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1 **Spatiotemporal and risk analysis of H5 highly pathogenic avian influenza in Vietnam,**

2 **2014–2017**

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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

68

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

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; Delabouglise 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; Delabouglise 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; Delabouglise 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,

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[1] URL: http://www.diva-gis.org/gdata

8

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:

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

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:

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

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}:

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

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      $\phi_t \sim Normal(0, 1/\tau_\phi)$ (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:

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

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

15

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 (Delabouglise 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; Delabouglise 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; Delabouglise et al., 2017; Meyer et al., 2018).

382

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

405 **Acknowledgments**

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 (× 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 ($\times$ 1000)	60,709	964 (597)	131, 3400
Human population density in rural areas ($\times$ 1000.km^2)	-	0.77 (0.57)	0.12, 2.33
Density of domestic poultry, 2014 ($\times$ 1000.km^2)	-	4.25 (3.95)	0.24, 14.99
Density of domestic poultry, 2015 ($\times$ 1000.km^2)	-	4.4 (4.07)	0.25, 15.35
Density of domestic poultry, 2016 ($\times$ 1000.km^2)	-	4.59 (4.16)	0.26, 15.84
Density of domestic poultry, 2017 ($\times$ 1000.km^2)	-	4.93 (4.4)	0.28, 16.89
Density of domestic chickens, 2014 ($\times$ 1000.km^2)	-	3.19 (3.1)	0.21, 12.02
Density of domestic chickens, 2015 ($\times$ 1000.km^2)	-	3.33 (3.23)	0.22, 12.89
Density of domestic chickens, 2016 ($\times$ 1000.km^2)	-	3.51 (3.34)	0.23, 13.63
Density of domestic chickens, 2017 ($\times$ 1000.km^2)	-	3.78 (3.54)	0.25, 14.54
Density of domestic ducks, 2014 ($\times$ 1000.km^2)	-	1.03 (1.13)	0, 6.29
Density of domestic ducks, 2015 ($\times$ 1000.km^2)	-	1.28 (1.27)	0.02, 5.83
Density of domestic ducks, 2016 ($\times$ 1000.km^2)	-	1.34 (1.45)	0.02, 6.88
Density of domestic ducks, 2017 ($\times$ 1000.km^2)	-	1.4 (1.47)	0.02, 7.08
Density of domestic Muscovy ducks, 2014 ($\times$ 1000.km^2)	-	0.18 (0.27)	0, 1.55
Density of domestic Muscovy ducks, 2015 ($\times$ 1000.km^2)	-	0.18 (0.26)	0, 1.56
Density of domestic Muscovy ducks, 2016 ($\times$ 1000.km^2)	-	0.17 (0.21)	0, 0.94
Density of domestic Muscovy ducks, 2017 ($\times$ 1000.km^2)	-	0.19 (0.21)	0, 0.93
Density of domestic geese, 2014 ($\times$ 1000.km^2)	-	0.01 (0.01)	0, 0.05
Density of domestic geese, 2015 ($\times$ 1000.km^2)	-	0.01 (0.01)	0, 0.06
Density of domestic geese, 2016 ($\times$ 1000.km^2)	-	0.01 (0.01)	0, 0.06
Density of domestic geese, 2017 ($\times$ 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 (× 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.

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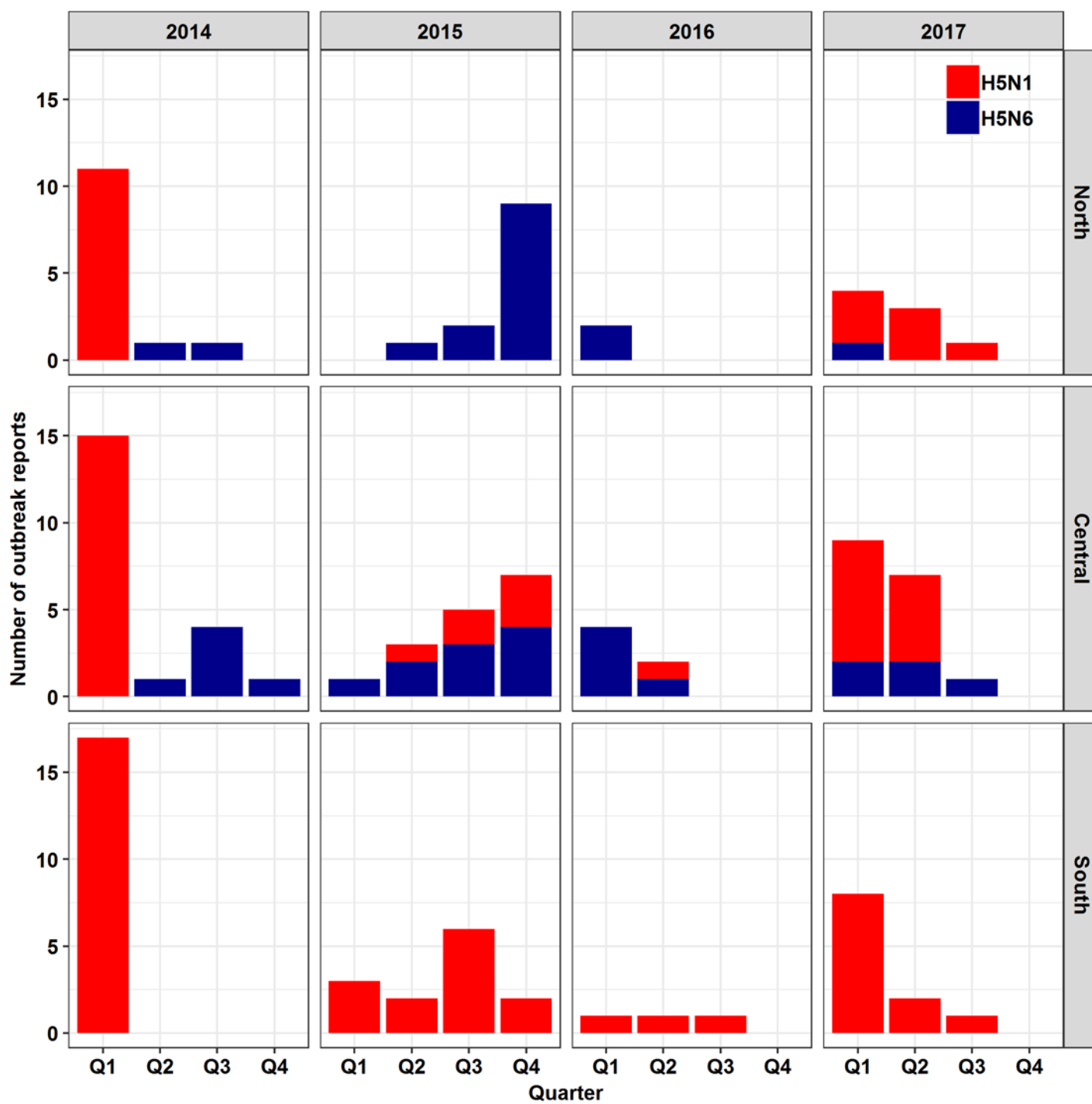
Fig. 1A.
Nguyen *et al.*,

