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**Spatiotemporal and risk analysis of H5 highly pathogenic avian influenza in Vietnam,
2014–2017**

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Abstract

The aim of this study was to describe the spatiotemporal distribution of H5 HPAI outbreak reports for the period 2014 to 2017 and to identify factors associated with H5 HPAI outbreak reports. Throughout the study period, a total of 139 outbreaks of H5 HPAI in poultry were reported, due to either H5N1 (96 outbreaks) or H5N6 (43 outbreaks) subtype viruses. H5N1 HPAI outbreaks occurred in all areas of Vietnam while H5N6 HPAI outbreaks were only reported in the northern and central provinces. We counted the number of H5N1 and H5N6 outbreak report-positive districts per province over the four-year study period and calculated the provincial-level standardized morbidity ratio for H5N1 and H5N6 outbreak reports as the observed number of positive districts divided by the expected number. A mixed-effects, zero-inflated Poisson regression model was developed to identify risk factors for outbreak reports of each H5N1 and H5N6 subtype virus. Spatially correlated and uncorrelated random effects terms were included in this model to identify areas of the country where outbreak reports occurred after known risk factors had been accounted-for. The presence of an outbreak report in a province in the previous 6-12 months increased the provincial level H5N1 outbreak report risk by a factor of 2.42 (95% Bayesian credible interval [CrI] 1.27 to 4.60) while 1000 bird increases in the density of chickens decreased provincial level H5N6 outbreak report risk by a factor of 0.64 (95% CrI 0.38 to 0.97). We document distinctly different patterns in the spatial and temporal distribution of H5N1 and H5N6 outbreak reports. Most of the variation in H5N1

report risk was accounted-for by the fixed effects included in the zero-inflated Poisson model. In contrast, the amount of unaccounted-for risk in the H5N6 model was substantially greater than the H5N1 model. For H5N6 we recommend that targeted investigations should be carried out in provinces with relatively large spatially correlated random effect terms to identify likely determinants of disease. Similarly, investigations should be carried out in provinces with relatively low spatially correlated random effect terms to identify protective factors for disease and/or reasons for failure to report.

Keywords: H5 highly pathogenic avian influenza; Vietnam; spatial temporal analysis; risk factors, outbreaks, poultry

1. Introduction

Highly pathogenic avian influenza (HPAI) in Asia caused by H5Nx subtype viruses first emerged in 1996 in Guangdong, China. Viruses in this lineage (A/goose/Guangdong/1/1996 (H5N1), abbreviated as Gs/GD/96-lineage) consequently caused devastating morbidity/mortality in domestic poultry (Xu et al., 1999; Sims et al., 2005). Importantly, viruses in this lineage have spread globally via migratory wild birds and/or trade of poultry commodities, posing a major concern to the poultry industry worldwide (Lycett et al., 2016; Sims et al., 2017). In addition, H5 HPAI viruses pose a threat to human health due to their zoonotic potential (WHO, 2018).

In Vietnam, the first outbreaks of Gs/GD/96-lineage H5 HPAI in poultry were reported in late 2003. Thereafter the disease spread rapidly and triggered severe epidemics in domestic birds across the country between 2003 and 2005 (Nguyen, 2005). Despite intensive control efforts, H5 HPAI outbreaks continue to occur in Vietnam (OIE, 2018). Several studies have been carried out to clarify the ecological and epidemiological features of H5 HPAI in Vietnam, however the determinants of disease occurrence are still not fully understood. In some countries, H5 HPAI viruses are maintained through circulation in wild birds and domestic waterfowl such as ducks, Muscovy ducks and geese (Hulse-Post et al., 2005; Kida, 2008; Pantin-Jackwood et al., 2017). Limitations on identifying key risk factors and sources of H5 HPAI and incompletely

effective interventions to limit the impact of identified risk factors have impeded control efforts for H5 HPAI in Vietnam (Pfeiffer et al., 2013; Sims et al., 2017).

A number of studies have demonstrated the complexity of agro-ecological, anthropogenic and topographic risk factors associated with H5 HPAI disease dynamics (Gilbert and Pfeiffer, 2012; Paul et al., 2014; Delabougliise et al., 2017). In particular, eco-anthropogenic interaction is thought to be one of the most important drivers for H5 HPAI spread (Pfeiffer et al., 2013; Delabougliise et al., 2017). A characteristic of Vietnamese agriculture is its traditional farming practice of intensive rice cultivation associated with poultry production, where ducks are used to scavenge leftover grains from rice paddies. This can lead to exposure of domestic poultry to infected waterfowl or wild birds (Sims et al., 2005; Pfeiffer et al., 2013). Furthermore, the Vietnamese poultry industry is comprised of large numbers of backyard and small-scale producers with approximately half of the households in rural areas raising backyard poultry (Otte et al., 2006). Continuous mixing of poultry species together with a low level of biosecurity in backyard flocks facilitates incursion and maintenance of H5 HPAI viruses, especially given that many of these birds are sold through live poultry markets that have limited or no control on the health status of birds submitted for sale.

