight into HPAI-H5N1 infection dynamics in Vietnam, showing that transmission of disease occurs by a combination of local (flock-to-flock) spread and long-distance spread (most likely mediated by animal movement through the LBM trading networks (Fournie et al., 2016)). Early detection of HPAI and timely implementation of control measures such as restriction of the movement of birds (and ideally people) should be prioritised to reduce the likelihood of long-distance spread of HPAI. The findings of this study support the need to maintain high biosecurity standards on poultry holdings that are in close proximity to identified flock outbreaks. The Ministry of Agriculture and Rural Development (MARD, 2014) issued disease control guidelines and these are described in the legal framework outlining responses to zoonotic diseases in Circular 7 (MARD, 2016). This circular was issued by the Ministry of Agriculture and Rural Development in 2016 and is used by the 63 provincial animal health authorities as a guide when responding to zoonotic and other animal diseases. Circular 7 contains technical information on biosecurity, transport, reporting, diagnostics, outbreak investigation methods, the management of sick animals and vaccination (as either a preventive or control measure). In contrast, the National Plan on H5N1 Avian Influenza Prevention and Control 2014-2018 (MARD, 2014) outlines the national approach for the control of HPAI-H5N1. The National Plan, in addition to Circular 7, provides details on the conduct of surveillance, quarantine, poultry sector restructuring, communication and research. The level of implementation and adherence to the directives provided in Circular 7 and the National Plan depend largely on the political support and resources from provincial authorities.

Our analyses indicated shortfalls in the effectiveness of control measures used to control HPAI-H5N1 throughout the study period. Development of a better understanding of the relative impact of HPAI-H5N1 control measures (depopulation of infected flocks, preventive vaccination, vaccination of at-risk farms, movement restrictions) on space-time interaction would allow animal health authorities to focus their efforts during an outbreak response on those measures shown to have the greatest relative effect. Better understanding of the relative effectiveness of the tools used to control HPAI-H5N1 outbreaks would arise from analysis of data recorded to a high level of detail including the date of onset of clinical signs in affected flocks, the date of first examination, the date of previous vaccination (to assess flock immunity status) , details of vaccine and vaccinators, the date of depopulation start and end, and the method of disposal of culled birds. Details to assess the effectiveness of the vaccine cold chain would also be of value. If, for example, vaccination of at-risk farms, was found to have the greatest impact on suppression of space-time interaction during an outbreak of HPAI-H5N1, then efforts to enhance the efficacy of vaccination (use of vaccines protective against the circulating HPAI field strains, maintenance of cold chain and optimisation of vaccination technique) should receive major emphasis during outbreak responses. An additional point to consider is that there is likely to be geographical variation in outbreak control measure effectiveness. To protect flocks and prevent outbreaks, post vaccination serological surveys should be carried out on an ongoing basis to identify shortfalls in levels of protection that might vary geographically and over time (León et al., 2014; Nguyen, 2011).

A number of factors may have impacted on the external validity of the findings reported in this paper. First, it is a reasonable assumption that the sensitivity of outbreak detection was relatively uniform across the country and over time, given a relatively high level of awareness of the disease among commercial and non-commercial flock owners as a result of the large number of outbreaks of HPAI-H5N1 that occurred in Vietnam from 2004 on (FAO Vietnam, 2017). However, previous studies have pointed out the lack of sensitivity of the passive surveillance system in Viet Nam (Delabouglise et al., 2016; Minh et al., 2009). The lack of effective compensation schemes and other economic and social consequences of reports are likely to be critical in defining farmers' reporting behaviors, and it is assumed that there was still considerable under-reporting in the study period. This being the case, it is our assessment that the estimates of space-time interaction reported in this paper are likely to be relatively biased estimates of the true population value. However, the findings were not necessarily incorrect, as more outbreaks would probably increase space-time interaction, especially locally as reported previously (Minh et al., 2010).   Second, our analyses have used the date of the first veterinary investigation and diagnostic sample collection, not the date on which clinical signs were first observed or the date of on which disease was believed to be first introduced into the flock. Given the reasonably uniform geographical coverage of local government district veterinarians across the country it is likely that the interval from first detection of clinical signs to the date of investigation was reasonably constant geographically and over time and therefore unlikely to bias the temporal component of our space-time K-function analyses to any great degree. Third, the exact location of infected flocks within a commune was unknown making it necessary to randomise the location of outbreaks within a commune for the space-time K-function analyses. The presence of statistically significant space-time interaction present across all levels of the Monte Carlo simulated data sets provide confidence that the space-time interaction effects identified in this paper were, in fact, real and not simply an artefact of our analytical methods.