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

H5N6

Observed number of
outbreaks per province

10.0
7.5
5.0
2.5
0.0
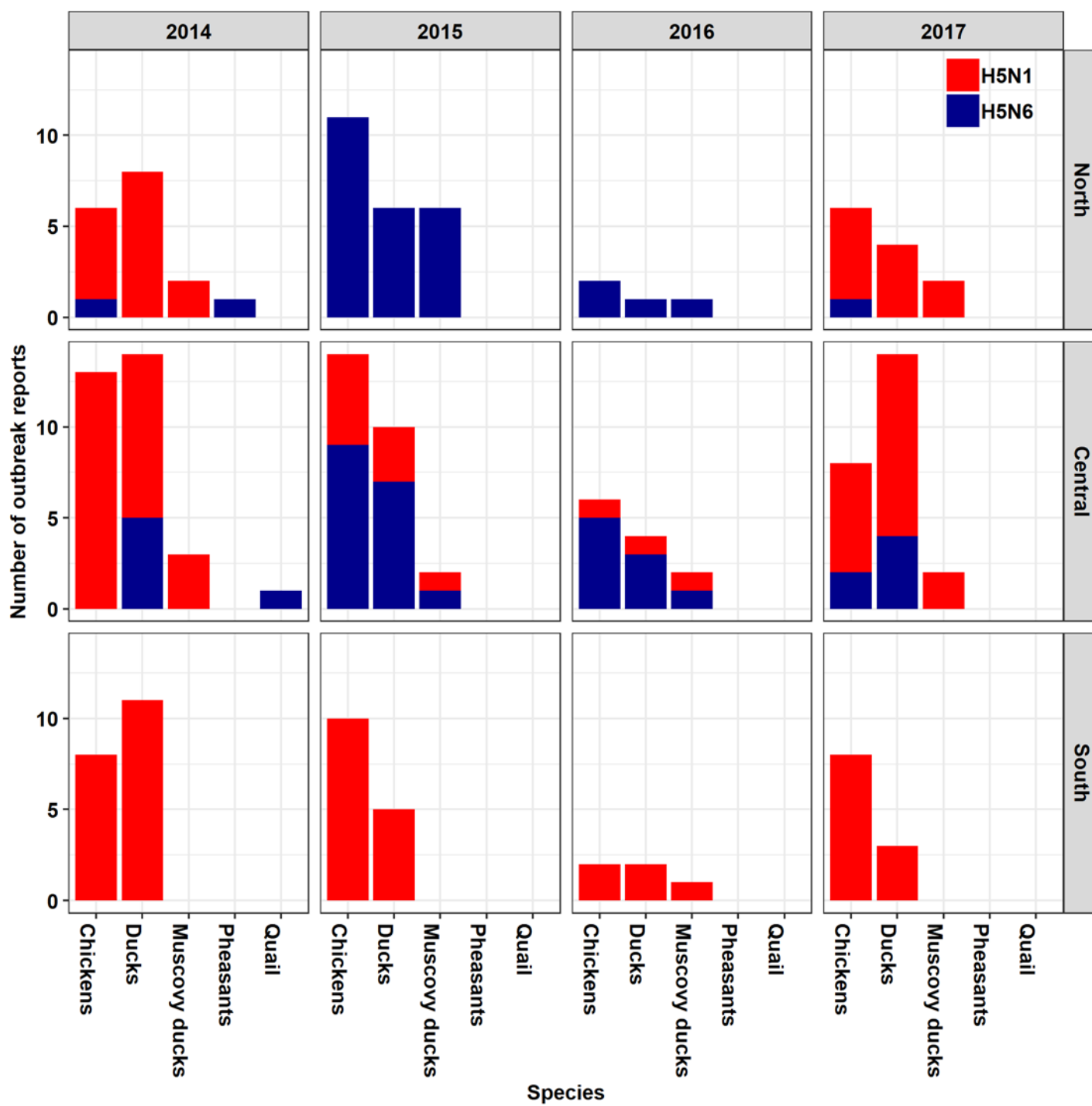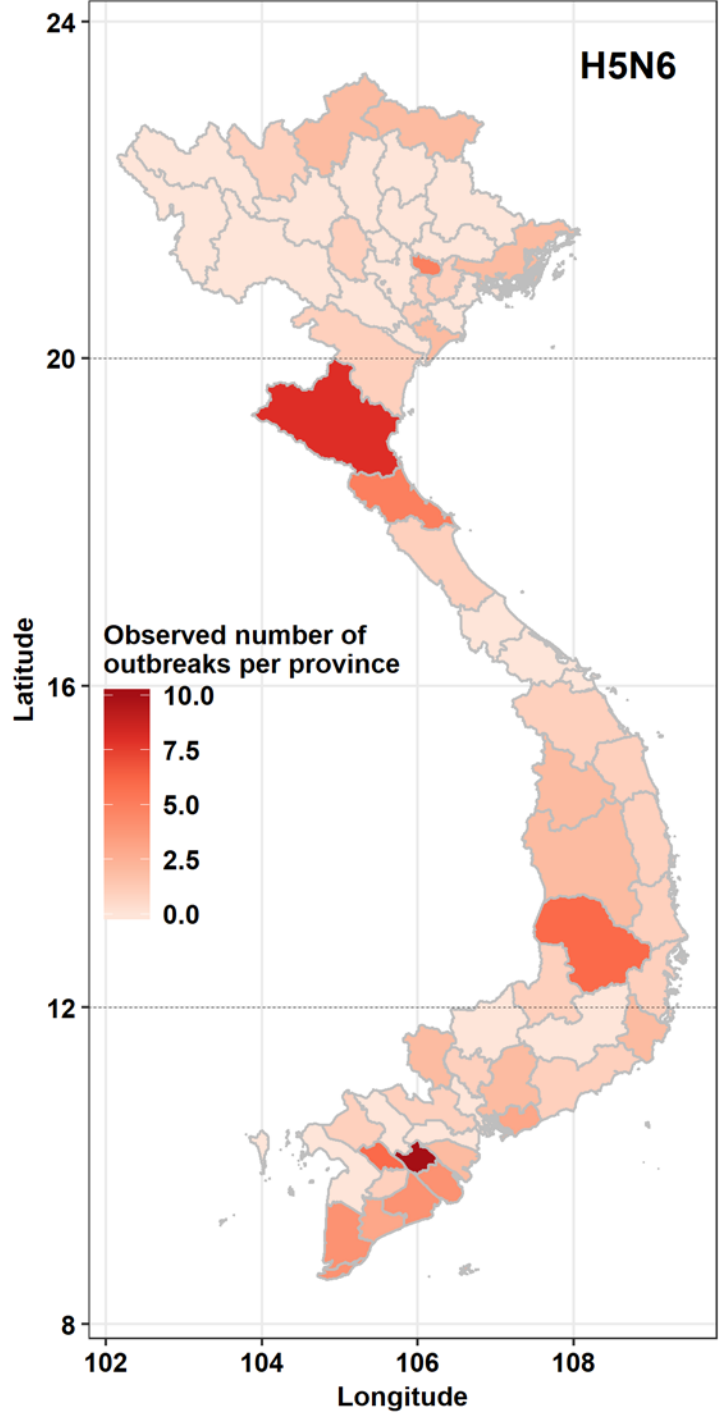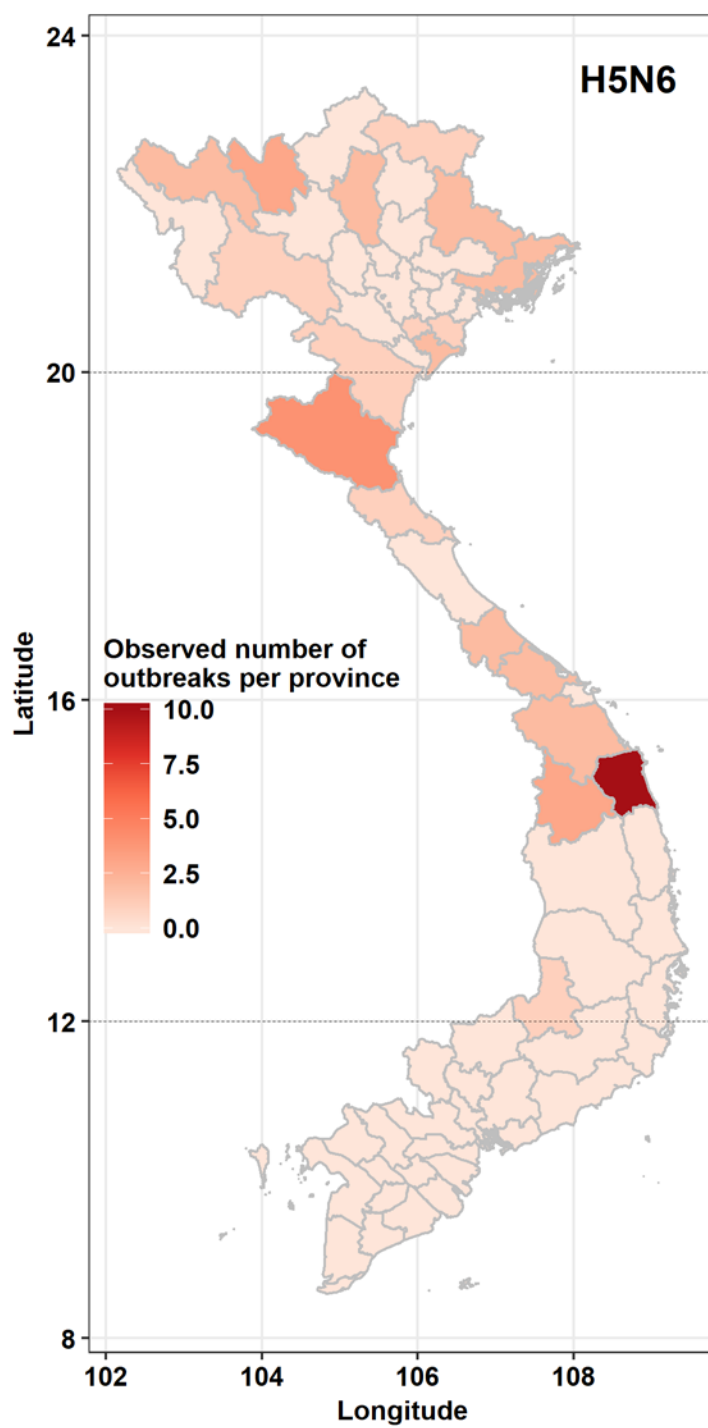
Fig. 2A.
Nguyen _et al._,