The Vietnamese poultry industry has experienced rapid growth in recent years, mainly due to an increase in the number of intensively managed, commercial sector farms. While total

bird numbers have increased, commercial sector farms still account for only a relatively small proportion (approximately 3.25%) of the total number of poultry farms in Vietnam (World Bank, 2017). Anthropogenic factors such as cultural practices, food preferences and trading activities are important drivers of H5 HPAI spread (Fournie et al., 2016; Delabougliise et al., 2017; Meyer et al., 2018). In regards to topography, several characteristics have been identified as likely risk factors for H5 HPAI, including the density of paddy fields, proximity of poultry flocks to water, annual precipitation and elevation (Loth et al., 2011; Paul et al., 2014). Places where H5 HPAI viruses remain endemic tend to have complex poultry production and marketing chains, few restrictions on movement and veterinary services that are still developing the capacity to monitor all poultry flocks (FAO, 2011).

In Vietnam, a number of studies have been carried out to describe and explain the spatiotemporal distribution of outbreak occurrence during the early phase of the H5 HPAI epidemic (Pfeiffer et al., 2007; Minh et al., 2009). Most recently, Mellor et al. (2018) investigated the spatiotemporal epidemiology of H5N1 and H5N6 HPAI viruses using active surveillance programs deployed in live bird markets during 2011–2015. Because H5 HPAI outbreaks continue to occur throughout Vietnam, there is a need to provide better understanding of characteristics that increase the risk of disease.

With this background, the objectives of this study were to: (1) describe the spatial and temporal distribution of H5 HPAI outbreaks at the provincial level in Vietnam for the period

2014 to 2017; and (2) identify risk factors for H5 HPAI outbreak reports. Outcomes of this study provide impetus for targeted assessments of provinces identified as either low or high risk of H5. In particular, for low risk provinces it is of critical importance to identify characteristics that are truly protective for disease and/or determine if low risk is simply a consequence of failure to report.

2. Materials and methods

2.1. Study areas and period

Administrative units of Vietnam are organized into three hierarchical levels: provinces/centrally-governed cities, districts and communes (wards). The country is comprised of 63 provinces/centrally-governed cities, 678 districts and 10,805 communes (according to the Geographic Information System (GIS) data). The spatial unit of interest in this study was the province. Provincial level datasets and digital maps were retrieved from the open-source DIVA GIS website.¹ The period of interest for this study was January 01, 2014 to December 31, 2017.

2.2. Outbreak information, definition of outbreak cases and outbreak districts

Details of officially confirmed outbreaks of H5 HPAI in poultry in Vietnam from January 01, 2014 to December 31, 2017 were obtained from the EMPRES-i database (FAO,

¹ URL: <http://www.diva-gis.org/gdata>

2018). The EMPRES-i data were collated with details compiled by the Vietnamese Department of Animal Health (DAH) to ensure a complete set of outbreak reports (DAH, 2014–2017). The final outbreak dataset comprised details of each reported disease investigation including the names and numeric identifiers of the affected province, district and commune in which the first affected flock in each outbreak occurred. Additional details included the first detection date of clinical signs, the affected species and the virus subtype responsible for the outbreak. Details of the number of birds at risk, the numbers of birds that died and the number of birds culled as a result of the outbreak were recorded but not used in these analyses. The frequency of detected H5 HPAI outbreaks at the provincial level was quantified as the number of districts where H5 HPAI outbreaks were reported (outbreak districts) per 100 districts at risk per year (DAH, 2015).

2.3. Data census of poultry population and demography

Datasets providing details of the number of poultry enterprises including details of the approximate number of domestic chickens, ducks, Muscovy ducks and geese per province per year were obtained from census datasets of the General Statistics Office (GSO) (GSO, 2014–2017) and DAH (DAH, 2014–2017) (Supplementary Table 1). The GSO also provided estimates of human population counts and human population counts in agricultural areas at the provincial level for the same time frame. Human population density was expressed as the

number of people per square kilometer of agricultural land. Poultry population densities were expressed in units of 1000 birds per square kilometer of agricultural land. Each of the population density explanatory variables were rescaled to have a mean of zero.

