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1 **Spatiotemporal and risk analysis of H5 highly pathogenic avian influenza in Vietnam,**
2 **2014–2017**

3

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38

39 **Abstract**

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

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

65

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

68

69 1. Introduction

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

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

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

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

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

106 bird numbers have increased, commercial sector farms still account for only a relatively small
107 proportion (approximately 3.25%) of the total number of poultry farms in Vietnam (World
108 Bank, 2017). Anthropogenic factors such as cultural practices, food preferences and trading
109 activities are important drivers of H5 HPAI spread (Fournie et al., 2016; Delabougliuse et al.,
110 2017; Meyer et al., 2018). In regards to topography, several characteristics have been identified
111 as likely risk factors for H5 HPAI, including the density of paddy fields, proximity of poultry
112 flocks to water, annual precipitation and elevation (Loth et al., 2011; Paul et al., 2014). Places
113 where H5 HPAI viruses remain endemic tend to have complex poultry production and
114 marketing chains, few restrictions on movement and veterinary services that are still
115 developing the capacity to monitor all poultry flocks (FAO, 2011).

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

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

125 2014 to 2017; and (2) identify risk factors for H5 HPAI outbreak reports. Outcomes of this
126 study provide impetus for targeted assessments of provinces identified as either low or high
127 risk of H5. In particular, for low risk provinces it is of critical importance to identify
128 characteristics that are truly protective for disease and/or determine if low risk is simply a
129 consequence of failure to report.

130

131 **2. Materials and methods**

132 *2.1. Study areas and period*

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

139

140 *2.2. Outbreak information, definition of outbreak cases and outbreak districts*

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

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

143 2018). The EMPRES-i data were collated with details compiled by the Vietnamese Department
144 of Animal Health (DAH) to ensure a complete set of outbreak reports (DAH, 2014–2017). The
145 final outbreak dataset comprised details of each reported disease investigation including the
146 names and numeric identifiers of the affected province, district and commune in which the first
147 affected flock in each outbreak occurred. Additional details included the first detection date of
148 clinical signs, the affected species and the virus subtype responsible for the outbreak. Details
149 of the number of birds at risk, the numbers of birds that died and the number of birds culled as
150 a result of the outbreak were recorded but not used in these analyses. The frequency of detected
151 H5 HPAI outbreaks at the provincial level was quantified as the number of districts where H5
152 HPAI outbreaks were reported (outbreak districts) per 100 districts at risk per year (DAH,
153 2015).

154

155 *2.3. Data census of poultry population and demography*

156 Datasets providing details of the number of poultry enterprises including details of the
157 approximate number of domestic chickens, ducks, Muscovy ducks and geese per province per
158 year were obtained from census datasets of the General Statistics Office (GSO) (GSO, 2014–
159 2017) and DAH (DAH, 2014–2017) (Supplementary Table 1). The GSO also provided
160 estimates of human population counts and human population counts in agricultural areas at the
161 provincial level for the same time frame. Human population density was expressed as the

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

165

166 2.4. Descriptive spatial analyses

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

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

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

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

173

174 2.5. Spatiotemporal regression analyses

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

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

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

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

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

189 In Equation 4, the terms γ_t and ϕ_t are parameters to account for non-linear change in H5 risk
 190 over time with γ_t representing a temporally structured effect modelled dynamically using a
 191 random walk of order 2 and ϕ_t specified using a Gaussian exchangeable prior where
 192 $\phi_t \sim \text{Normal}(0, 1/\tau_\phi)$ (Blangiardo and Cameletti, 2015).

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

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

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

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

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

213 $w_{ij} = 0$ otherwise. For each province neighbor pair, a weight term set to equal the proportion
214 of the province perimeter that was shared provided a quantitative measure of the strength of
215 the association between provinces defined as adjacent. The length of the common boundary
216 between provinces was calculated using the Geographical Analysis Support System, GRASS
217 (GRASS Development Team, 2017). The provincial level unstructured heterogeneity terms U_i
218 were estimated as having a normal distribution with mean 0 and precision τ .

219 A three-stage approach was used to identify provincial level risk factors for each of the
220 H5N1 and H5N6 HPAI data sets. In the first stage, transformed provincial H5 HPAI SMRs
221 were plotted as a function of each of the candidate explanatory variable estimates. The
222 association between the provincial H5 HPAI SMRs and each of the candidate explanatory
223 variables were quantified using Spearman's rank correlation coefficient. In the second stage,
224 explanatory variables showing a relationship with H5 HPAI SMR at an alpha level of less than
225 0.10 from the Spearman's rank correlation analyses were included in a mixed-effects ZIP
226 model using the integrated nested Laplace approximation (INLA) approach for approximate
227 Bayesian inference (Rue et al., 2009). The final model was developed based on the Watanabe-
228 Akaike information criterion as a means for guiding explanatory variable selection (Watanabe.,
229 2010) and consistency of the parameterized explanatory variables with the previously
230 published H5 HPAI literature. The presence or absence of a previous outbreak report in a
231 province was forced into the model as a categorical variable comprised of three levels: no

232 outbreak reported in the previous 12 months; one or more outbreaks reported in the province
233 in the previous 1–6 months, and one or more outbreaks reported in the province in the previous
234 6–12 months. No outbreak reports in the previous 12 months was set as the reference category.

235

236 *2.6. Data execution and statistical analyses*

237 Data collation, checking and initial manipulation was undertaken using Microsoft Excel.
238 Statistical analyses, graphing and spatial visualization were carried out using R version 3.4.4
239 (R Core Team, 2018) using the contributed packages ggplot2 (Wickham, 2016), rgdal (Bivand
240 et al., 2014), rgeos (Bivand, 2018), sp (Pebesma and Bivand, 2005), spdep (Bivand and Piras,
241 2015) and INLA (Rue et al., 2009).

242

243 **3. Results**

244 *3.1. Descriptive analysis of H5N1 and H5N6 HPAI outbreaks*

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

251 Four provinces (Kon Tum, Nghe An, Quang Ngai and Can Tho) reported outbreaks in all four
252 years. H5N6 outbreaks ($n = 43$ outbreaks) were only reported from the north and central
253 regions while H5N1 outbreaks ($n = 96$ outbreaks) were reported in south, central and north
254 regions. Forty-three of the 96 H5N1 outbreaks were recorded in the first quarter of 2014 (prior
255 to the establishment of H5N6 in Vietnam). The number of outbreaks peaked in the first quarter
256 of 2014 ($n = 43$) and 2017 ($n = 18$) which was much greater than the number of outbreaks that
257 occurred in each of the following quarters of the years (Figure 1A and Supplementary Figure
258 2A-D). There were no peaks in H5N1 reported outbreaks in the first quarters of 2015 ($n = 3$)
259 and 2016 ($n = 1$). Similar patterns were not detected for H5N6 outbreaks which were reported
260 year-round.