Fig. 2B.
Nguyen *et al.,*
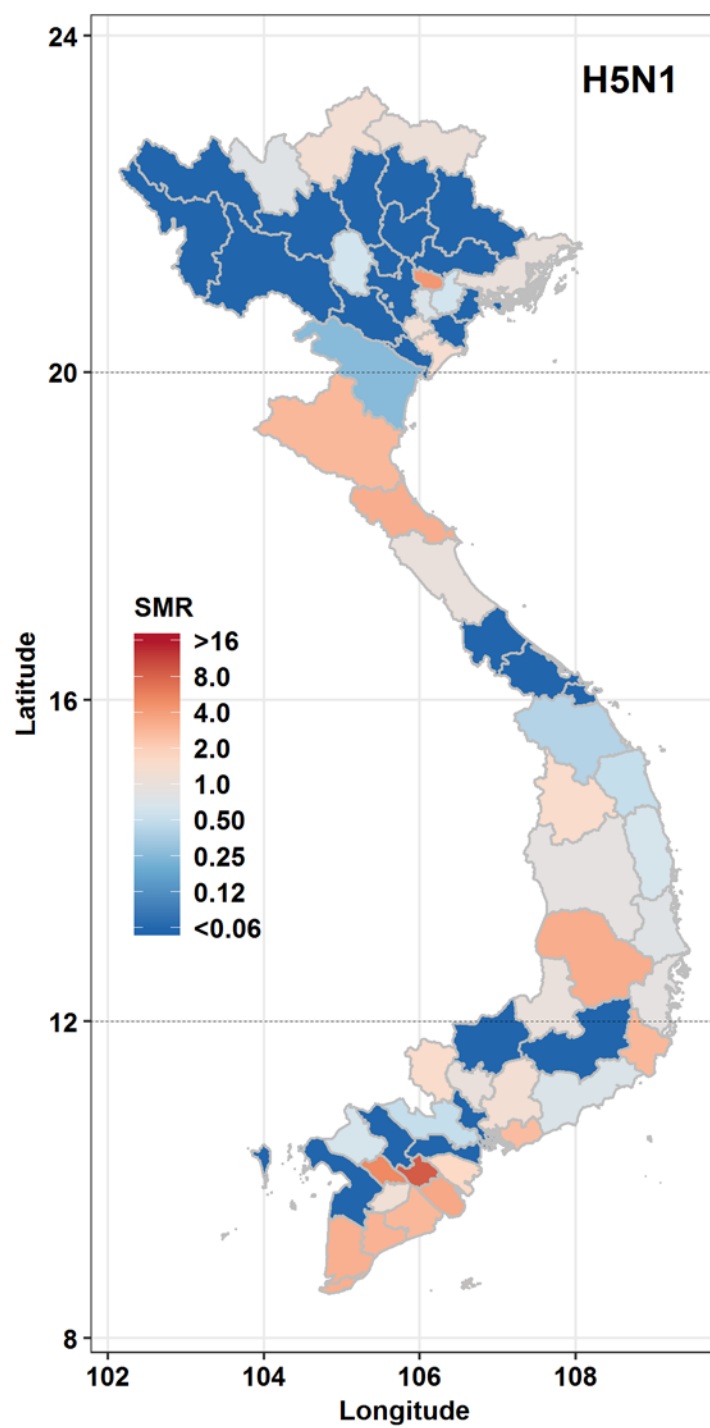
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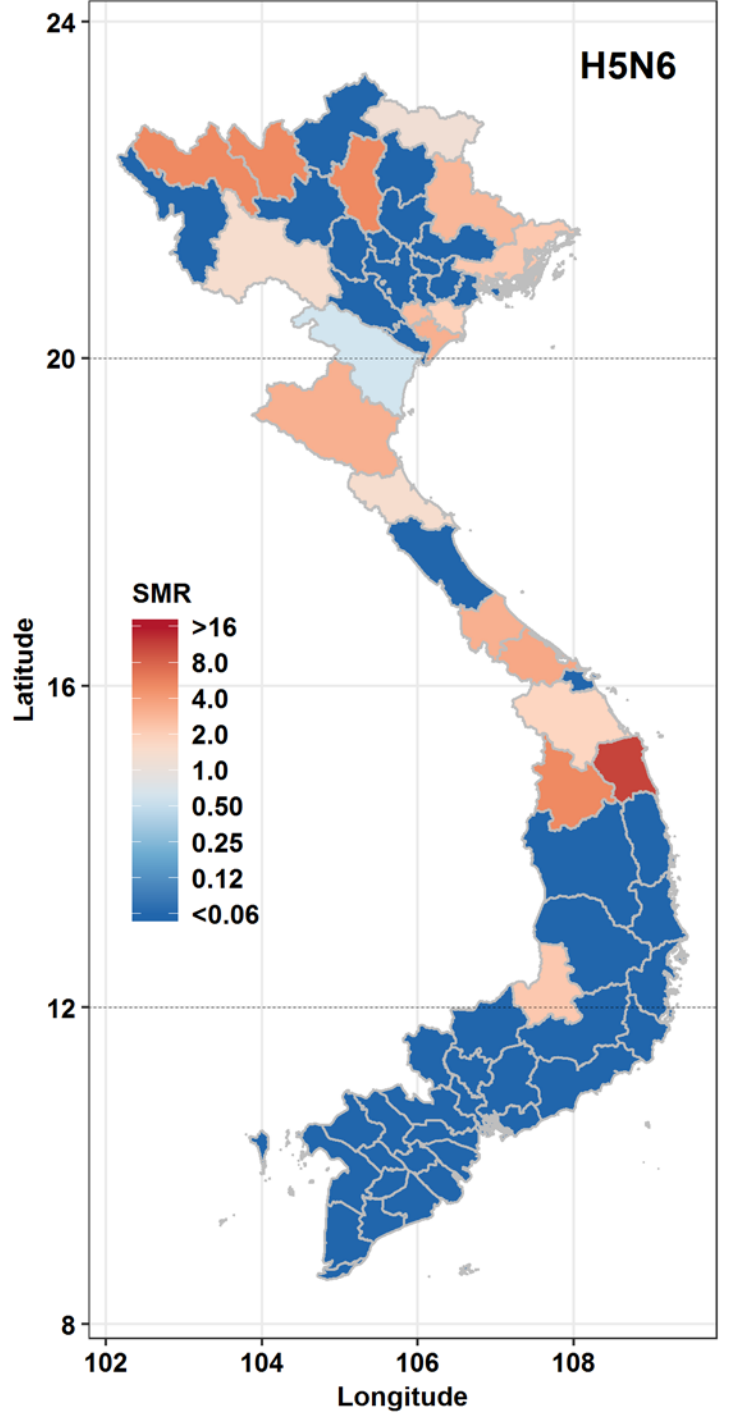