2.4. Descriptive spatial analyses

Standardized morbidity ratios (SMRs) were used to describe the spatial distribution of H5 HPAI risk at the provincial level for the duration of the study period. Expected counts of the number of H5 HPAI outbreak districts per province e_i where calculated as:

$$e_i = \frac{\sum_{i=1}^{N=63} y_i}{\sum_{i=1}^{N=63} n_i} \cdot n_i \quad (\text{Equation 1})$$

where y_i denotes the total number of outbreak districts in province i over the four-year study period and n_i is the total number of administrative district-years at risk in province i . Provincial level H5N1 and H5N6 SMRs where then calculated as:

$$SMR_i = \frac{y_i}{e_i} \quad (\text{Equation 2})$$

2.5. Spatiotemporal regression analyses

Due to the relatively large number of province-years that had districts where H5N1 and H5N6 HPAI outbreaks were not reported (either because outbreaks did not occur or outbreaks did occur but were not reported, Supplementary Figure 3 A–B) regression coefficients and their standard deviations were estimated using a Bayesian zero-inflated Poisson (ZIP) model

(Lambert, 1992). This technique addresses over dispersion in the data and allowed us to quantify the effect of factors influencing the number of reported H5 HPAI outbreak districts in each province. Using this approach, the predicted number of outbreak districts per province for each of the $n = 16$ quarters (January to March, April to June, July to September, October to December for 2014 to 2017) throughout the study period Z_{it} was modelled conditional on the observed number of outbreak districts per province per quarter, y_{it} :

$$Z_{it} \sim \begin{cases} \text{Bernoulli } (p) \text{ with probability } p_{it} \text{ if } y_{it} = 0, \\ \text{Poisson } (\mu) \end{cases} \quad (\text{Equation 3})$$

In Equation 3, y_{it} was an independent Bernoulli random variable with a mean of p if $y_{it} = 0$; otherwise y_{it} was assumed to follow a Poisson distribution with mean μ . The parameter μ was allowed to vary for each province and quarter as a function of a series of explanatory variables as follows:

$$\mu_{it} = \beta_0 + \beta_1 x_{1it} + \beta_2 x_{2it} \dots + \beta_m x_{mit} + \gamma_t + \phi_t \quad (\text{Equation 4})$$

In Equation 4, the terms γ_t and ϕ_t are parameters to account for non-linear change in H5 risk over time with γ_t representing a temporally structured effect modelled dynamically using a random walk of order 2 and ϕ_t specified using a Gaussian exchangeable prior where $\phi_t \sim \text{Normal}(0, 1/\tau_\phi)$ (Blangiardo and Cameletti, 2015).

Residuals from the fixed-effects ZIP model described in Equation 4 were plotted as a choropleth map and the presence of spatial autocorrelation in the model residuals quantified

using Moran's I statistic (Moran, 1950). Moran's I statistics for the model residuals for a series of spatial lags were calculated and plotted as a correlogram. A Moran's I statistic greater than its expected value over one or more spatial lags was indicative of unaccounted-for spatial autocorrelation in the data. To account for unaccounted-for spatial autocorrelation in the data, the Poisson component of the model (shown in Equation 4) was extended to a mixed-effects Poisson model as follows:

$$\mu_{it} = \beta_0 + \beta_1 x_{1it} + \beta_2 x_{2it} \dots + \beta_m x_{mit} + \gamma_t + \phi_t + S_i + U_i \quad (\text{Equation 5})$$

In Equation 5, the terms S_i and U_i represent structured (spatially correlated) and unstructured (spatially uncorrelated) heterogeneity (random effect) terms to account for unobserved spatially correlated and spatially uncorrelated risk factors for H5N1 and H5N6 outbreaks in each of the i provinces (Besag et al., 1991; Mollié, 1996).

We assumed uninformed normal prior distributions for the intercepts and each of the regression coefficients for Poisson components of the model. The structured heterogeneity terms were computed by assuming a conditional intrinsic Gaussian autoregressive (CAR) structure with mean 0 and precision λ (Besag et al., 1991; Besag and Kooperberg, 1995; Stevenson et al., 2005). The CAR structure models the relative risk in province i , conditional on the risks in all other provinces $i \neq j$ being normally distributed about the weighted mean of the relative risks in the remaining provinces, with the variance inversely proportional to the sum of a spatial proximity matrix where $w_{ij} = 1$ if provinces shared a common boundary and

$w_{ij} = 0$ otherwise. For each province neighbor pair, a weight term set to equal the proportion of the province perimeter that was shared provided a quantitative measure of the strength of the association between provinces defined as adjacent. The length of the common boundary between provinces was calculated using the Geographical Analysis Support System, GRASS (GRASS Development Team, 2017). The provincial level unstructured heterogeneity terms U_i were estimated as having a normal distribution with mean 0 and precision τ .

A three-stage approach was used to identify provincial level risk factors for each of the H5N1 and H5N6 HPAI data sets. In the first stage, transformed provincial H5 HPAI SMRs were plotted as a function of each of the candidate explanatory variable estimates. The association between the provincial H5 HPAI SMRs and each of the candidate explanatory variables were quantified using Spearman's rank correlation coefficient. In the second stage, explanatory variables showing a relationship with H5 HPAI SMR at an alpha level of less than 0.10 from the Spearman's rank correlation analyses were included in a mixed-effects ZIP model using the integrated nested Laplace approximation (INLA) approach for approximate Bayesian inference (Rue et al., 2009). The final model was developed based on the Watanabe-Akaike information criterion as a means for guiding explanatory variable selection (Watanabe., 2010) and consistency of the parameterized explanatory variables with the previously published H5 HPAI literature. The presence or absence of a previous outbreak report in a province was forced into the model as a categorical variable comprised of three levels: no

outbreak reported in the previous 12 months; one or more outbreaks reported in the province in the previous 1–6 months, and one or more outbreaks reported in the province in the previous 6–12 months. No outbreak reports in the previous 12 months was set as the reference category.