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

265

266 3.2. Provincial level standardized morbidity ratios

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

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

274

275 *3.3. Risk factor analyses*

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

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

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

294

295 **4. Discussion**

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

303 Our descriptive spatial analyses confirm previous reports of the spatial and temporal
304 epidemiology of H5 HPAI in Vietnam with a distinct spatial distribution of the two subtype
305 viruses causing H5 HPAI (Figures 2A and 2B). H5N6 outbreaks were only reported in the
306 northern and central regions whereas H5N1 outbreaks occurred throughout the country
307 (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

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

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

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

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

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

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

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

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

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

382

383 **5. Conclusion**

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

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402 **Conflict of interest**

403 The authors have declared that no competing interests exist.

404

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414

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551

552 Table 1: Spatiotemporal risk analysis of H5 highly pathogenic avian influenza in Vietnam,
 553 2014–2017. Estimated regression coefficients and their standard deviations from the mixed-
 554 effects zero-inflated Poisson regression model of provincial level H5N1 HPAI outbreak
 555 reporting risk.

556

| 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 | |

557

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

559 ^a Interpretation: The presence of an H5N1 HPAI outbreak report in the same province in the previous 6 to 12
 560 months increased the risk of an H5N1 outbreak report during the current quarter by a factor of 2.42 (95% CrI
 561 1.27 to 4.60).

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

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

564

565 Table 2: Spatiotemporal risk analysis of H5 highly pathogenic avian influenza in Vietnam,
 566 2014–2017. Estimated regression coefficients and their standard deviations from the mixed-
 567 effects zero-inflated Poisson regression model of provincial level H5N6 HPAI outbreak
 568 reporting risk.
 569

| 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 | |

570

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

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

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

574 ^c Interpretation: One thousand unit increases in the number of chickens per square kilometer of agricultural land
 575 decreased the risk of an H5N6 outbreak report during the current quarter by a factor of 0.65 (95% CrI 0.38 to
 576 0.97).

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

580

| 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 |

581

582

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

587

| 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 | |

588

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

590 ^a Interpretation: The presence of an H5N1 HPAI outbreak report in the same province in the previous 6 to 12
 591 months increased the risk of an H5N1 outbreak report during the current quarter by a factor of 3.03 (95% CrI
 592 1.73 to 5.14).

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

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

595

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

600

| 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 | |

601

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

603 ^a Interpretation: The presence of an H5N6 HPAI outbreak report in the same province in the previous 1 to 6
 604 months increased the risk of an H5N6 outbreak report during the current quarter by a factor of 4.51 (95% CrI
 605 2.01 to 9.70).

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

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

608 **Figure legends**

609

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

613

614 **Figure 1B.** Bar plot showing the number of H5N1 and H5N6 outbreak reports by primary
615 species affected conditioned by region of the country (north, central and south) and year (2014,
616 2015, 2016 and 2017).

617

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

620

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

623

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

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

630

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

634

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

638

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

643

644 **Supplementary Figure 2.** Point maps showing the location of districts in which H5N1 and
645 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.