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Nguyen *et al*.,
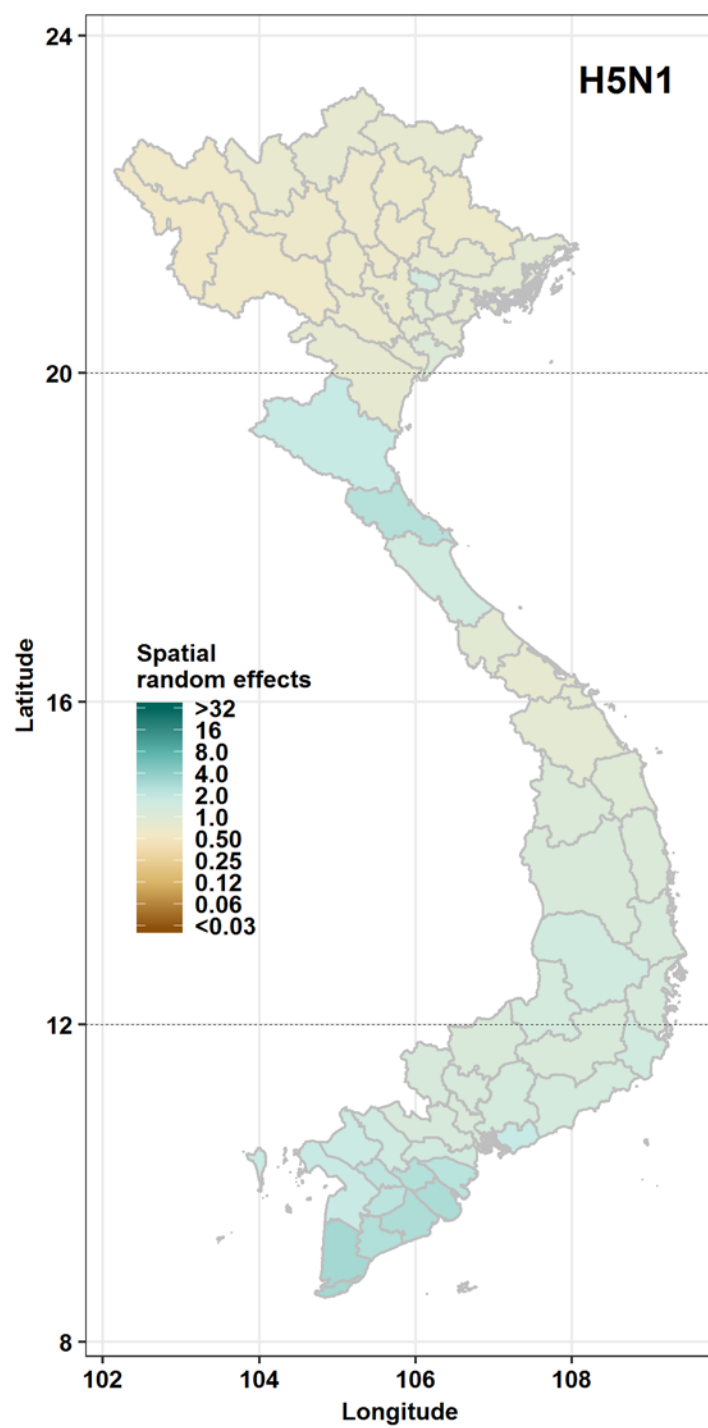
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