2.6. Data execution and statistical analyses

Data collation, checking and initial manipulation was undertaken using Microsoft Excel. Statistical analyses, graphing and spatial visualization were carried out using R version 3.4.4 (R Core Team, 2018) using the contributed packages ggplot2 (Wickham, 2016), rgdal (Bivand et al., 2014), rgeos (Bivand, 2018), sp (Pebesma and Bivand, 2005), spdep (Bivand and Piras, 2015) and INLA (Rue et al., 2009).

3. Results

3.1. Descriptive analysis of H5N1 and H5N6 HPAI outbreaks

For the period 2014 to 2017 a total of 139 H5 HPAI outbreaks, caused by one of the two H5N1 or H5N6 subtype viruses, were reported in all regions of Vietnam. There was considerable variation in the number of outbreak reports per region, per year and quarter for each subtype virus (Figure 1A and Supplementary Figure 1A-D). Six provinces (Dak Lak, Ha Tinh, Nghe An and Quang Ngai in the central region and Can Tho, Vinh Long in the South) had more than six outbreak reports in all years, accounting for 37% of the total outbreak reports.

Four provinces (Kon Tum, Nghe An, Quang Ngai and Can Tho) reported outbreaks in all four years. H5N6 outbreaks ($n = 43$ outbreaks) were only reported from the north and central regions while H5N1 outbreaks ($n = 96$ outbreaks) were reported in south, central and north regions. Forty-three of the 96 H5N1 outbreaks were recorded in the first quarter of 2014 (prior to the establishment of H5N6 in Vietnam). The number of outbreaks peaked in the first quarter of 2014 ($n = 43$) and 2017 ($n = 18$) which was much greater than the number of outbreaks that occurred in each of the following quarters of the years (Figure 1A and Supplementary Figure 2A-D). There were no peaks in H5N1 reported outbreaks in the first quarters of 2015 ($n = 3$) and 2016 ($n = 1$). Similar patterns were not detected for H5N6 outbreaks which were reported year-round.

Figure 1B is a bar plot showing the number of H5N1 and H5N6 outbreak reports by primary species affected conditioned by region of the country (north, central and south) and year (2014, 2015, 2016 and 2017). Chickens ($n = 94$) and ducks ($n = 81$) were the species most frequently listed in outbreak reports.

3.2. Provincial level standardized morbidity ratios

Figures 2A and 2B show the reported number of outbreaks per province over the study period. Figures 3A and 3B show provincial level SMR estimates of H5N1 and H5N6 HPAI. The reported number of outbreaks per province and provincial SMRs for H5N1 were

heterogeneous across the northern, central and southern regions (Figure 2A and 3A) while outbreak reports for H5N6 were only observed in the northern and central regions of the country (Figure 2B and 3B). Provincial H5N1 and H5N6 HPAI SMRs were, on the whole, greater in the central region compared with other parts of Vietnam.

3.3. Risk factor analyses

Tables 1 and 2 present the posterior means and standard deviations of the regression coefficients for the mixed-effects ZIP model of H5N1 and H5N6 HPAI outbreak reports, respectively. The explanatory variables included in each model were the presence/absence of a previous outbreak report in the province and the density of humans, domestic chickens and ducks. Regression coefficients and their 95% credible intervals (CrIs) for the models for H5N1 and H5N6 excluding the structured and unstructured random effect terms are shown in Supplementary Tables 2 and 3, respectively. In Table 1, the presence of an H5N1 outbreak in the same province within 6–12 months increased the risk of a H5N1 HPAI outbreak report by a factor 2.42 (95% CrI 1.27 to 4.60). One thousand unit increases in the number of chickens per square kilometer of agricultural land decreased the risk of an H5N6 outbreak report by a factor 0.65 (95% CrI 0.38 to 0.97, Table 2).

Choropleth maps of the exponentiated spatially structured random effect terms from the mixed-effects model of H5N1 and H5N6 HPAI outbreaks (presented in Table 1 and 2) are

shown in Figures 4A and 4B, respectively. The spatially correlated random effect terms for the H5N6 model (variance 1.3210 Table 2, Figure 4B) showed greater variation compared with the spatially correlated random effect terms for the H5N1 model (variance 0.3408 Table 1, Figure 4A). This means that there were factors, unaccounted-for in our H5N6 HPAI model, that influenced H5N6 reporting risk over spatially adjacent provinces.