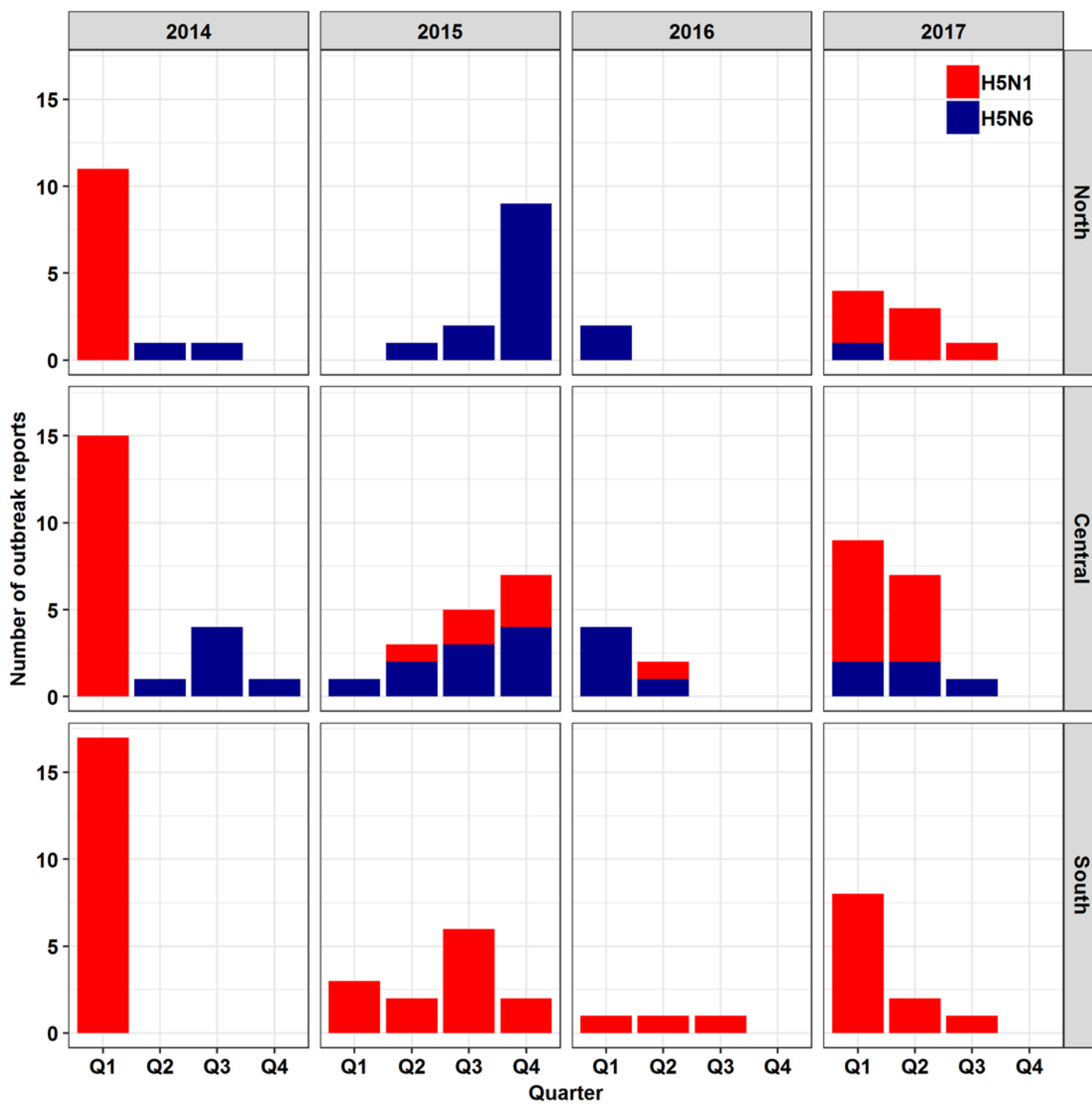


Fig. 1A.
Nguyen *et al.*,

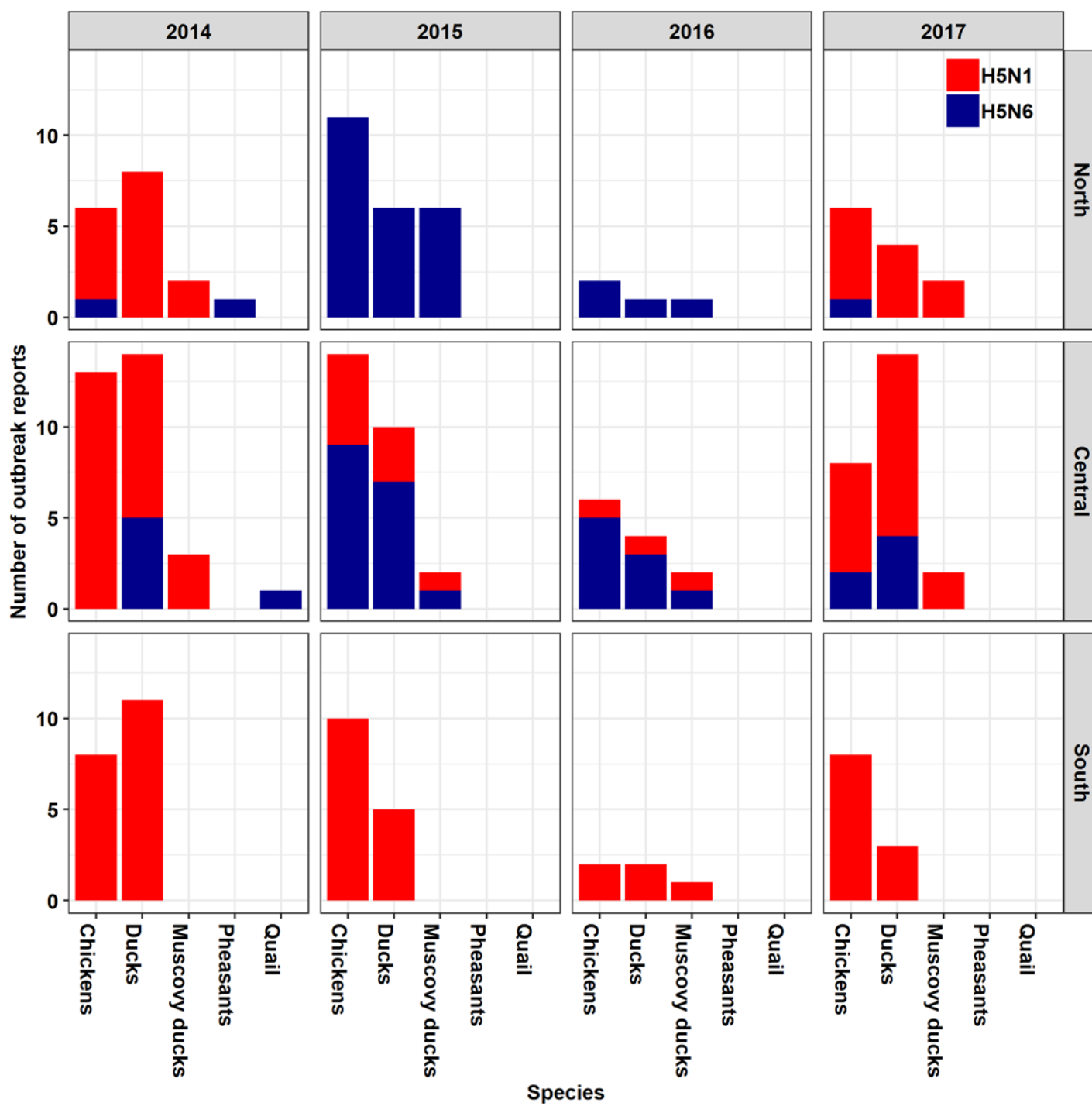