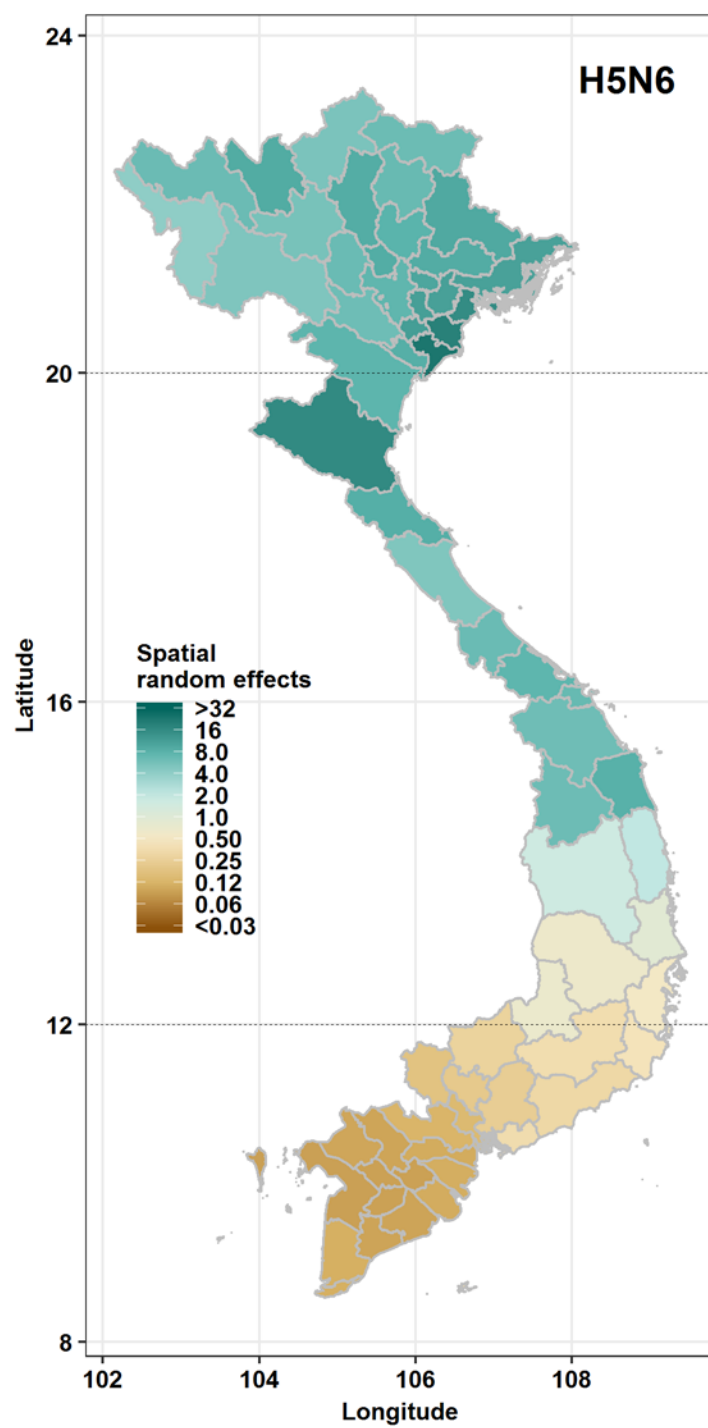
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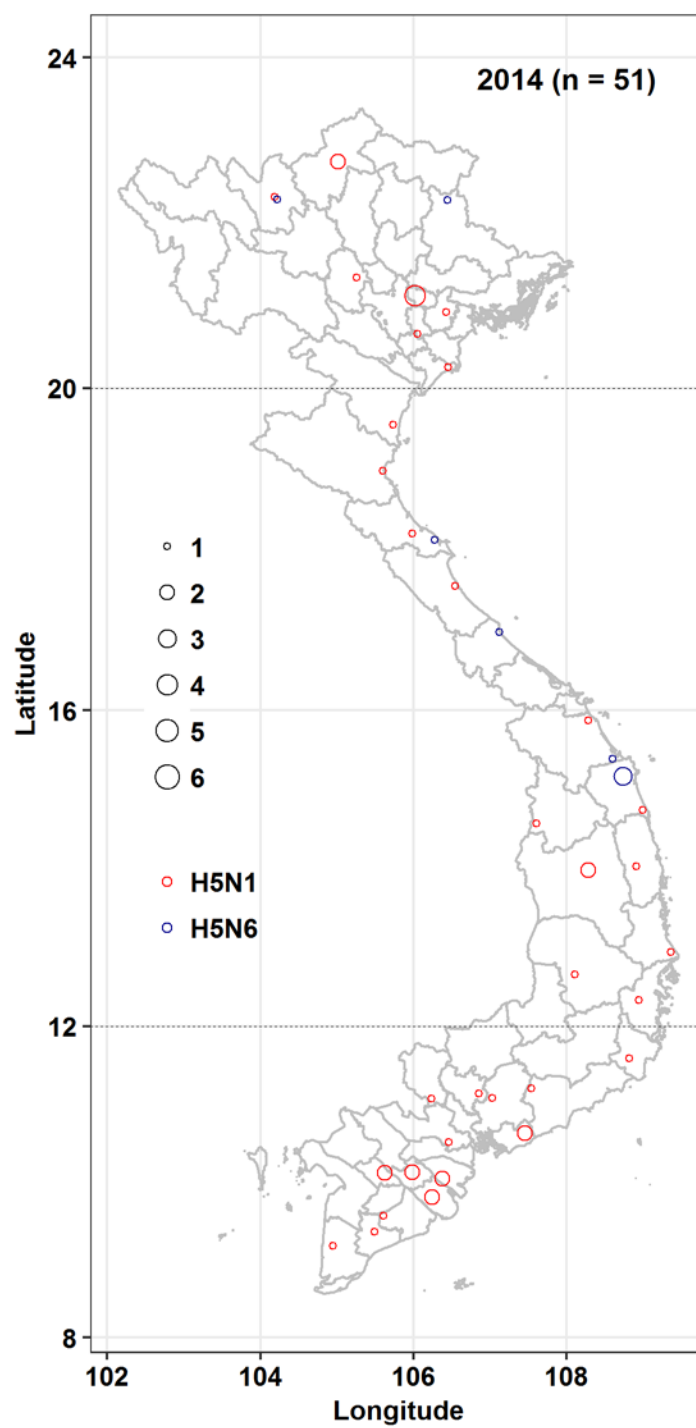