4. Discussion

After triggering enormous devastation in 2003 and 2004, H5 HPAI viruses have persisted and caused significant damage to the poultry industry and occasional human deaths in Vietnam. The disease is constantly changing in association with variability of viral strains and dynamics, changes in the composition and distribution of the host population and the effect of interventions to control disease such as the use of vaccination. For these reasons, there is a need to continuously monitor the ever-changing pattern of H5 HPAI occurrence to better direct disease control efforts.

Our descriptive spatial analyses confirm previous reports of the spatial and temporal epidemiology of H5 HPAI in Vietnam with a distinct spatial distribution of the two subtype viruses causing H5 HPAI (Figures 2A and 2B). H5N6 outbreaks were only reported in the northern and central regions whereas H5N1 outbreaks occurred throughout the country (Nguyen et al., 2016). H5N1 HPAI outbreaks occurred throughout the year with greater

308 numbers of cases in the months close to the Lunar New Year holidays (January to March) in
309 two years, 2014 and 2017 (Delabougliise et al., 2017; Mellor et al., 2018). The Lunar New Year
310 holiday is a period associated with a higher intensity of poultry production and poultry
311 movement in response to an increase in demand for poultry over the festive period (Pfeiffer et
312 al., 2007; Minh et al., 2009; Delabougliise et al., 2017).

313 The provincial H5N1 and H5N6 HPAI SMRs were heterogeneous across the country
314 with aggregations of neighboring provinces with similar SMR estimates. Provinces around Ha
315 Noi and to the north of Ho Chi Minh City had SMRs of less than unity whereas provinces
316 located along the northern border of the country had SMRs greater than unity (Figures 3A and
317 3B) implying the presence of geographic variability in either the risk of H5 HPAI virus
318 incursion (Desvaux et al., 2016), the likelihood of reporting the presence of outbreaks and/or
319 H5 HPAI control efforts (for example, the completeness and effectiveness of vaccination
320 coverage). Indeed, large numbers of commercial poultry enterprises are known to be present in
321 the provinces around Ha Noi and to the north of Ho Chi Minh City (data not shown) so stricter
322 biosecurity measures in commercial poultry enterprises might explain the lower overall
323 provincial risk of H5 HPAI in these provinces. This pattern is different to the high SMR
324 estimates in some provinces in the central region of the country. The low SMRs for H5N1
325 outbreaks in provinces adjacent to the Cambodian border (Figure 3A) are inconsistent with this
326 hypothesis and may be due to either a lower frequency of H5 HPAI in poultry from Cambodia

moving across the border into Vietnam and/or under-detection or under-reporting of H5 HPAI outbreaks in this area of the country (Henning et al., 2013; Nguyen et al., 2014).

The presence of a previous provincial H5 HPAI report increased the risk of a H5 HPAI report during a given quarter (Tables 1 and 2). This result implies that either the virus persists in the environment (due to favorable climatic conditions) or activities (e.g. poultry movement, vaccination, rice-cropping intensity) that influence the introduction of virus into a given area are consistent over time. If the latter is, in fact true, surveillance for H5 HPAI should target those provinces with a prior history of H5 HPAI outbreaks, particularly in the lead-up period to the Lunar New Year.

We identified a negative association between the density of chickens and H5N6 outbreak report risk (Table 2). The majority of H5 HPAI outbreak reports during the study period involved chickens and ducks (only in small-scale/backyard farms) in the northern and central regions (see Figure 1B and DAH, 2014–2017). It is our assessment that chicken density is likely to be acting as a proxy variable for the level of intensification of the poultry industry within a province which in turn influences factors protective of H5 outbreaks such as vaccination coverage and biosecurity. Inclusion of the spatially correlated and spatially uncorrelated random effect terms in each model resulted in the 95% CrIs of the relative risk for poultry density including unity which indirectly implies that the effect of intensification of the poultry sector and vaccination as determinants of H5 HPAI risk varied throughout the country.

Consistent with other studies (Hulse-Post et al., 2005; Kida, 2008; Henning et al., 2013) and biological plausibility provincial-level estimates of the densities of domestic ducks increased the risk of H5N1 and H5N6 HPAI outbreak reports (RR 1.21, 95% CrI 0.92 to 1.56 and RR 1.30, 95% CrI 0.67 to 2.35, respectively, Tables 1 and 2). We note that the 95% CrIs for the relative risk estimates for duck density included one, meaning that there was a chance that the density of ducks was not associated with H5 HPAI outbreaks. In this study, we identified no marked association between the density of humans and H5 HPAI outbreak reporting risk.

Our spatial regression analyses showed that the spatially correlated random effects of H5N6 outbreak reports were much greater compared with the equivalent metrics for H5N1 (compare Figure 4B with 4A). Based on these findings we recommend that targeted investigations should be carried out in provinces with relatively large spatially correlated H5N6 random effect terms to identify the likely determinants of disease. Similarly, investigations should be carried out in provinces with relatively low spatially correlated random effect terms to identify protective factors for disease and/or reasons for absence of report.