Fig. 1B.
Nguyen *et al.*,

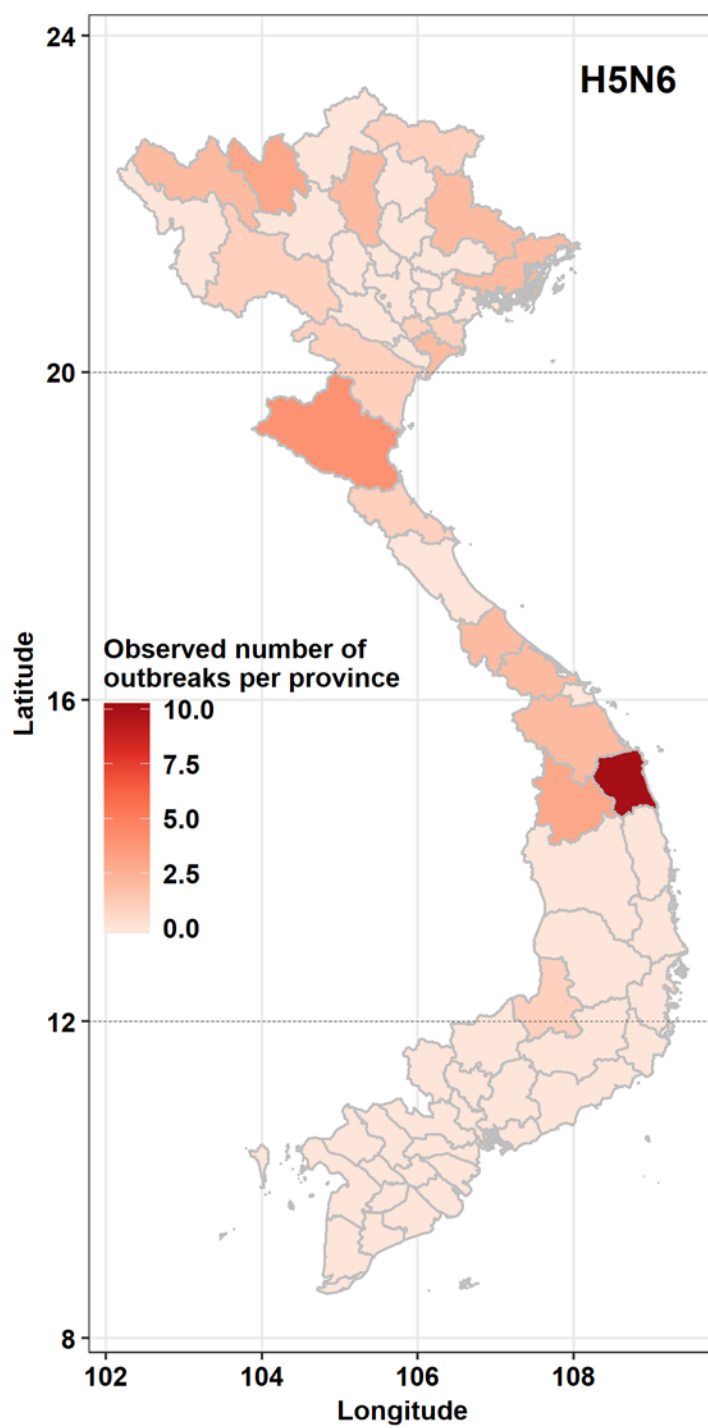


Fig. 2B.
Nguyen *et al.*,