S. Fig. 1A.
Nguyen *et al.*,
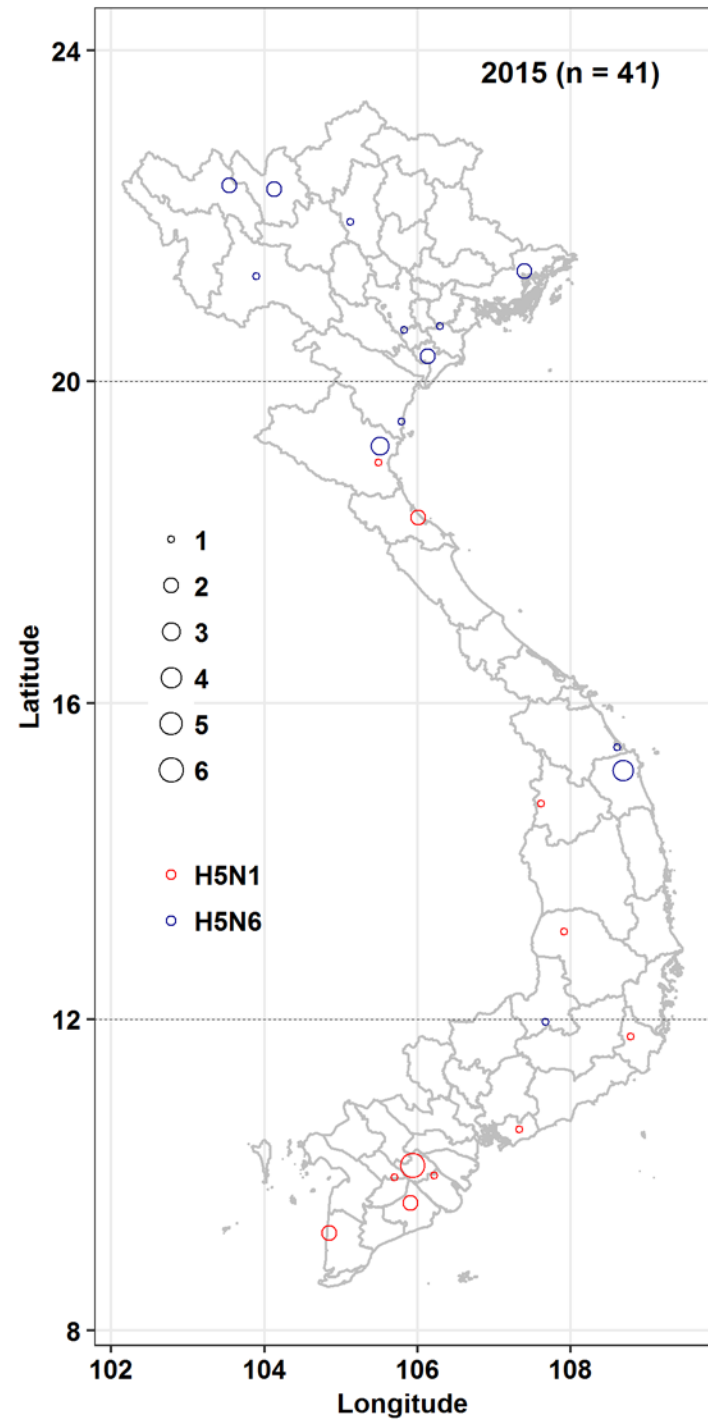
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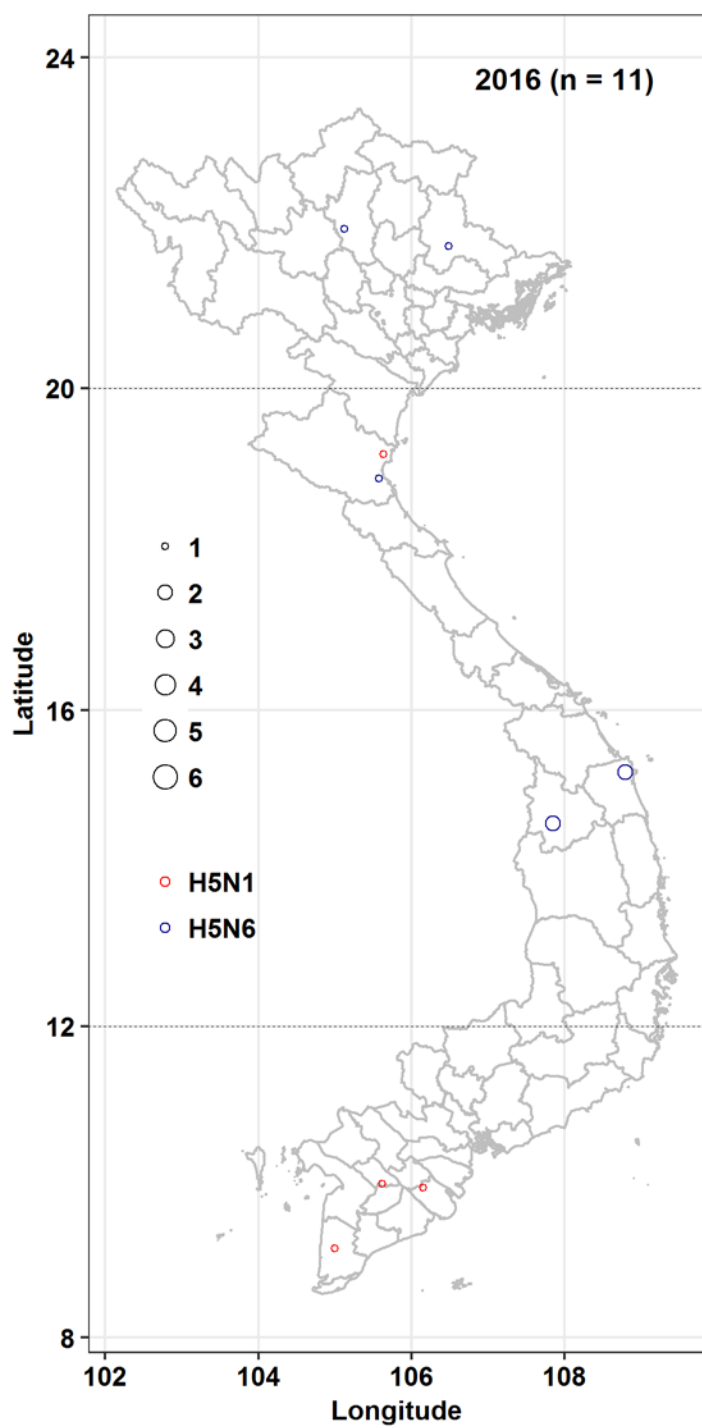