Additional research should include assessment of the role of LBMs in disease transmission and using LBM surveillance results as a means for predicting and then preventing flock-level HPAI outbreaks. A previous study found no correlation between HPAI outbreaks on farms and HPAI infected poultry at LBMs (Nguyen et al., 2014). Unpublished data showed high infection rates of HPAI-H5N1 of poultry in LBMs in 2016 and 2017 (L.Loth, personal communication), but the inclusion of the LBM surveillance data in the spatio-temporal analyses reported in this paper was not possible because of temporal misalignment between the outbreak report data and the timing and location of the LBM surveillance studies [only 134 markets were surveyed out of a total of 8,580 registered LBMs (GSO, 2019) throughout Vietnam, at infrequent intervals]. Secondly, it may be of interest to investigate virus movement, by examining the possible correlation between molecular genetic data and spatio-temporal clusters. Unfortunately, during the reporting period, very few HPAI-H5N1 outbreak virus isolates were sequenced, and no inferences/conclusions could be made.  Finally, the potential interaction between farmer and trader responses to the coexisting endemic HPAI-H5N6 and the spread of HPAI-H5N1 between poultry farms should be investigated.

The results of this study showed that there was a prolonged disease control shortfall, and this should encourage the authorities to reinforce and enhance disease control efforts. Additionally, the space-time analyses technique used in this study could be applied longitudinal on additional prospective outbreak data. This, to discover possible new space-time clusters timely and enhance or redirect disease response efforts accordingly.

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## Table

Table 1: Spatio-temporal distribution of outbreaks of highly pathogenic avian influenza virus subtype H5N1 clade 2.3.3.1c in Vietnam, 2015 to 2018. Details of the three statistically significant space-time clusters of HPAI H5N1 outbreaks identified by the space-time scan statistic. The cluster numbers refer to the locations shown in Figure 4.

| Cluster | Date | | Radius (km) | Number of outbreaks | Expected outbreaks | Observed to Expected ratio | P value |
|---|---|---|---|---|---|---|---|
| | Start | End | | | | | |
| 1 | 7 Mar 2017 | 16 Mar 2017 | 4.98 | 5 | 0.30 | 16.4 | <0.01 |
| 2 | 20 Jul 2015 | 15 Aug 2015 | 13.14 | 3 | 0.65 | 46 | 0.04 |
| 3 | 4 Aug 2017 | 13 Aug 2017 | 0 | 3 | 0.07 | 46 | 0.02 |

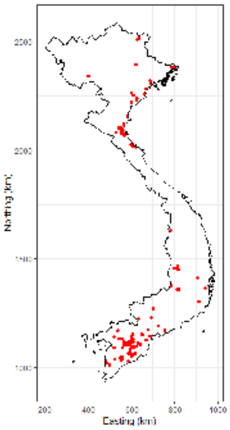
## Figure legends

Figure 1: Spatio-temporal distribution of outbreaks of highly pathogenic avian influenza virus subtype H5N1 clade 2.3.3.1c in Vietnam, 2015 to 2018. Map of the Socialist Republic of Vietnam showing the point location of the centroid of the 113 communes identified as HPAI-H5N1 positive during the period 24 December 2014 to 30 April 2018 (red dots).

Figure 2: Spatio-temporal distribution of outbreaks of highly pathogenic avian influenza virus subtype H5N1 clade 2.3.3.1c in Vietnam, 2015 to 2018. Frequency histogram showing the number of communes identified as HPAI-H5N1 positive per month, 24 December 2014 to 30 April 2018.

Figure 3: Spatio-temporal distribution of outbreaks of highly pathogenic avian influenza virus subtype H5N1 clade 2.3.3.1c in Vietnam, 2015 to 2018. Perspective plot showing the excess risk attributable to space-time interaction as a function of distance (in km) and time (in days) from an arbitrarily selected HPAI-H5N1 case for the $D_0(s,t)$ matrix corresponding to the 50th percentile of the summed values of $D(s,t)$, as described in the text. The red-shaded area indicates the space-time combinations for which the observed number of events was greater than that expected if space-time interaction was absent.

Figure 4: Spatio-temporal distribution of outbreaks of highly pathogenic avian influenza virus subtype H5N1 clade 2.3.3.1c in Vietnam, 2015 to 2018. Map of the south of Vietnam showing the location of HPAI H5N1 outbreaks at commune centroid level (red dots) and the location of the three statistically significant space-time clusters of HPAI H5N1 outbreaks detected by the space-time scan statistic.