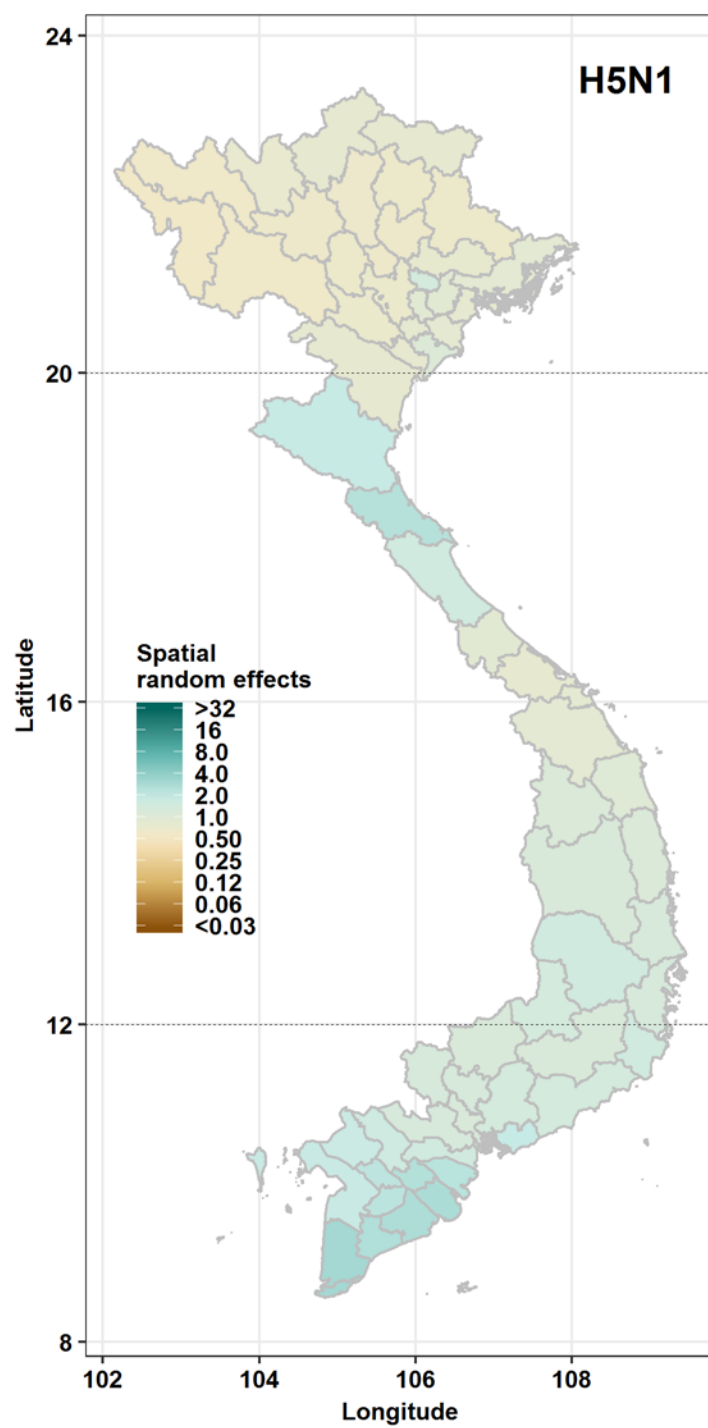


Fig. 4A.
Nguyen *et al.*,

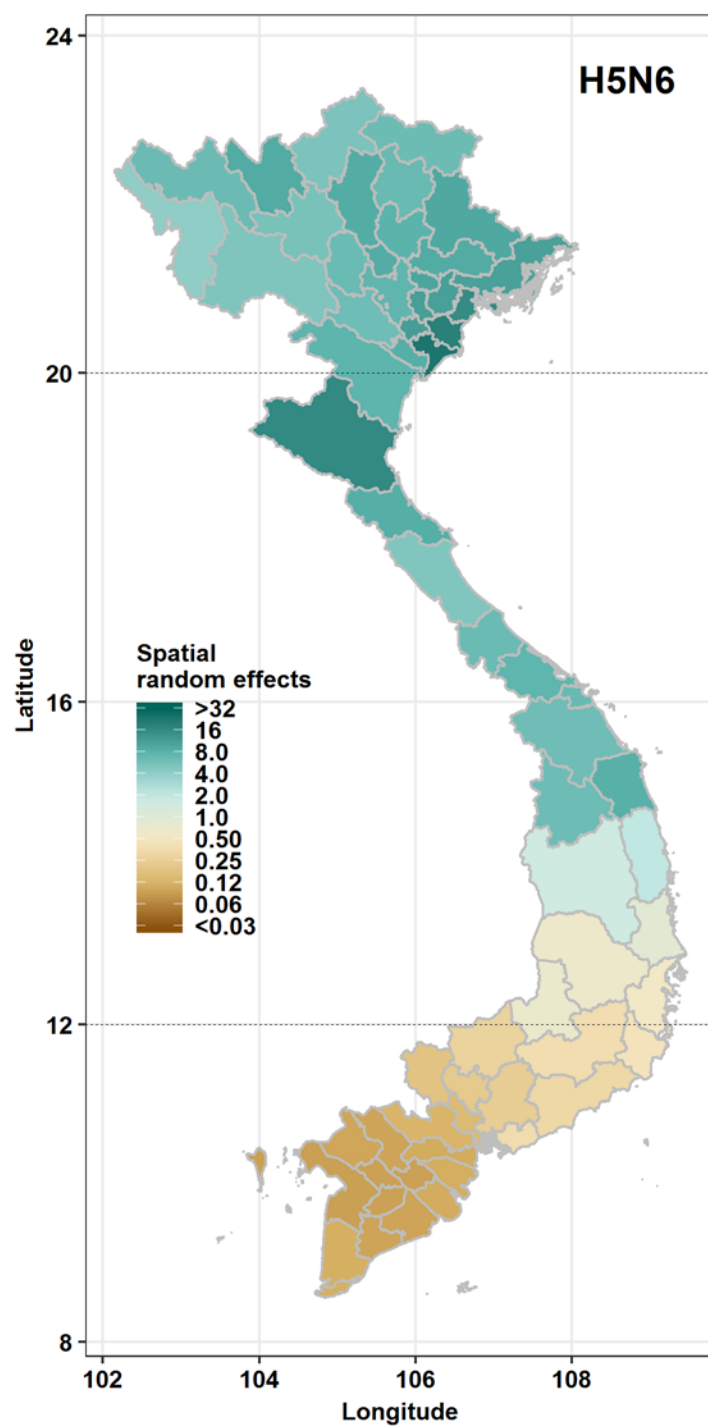