We note that for H5N1 the variance of the unstructured heterogeneity terms was similar to the variance of the spatially structured heterogeneity terms (Table 1). This means that the amount of unexplained H5N1 HPAI reporting risk operating within individual provinces was

similar to the unexplained H5N1 HPAI reporting risk operating across groups of spatially adjacent provinces.

While our results are biologically plausible and, for the most part, consistent with previous studies that have described and explained the epidemiology of H5 HPAI in Vietnam, we draw the reader's attention to the following limitations. Reporting bias is likely to be present in the outbreak notification data due to failure to detect and report the presence of disease by poultry owners, failure to detect and report the presence of disease by animal health authorities and/or failure to submit details of H5 HPAI outbreaks to the notification database. The 139 outbreaks reported over the entire 4-year study period were an unknown fraction of the actual number of outbreaks that occurred in Vietnam. Assuming there has been no substantial differential geographical bias in the reporting of H5 HPAI outbreaks we conclude that while the point estimates of the regression coefficients for each explanatory variable are accurate the precision of those estimates is likely to be less than if case ascertainment was complete.

The ability of our model to predict numbers of H5 HPAI cases would have benefited from inclusion of additional explanatory variables such as estimates of H5 HPAI vaccination coverage and vaccine antigens deployed by province (data not available), estimates of poultry movement events (difficult to measure) and estimates of the density of backyard poultry flocks (Kim et al., 2009; Soares Magalhães et al., 2010; Delabougliise et al., 2017; Meyer et al., 2018).

5. Conclusion

A total of 139 H5 HPAI outbreaks were reported in all regions of Vietnam during the period 2014 to 2017. All of the H5 HPAI outbreaks were caused by one of the two subtype viruses, H5N1 and/or H5N6. The frequency of outbreak reports of H5N1 and H5N6 varied by province, year and quarter. We document distinctly different patterns in the spatial and temporal distribution of H5N1 and H5N6 outbreak reports. Most of the variation in H5N1 report risk was accounted-for by the fixed effects included in the ZIP model presented in this paper. In contrast, the amount of unaccounted-for risk for the H5N6 was model was substantially greater than the H5N1 model, as indicated by the relatively large amount of variation in the spatially correlated random effect terms for the H5N6 model. For H5N6 we recommend that targeted investigations should be carried out in provinces with relatively large spatially correlated random effect terms to identify likely determinants of disease. Similarly, investigations should be carried out in provinces with relatively low spatially correlated random effect terms to identify protective factors for disease and/or reasons for failure to report.

402 **Conflict of interest**

403 The authors have declared that no competing interests exist.

404

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Table 1: Spatiotemporal risk analysis of H5 highly pathogenic avian influenza in Vietnam, 2014–2017. Estimated regression coefficients and their standard deviations from the mixed-effects zero-inflated Poisson regression model of provincial level H5N1 HPAI outbreak reporting risk.

Explanatory variable	Mean	SD	RR (95% CrI)
Intercept	-1.8205	0.3571	-
Previous outbreaks:			
None	Reference		1.00
1-6 months	-0.2123	0.6008	0.83 (0.23 to 2.44)
6-12 months	0.8829	0.3280	2.42 (1.27 to 4.60) ^a
Density of humans ^b	-0.4535	0.5438	0.65 (0.20 to 1.74)
Density of domestic chickens ^c	0.0047	0.1114	1.00 (0.81 to 1.25)
Density of domestic ducks ^c	0.1866	0.1349	1.21 (0.92 to 1.56)
Zero-inflation parameter	0.0370	0.0403	
Variance of random effect terms:			
Structured S_i	0.3408	0.3176	
Unstructured U_i	0.4625	0.8157	
Temporal trend, γ_t	2.0255	3.0285	
Temporal trend, ϕ_t	<0.001	<0.001	

SD: standard deviation; RR: risk ratio; CrI: Bayesian credible interval.

^a Interpretation: The presence of an H5N1 HPAI outbreak report in the same province in the previous 6 to 12 months increased the risk of an H5N1 outbreak report during the current quarter by a factor of 2.42 (95% CrI 1.27 to 4.60).

^b Number of individuals per square kilometer of agricultural land.

^c Number of birds ($\times 1000$) per square kilometer of agricultural land.

Table 2: Spatiotemporal risk analysis of H5 highly pathogenic avian influenza in Vietnam, 2014–2017. Estimated regression coefficients and their standard deviations from the mixed-effects zero-inflated Poisson regression model of provincial level H5N6 HPAI outbreak reporting risk.