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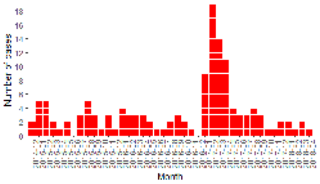

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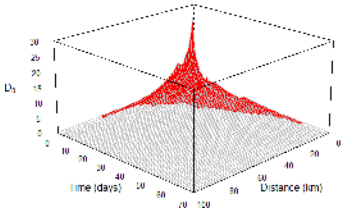

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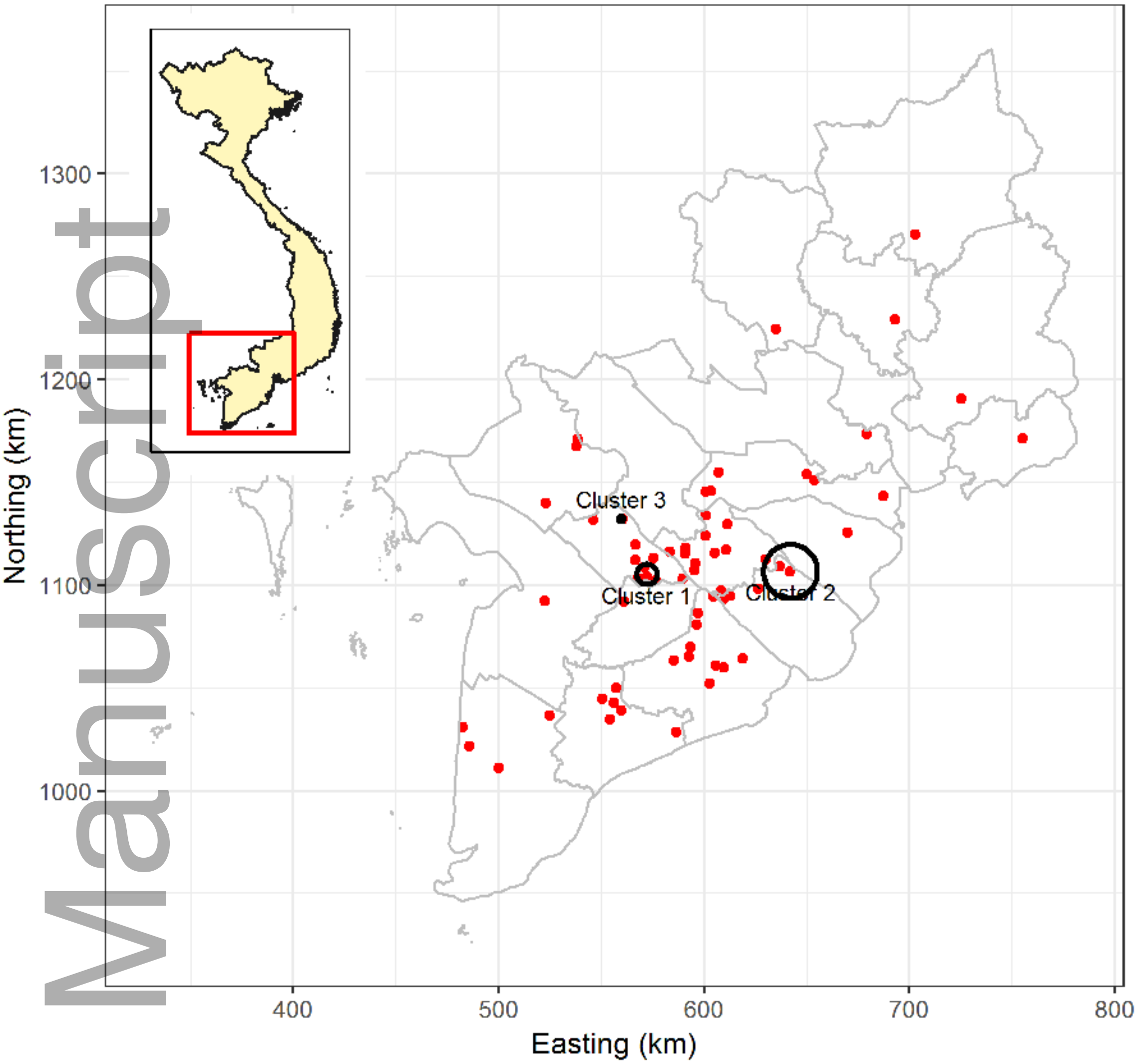

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