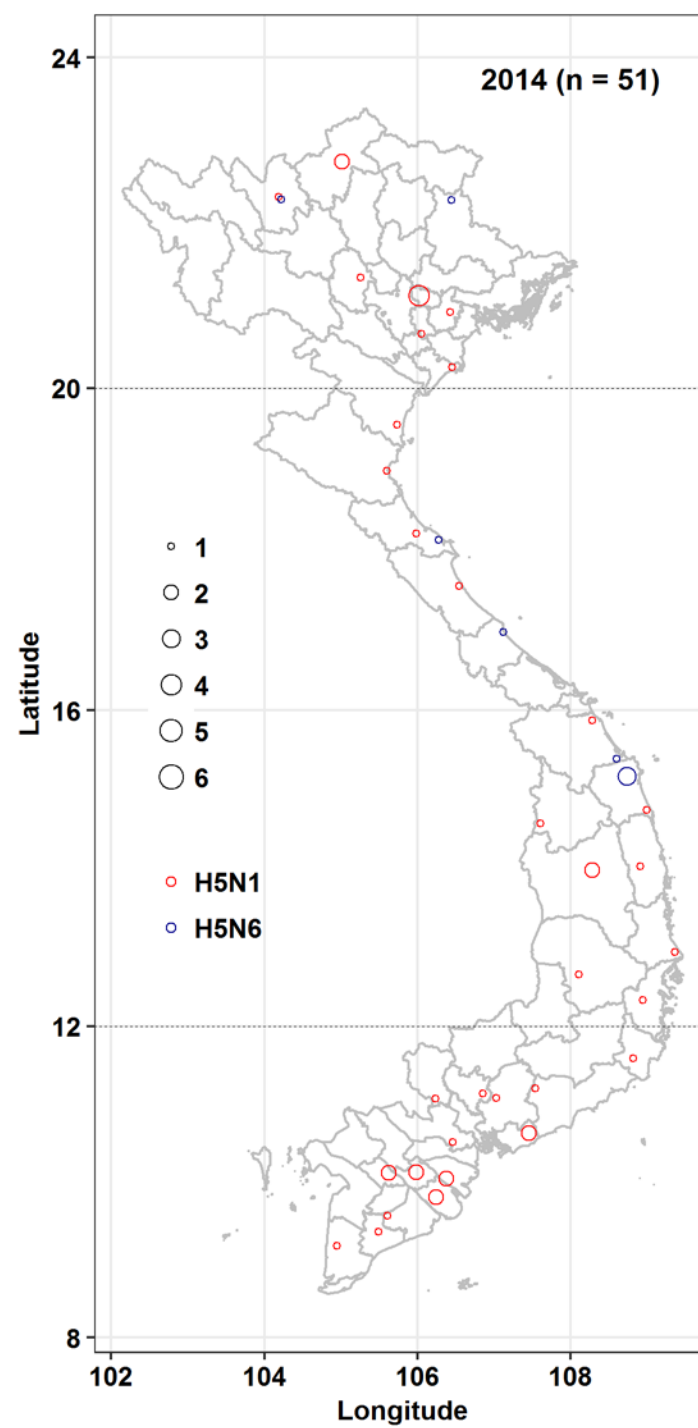
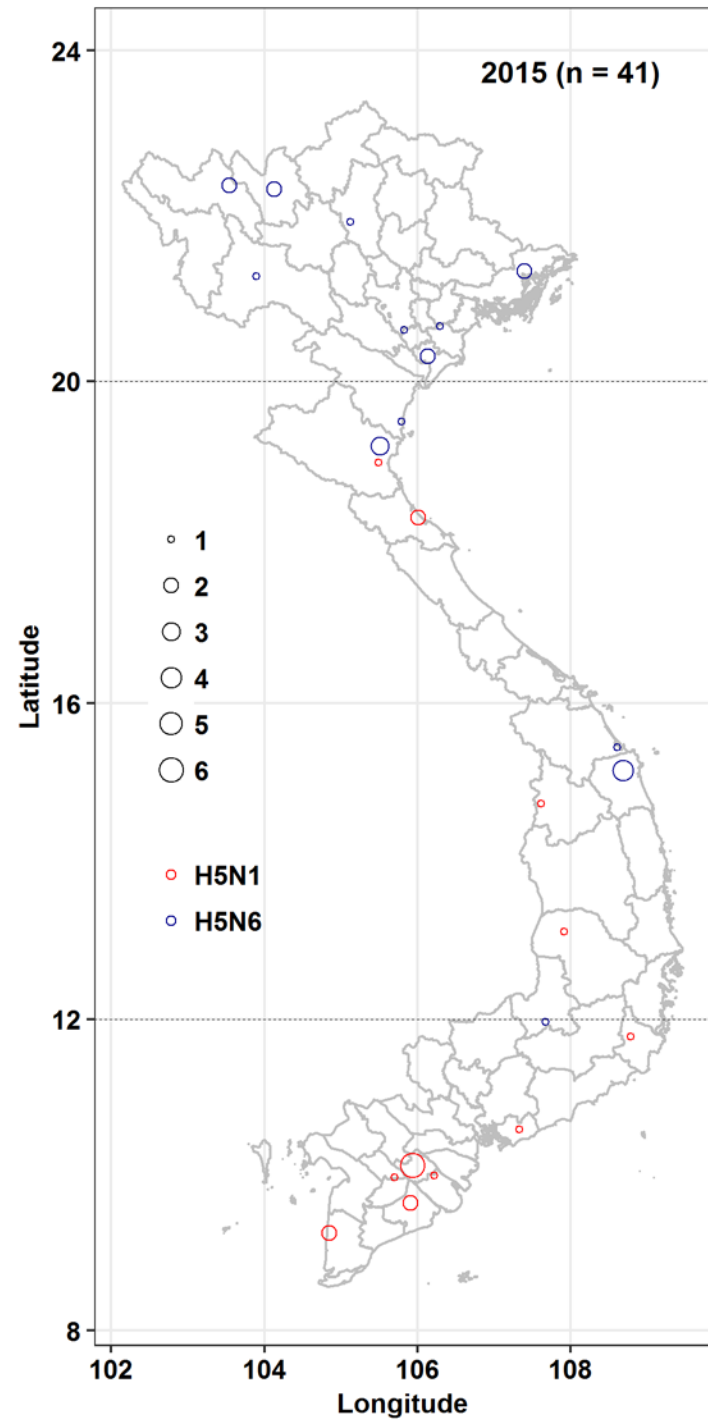
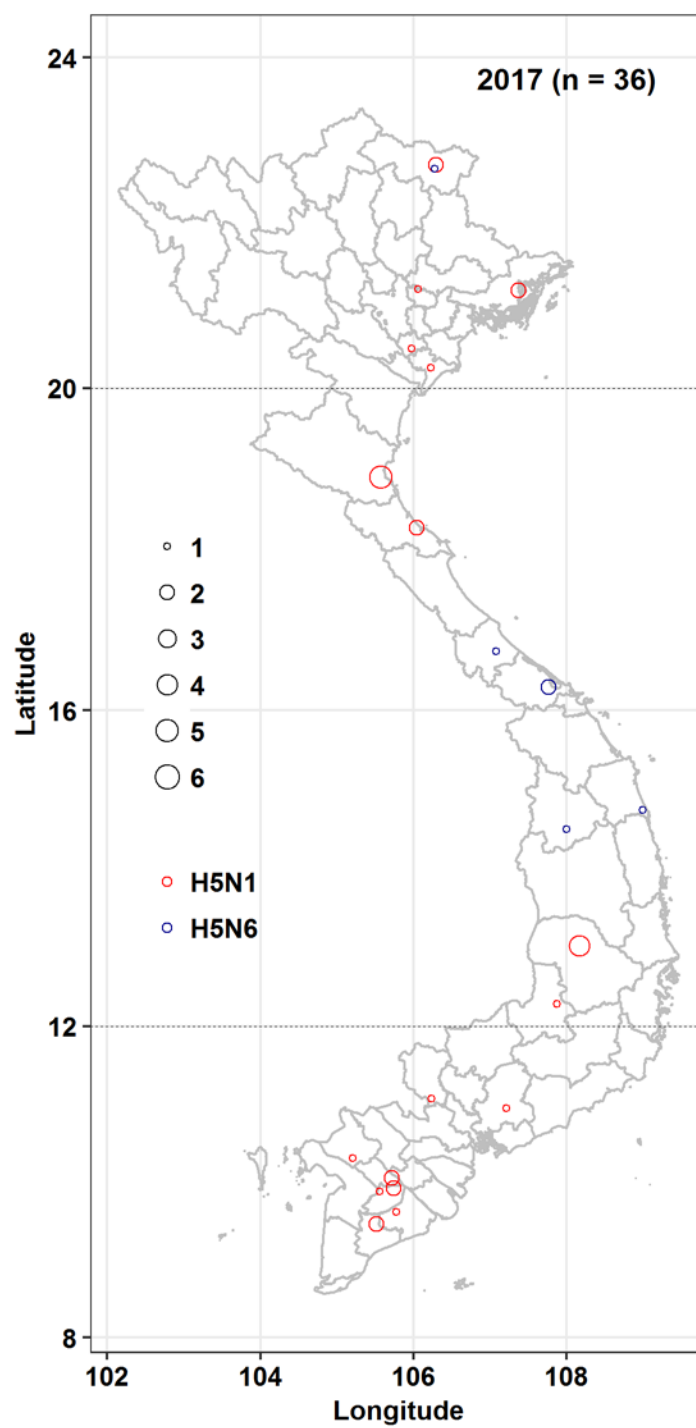