Explanatory variable	Mean	SD	RR (95% CrI)
Intercept	-1.7480	0.6595	-
Previous outbreaks:			
None	Reference		1.00
1-6 months	0.2925	0.5643	1.35 (0.43 to 3.96)
6-12 months	-0.1638	0.5485	0.86 (0.28 to 2.44)
Density of humans ^a	0.4590	0.9187	1.67 (0.22 to 8.45)
Density of domestic chickens ^b	-0.4512	0.2370	0.65 (0.38 to 0.97) ^c
Density of domestic ducks ^b	0.2529	0.3186	1.30 (0.67 to 2.35)
Zero-inflation parameter	0.1915	0.1886	
Variance of random effect terms:			
Structured S_i	1.3210	1.8997	
Unstructured U_i	0.4900	0.5627	
Temporal trend, γ_t	0.0018	0.0001	
Temporal trend, ϕ_t	<0.001	<0.001	

SD: standard deviation; RR: risk ratio; CrI: Bayesian credible interval.

^a Number of individuals per square kilometer of agricultural land.

^b Number of birds ($\times 1000$) per square kilometer of agricultural land.

^c Interpretation: One thousand unit increases in the number of chickens per square kilometer of agricultural land decreased the risk of an H5N6 outbreak report during the current quarter by a factor of 0.65 (95% CrI 0.38 to 0.97).

Supplementary Table 1: Spatiotemporal risk analysis of H5 highly pathogenic avian influenza in Vietnam, 2014–2017. Descriptive statistics of each of the candidate explanatory variables included in this study.

Explanatory variable	Total	Mean (SD)	Min, max
Agricultural land area per province (km ²)	115,291	1,830 (1,450)	68, 8014
Human population in rural areas (× 1000)	60,709	964 (597)	131, 3400
Human population density in rural areas (× 1000.km ²)	-	0.77 (0.57)	0.12, 2.33
Density of domestic poultry, 2014 (× 1000.km ²)	-	4.25 (3.95)	0.24, 14.99
Density of domestic poultry, 2015 (× 1000.km ²)	-	4.4 (4.07)	0.25, 15.35
Density of domestic poultry, 2016 (× 1000.km ²)	-	4.59 (4.16)	0.26, 15.84
Density of domestic poultry, 2017 (× 1000.km ²)	-	4.93 (4.4)	0.28, 16.89
Density of domestic chickens, 2014 (× 1000.km ²)	-	3.19 (3.1)	0.21, 12.02
Density of domestic chickens, 2015 (× 1000.km ²)	-	3.33 (3.23)	0.22, 12.89
Density of domestic chickens, 2016 (× 1000.km ²)	-	3.51 (3.34)	0.23, 13.63
Density of domestic chickens, 2017 (× 1000.km ²)	-	3.78 (3.54)	0.25, 14.54
Density of domestic ducks, 2014 (× 1000.km ²)	-	1.03 (1.13)	0, 6.29
Density of domestic ducks, 2015 (× 1000.km ²)	-	1.28 (1.27)	0.02, 5.83
Density of domestic ducks, 2016 (× 1000.km ²)	-	1.34 (1.45)	0.02, 6.88
Density of domestic ducks, 2017 (× 1000.km ²)	-	1.4 (1.47)	0.02, 7.08
Density of domestic Muscovy ducks, 2014 (× 1000.km ²)	-	0.18 (0.27)	0, 1.55
Density of domestic Muscovy ducks, 2015 (× 1000.km ²)	-	0.18 (0.26)	0, 1.56
Density of domestic Muscovy ducks, 2016 (× 1000.km ²)	-	0.17 (0.21)	0, 0.94
Density of domestic Muscovy ducks, 2017 (× 1000.km ²)	-	0.19 (0.21)	0, 0.93
Density of domestic geese, 2014 (× 1000.km ²)	-	0.01 (0.01)	0, 0.05
Density of domestic geese, 2015 (× 1000.km ²)	-	0.01 (0.01)	0, 0.06
Density of domestic geese, 2016 (× 1000.km ²)	-	0.01 (0.01)	0, 0.06
Density of domestic geese, 2017 (× 1000.km ²)	-	0.01 (0.01)	0, 0.08

Supplementary Table 2: Spatiotemporal risk analysis of H5 highly pathogenic avian influenza in Vietnam, 2014–2017. Estimated regression coefficients and their standard deviations from the zero-inflated Poisson regression model of province level H5N1 HPAI outbreak reporting risk including.

Explanatory variable	Mean	SD	RR (95% CrI)
Intercept	-1.3697	0.3302	-
Previous outbreaks:			
None	Reference		1.00
1-6 months	-0.1503	0.5520	0.89 (0.27 to 2.33)
6-12 months	1.1035	0.2766	3.03 (1.73 to 5.14) ^a
Density of humans ^b	-0.5097	0.4082	0.61 (0.25 to 1.27)
Density of domestic chickens ^c	-0.1033	0.0709	0.90 (0.79 to 1.04)
Density of domestic ducks ^c	0.4133	0.0798	1.52 (1.28 to 1.76)
Zero-inflation parameter	0.1528	0.0852	
Temporal trend, γ_t	2.1570	3.1918	
Temporal trend, ϕ_t	<0.001	<0.001	

SD: standard deviation; RR: risk ratio; CrI: Bayesian credible interval.