Fig. 4B.
Nguyen *et al.*,

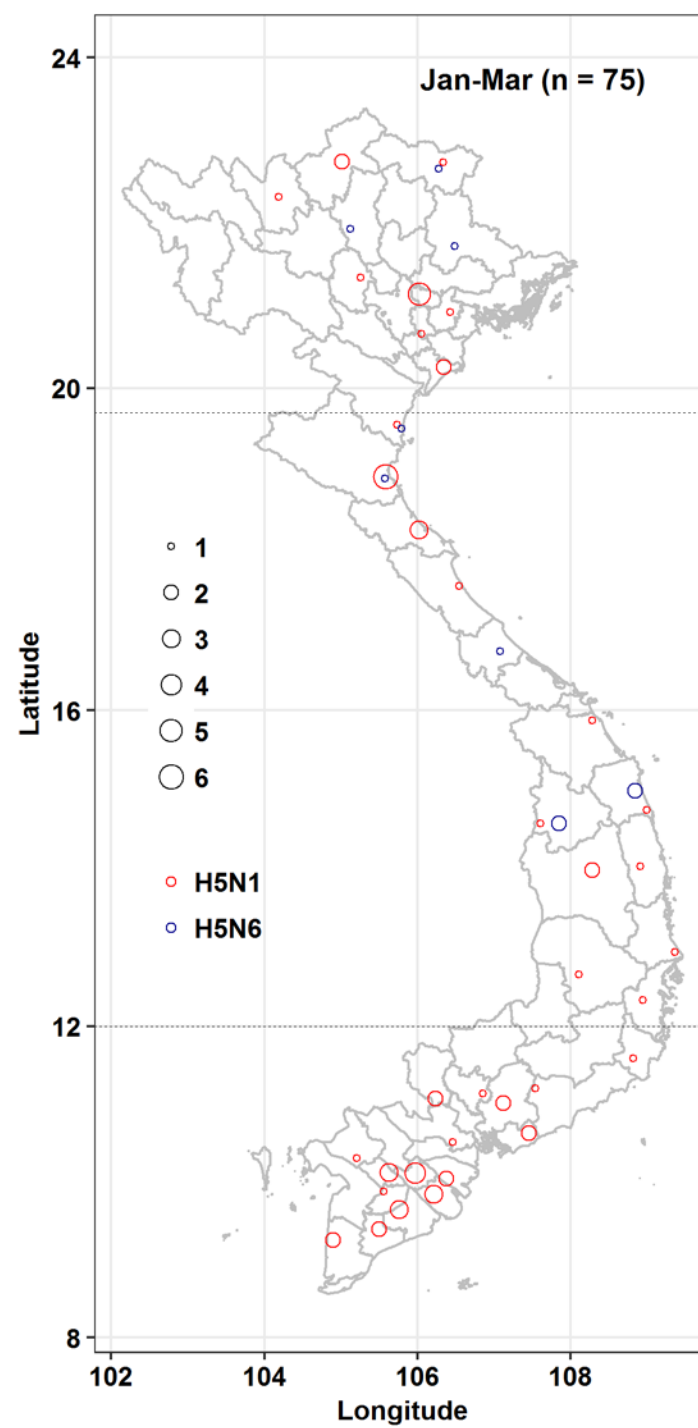




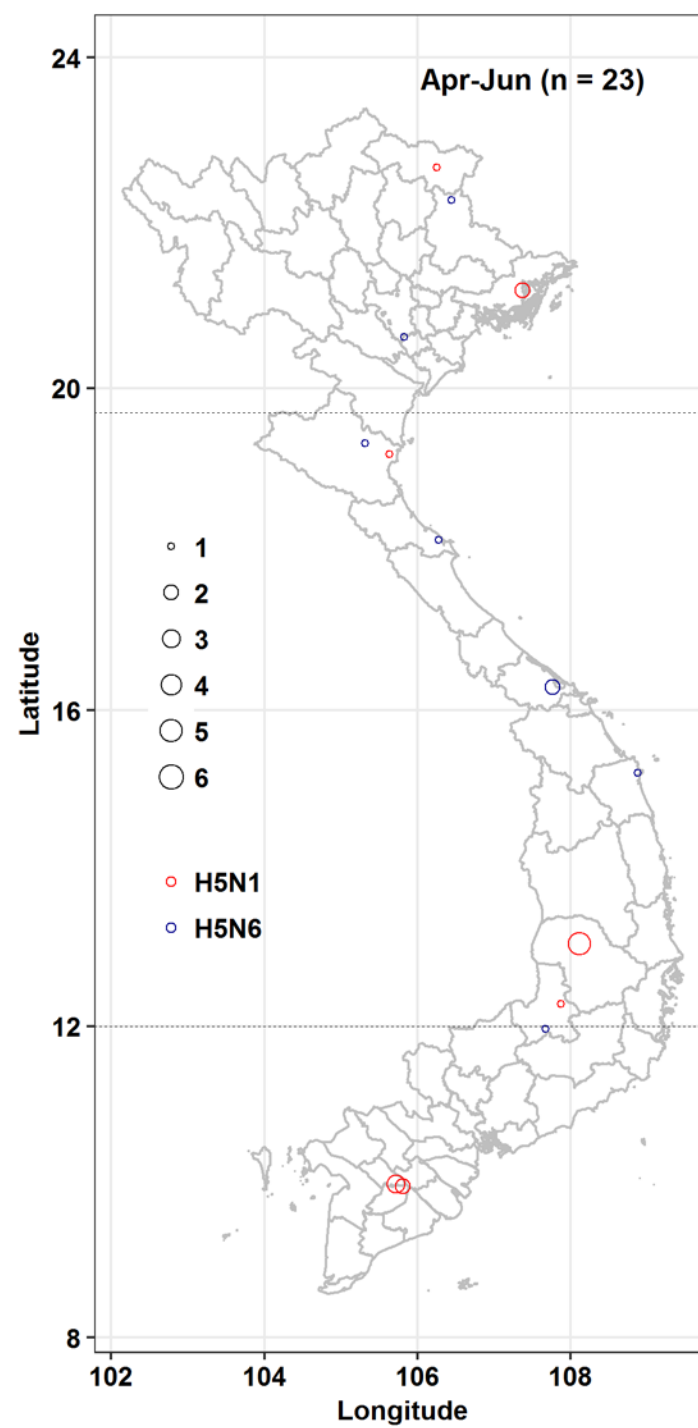
S. Fig. 1B.
Nguyen *et al.*,



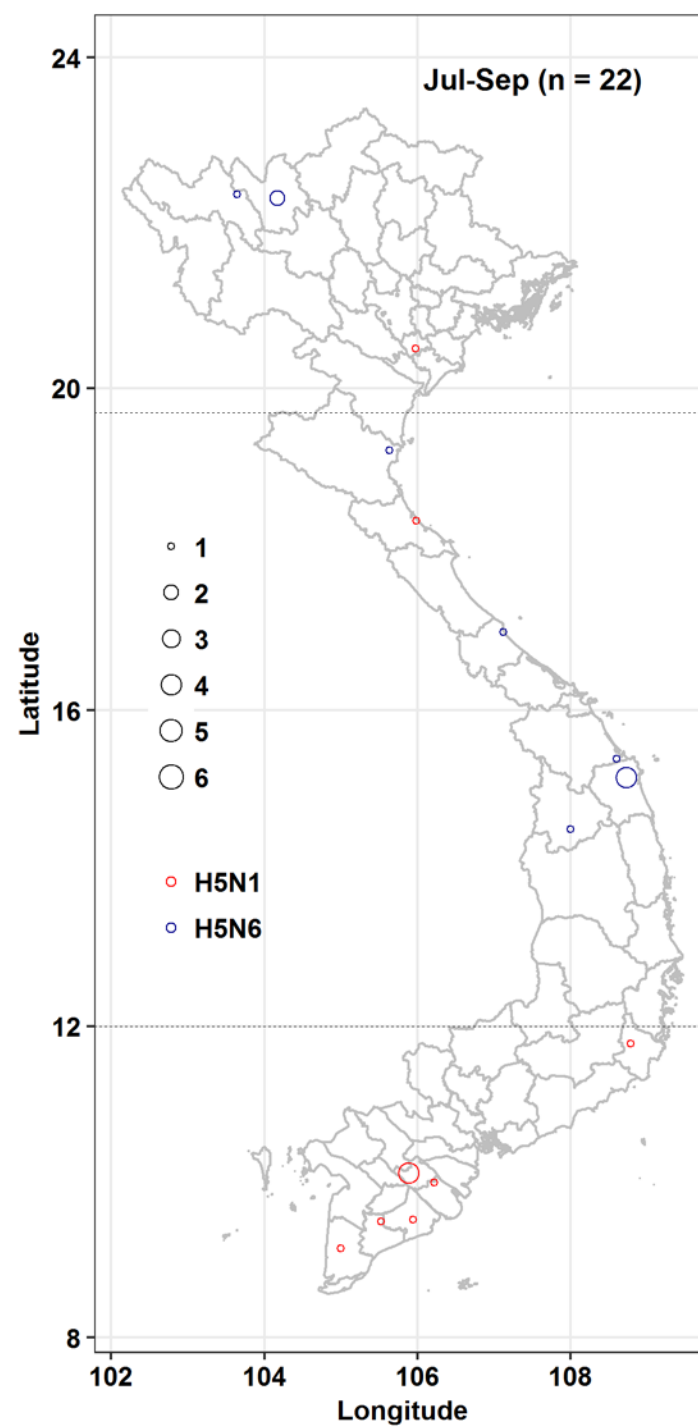
S. Fig. 1D.
Nguyen *et al.*,



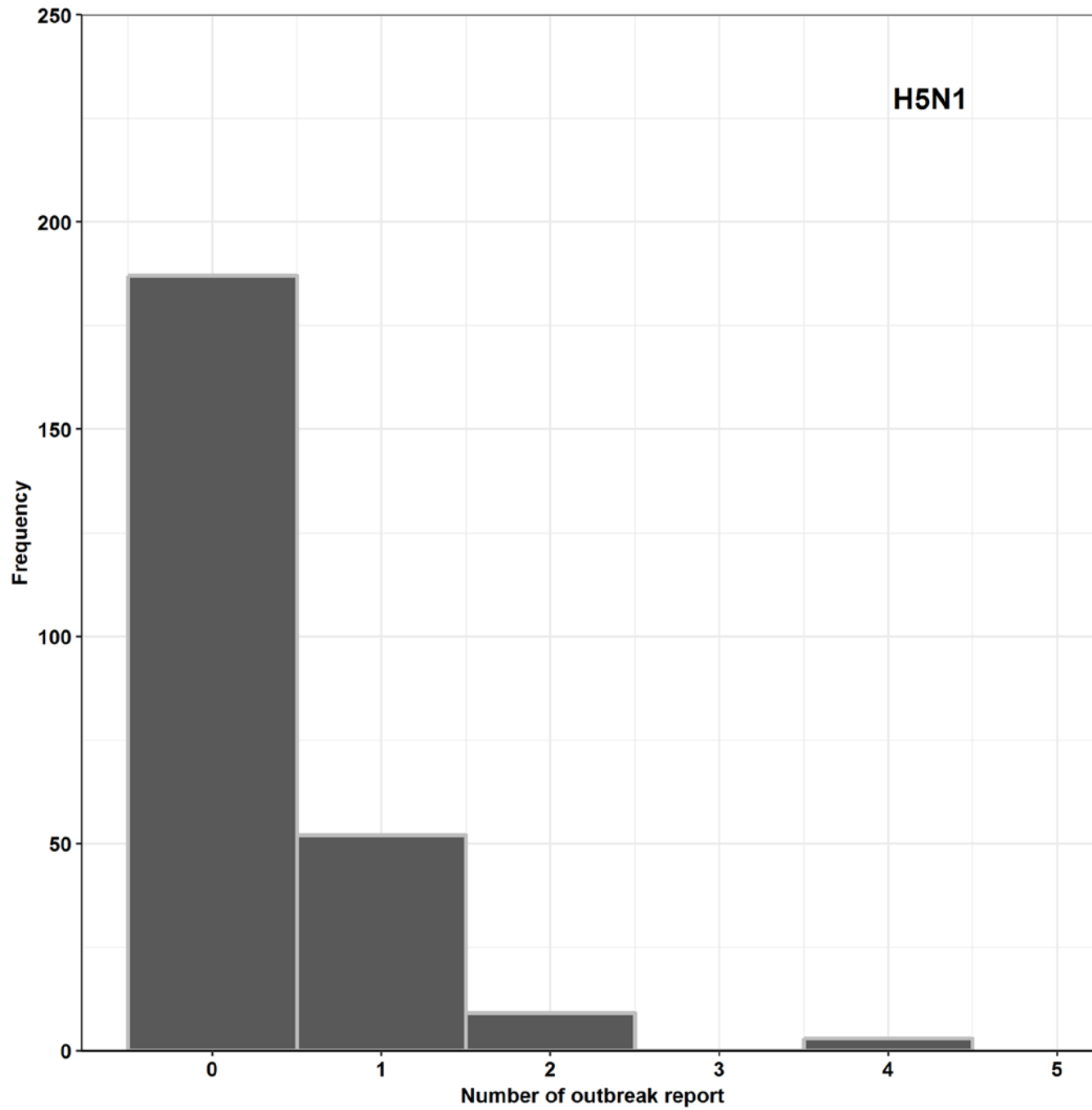
S. Fig. 2A.
Nguyen *et al.*,



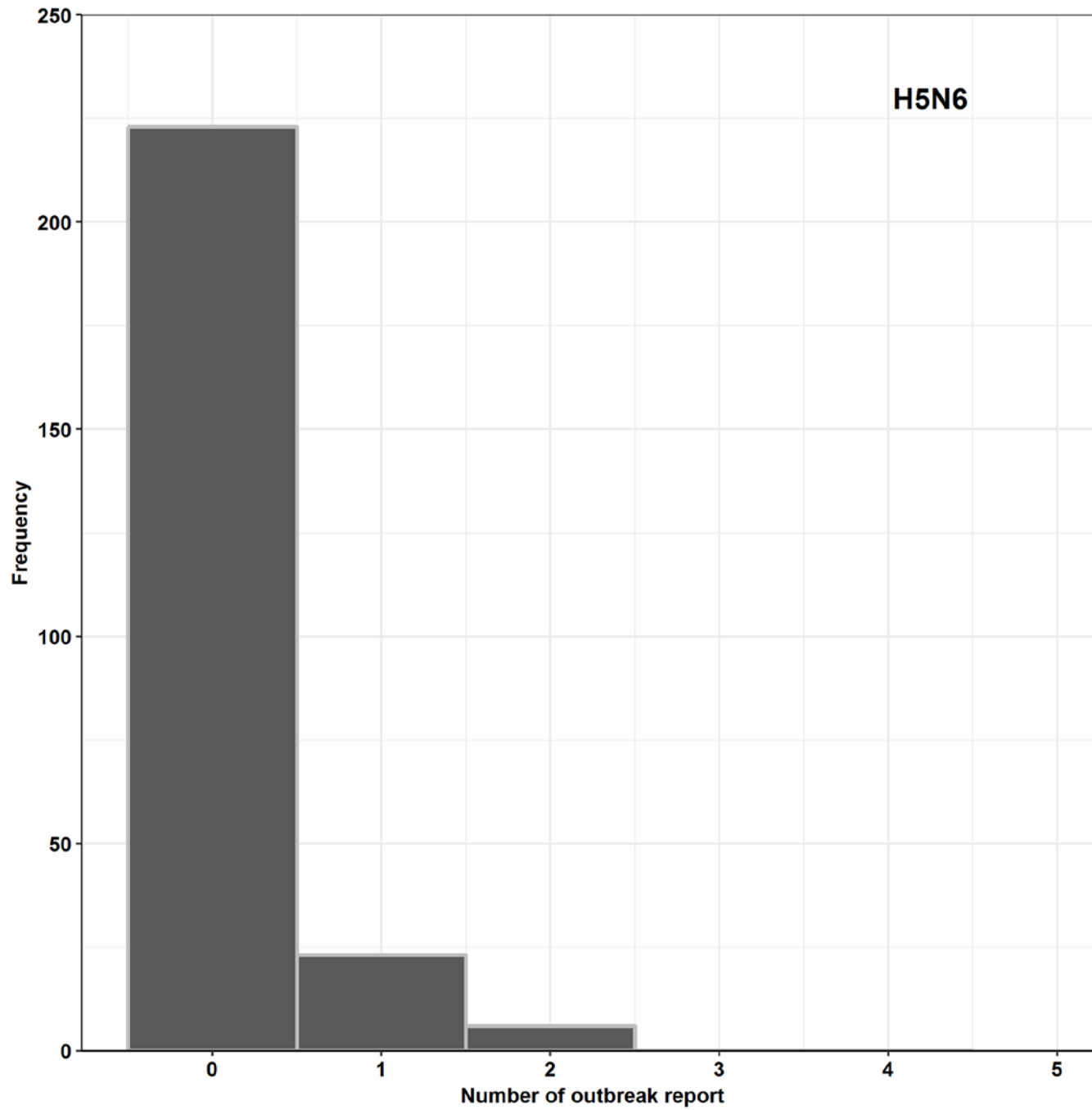
S. Fig. 2B.
Nguyen *et al.*,



S. Fig. 2C.
Nguyen *et al.*,



S. Fig. 3A.
Nguyen *et al.*,



S. Fig. 3B.
Nguyen *et al.*,