^a Interpretation: The presence of an H5N1 HPAI outbreak report in the same province in the previous 6 to 12 months increased the risk of an H5N1 outbreak report during the current quarter by a factor of 3.03 (95% CrI 1.73 to 5.14).

^b Number of individuals per square kilometer of agricultural land.

^c Number of birds ($\times 1000$) per square kilometer of agricultural land.

Supplementary Table 3: Spatiotemporal risk analysis of H5 highly pathogenic avian influenza in Vietnam, 2014–2017. Estimated regression coefficients and their standard deviations from the zero-inflated Poisson regression model of province level H5N6 HPAI outbreak reporting risk including.

Explanatory variable	Mean	SD	RR (95% CrI)
Intercept	0.8144	0.4500	-
Previous outbreaks:			
None	Reference		1.00
1-6 months	1.5003	0.4002	4.51 (2.01 to 9.70) ^a
6-12 months	0.3195	0.4680	1.39 (0.53 to 3.33)
Density of humans ^b	0.0344	0.5083	1.04 (0.37 to 2.78)
Density of domestic chickens ^c	-0.0478	0.1031	0.96 (0.77 to 1.16)
Density of domestic ducks ^c	-0.1479	0.2269	0.87 (0.53 to 1.30)
Zero-inflation parameter	0.5962	0.1718	
Temporal trend, γ_t	<0.001	<0.001	
Temporal trend, ϕ_t	<0.001	<0.001	

SD: standard deviation; RR: risk ratio; CrI: Bayesian credible interval.

^a Interpretation: The presence of an H5N6 HPAI outbreak report in the same province in the previous 1 to 6 months increased the risk of an H5N6 outbreak report during the current quarter by a factor of 4.51 (95% CrI 2.01 to 9.70).

^b Number of individuals per square kilometer of agricultural land.

^c Number of birds ($\times 1000$) per square kilometer of agricultural land.

Figure legends

Figure 1A. Bar plot showing the number of H5N1 and H5N6 outbreak reports per quarter (Q1: January–March, Q2: April–June, Q3: July–September, Q4: October–December) conditioned by region of the country (north, central and south) and year (2014, 2015, 2016 and 2017).

Figure 1B. Bar plot showing the number of H5N1 and H5N6 outbreak reports by primary species affected conditioned by region of the country (north, central and south) and year (2014, 2015, 2016 and 2017).

Figure 2A. Choropleth map showing the observed number of H5N1 outbreak reports per province for the period January 2014 to December 2017.

Figure 2B. Choropleth map showing the observed number of H5N6 outbreak reports per province for the period January 2014 to December 2017.

Figure 3A. Choropleth map showing provincial level standardized morbidity ratios for H5N1 (the observed number of H5N1 positive districts per province divided by the expected number) for the for the period January 2014 to December 2017.

Figure 3B. Choropleth map showing provincial level standardized morbidity ratios for H5N6 (the observed number of H5N6 positive districts per province divided by the expected number) for the for the period January 2014 to December 2017.

Figure 4A. Choropleth map showing the exponentiated spatially structured random effect terms derived from the mixed-effects zero-inflated Poisson regression model of provincial level H5N1 HPAI outbreak reporting risk presented in Table 1.

Figure 4B. Choropleth map showing the exponentiated spatially structured random effect terms derived from the mixed-effects zero-inflated Poisson regression model of provincial level H5N6 HPAI outbreak reporting risk presented in Table 2.

Supplementary Figure 1. Point maps showing the location of districts in which H5N1 and H5N6 were reported for: (A) 2014; (B) 2015; (C) 2016; and (D) 2017. In each plot the size of the circles is proportional to the number of outbreak reports. The horizontal dashed lines on each plot delineate the north, central and south regions of Vietnam.

Supplementary Figure 2. Point maps showing the location of districts in which H5N1 and H5N6 were reported for: (A) January to March; (B) April to June; (C) July to September; and

646 (D) October to December, for the period January 2014 to December 2017. In each plot the size
647 of the circles is proportional to the number of outbreak reports. The horizontal dashed lines on
648 each plot delineate the north, central and south regions of Vietnam.

649

650 **Supplementary Figure 3.** Frequency histograms showing the number of outbreak reports per
651 province for the period January 2014 to December 2017 for: (A) H5N1; and (B) H5N6.

Fig. 1A.
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Fig. 1B.
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Fig. 2A.
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Fig. 3A.
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Fig. 3B.
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Fig. 4A.
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Fig. 4B.
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S. Fig. 1A.
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S. Fig. 1C.
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S. Fig. 1D.
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S. Fig. 2A.
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S. Fig. 3A.
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S. Fig. 3B.
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