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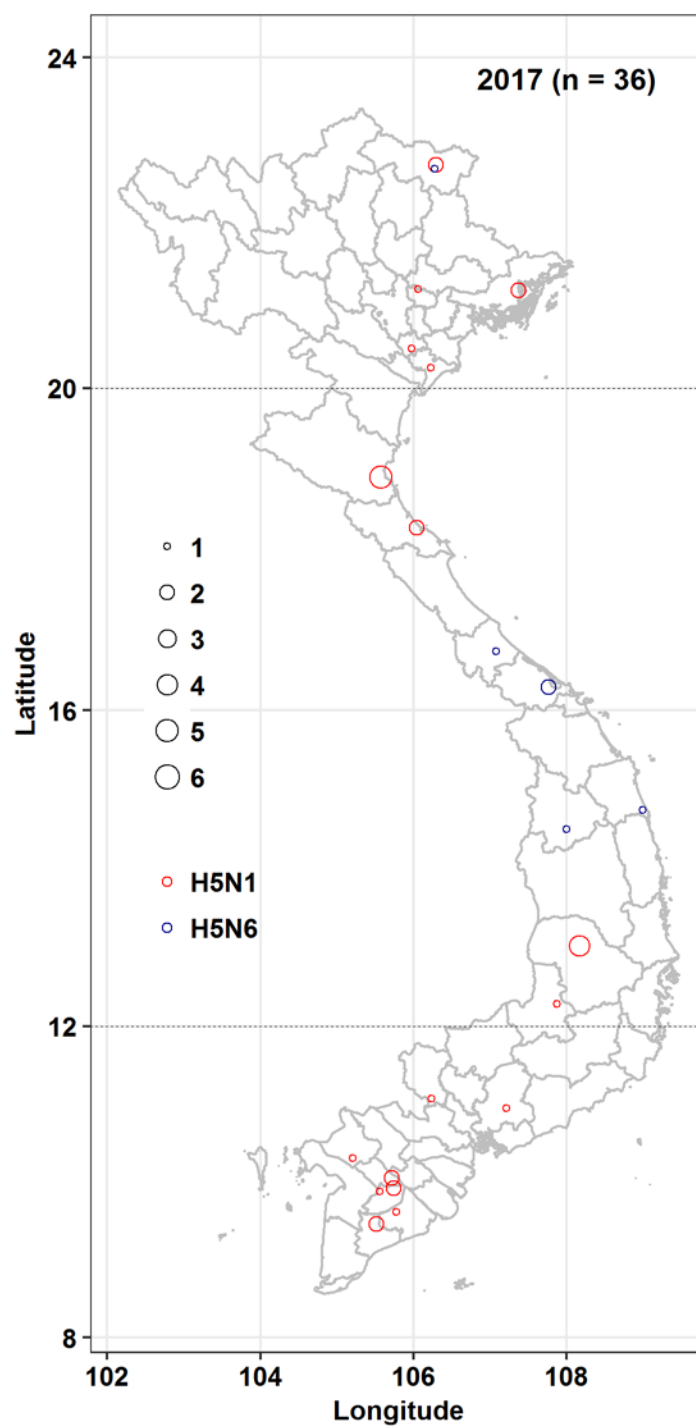
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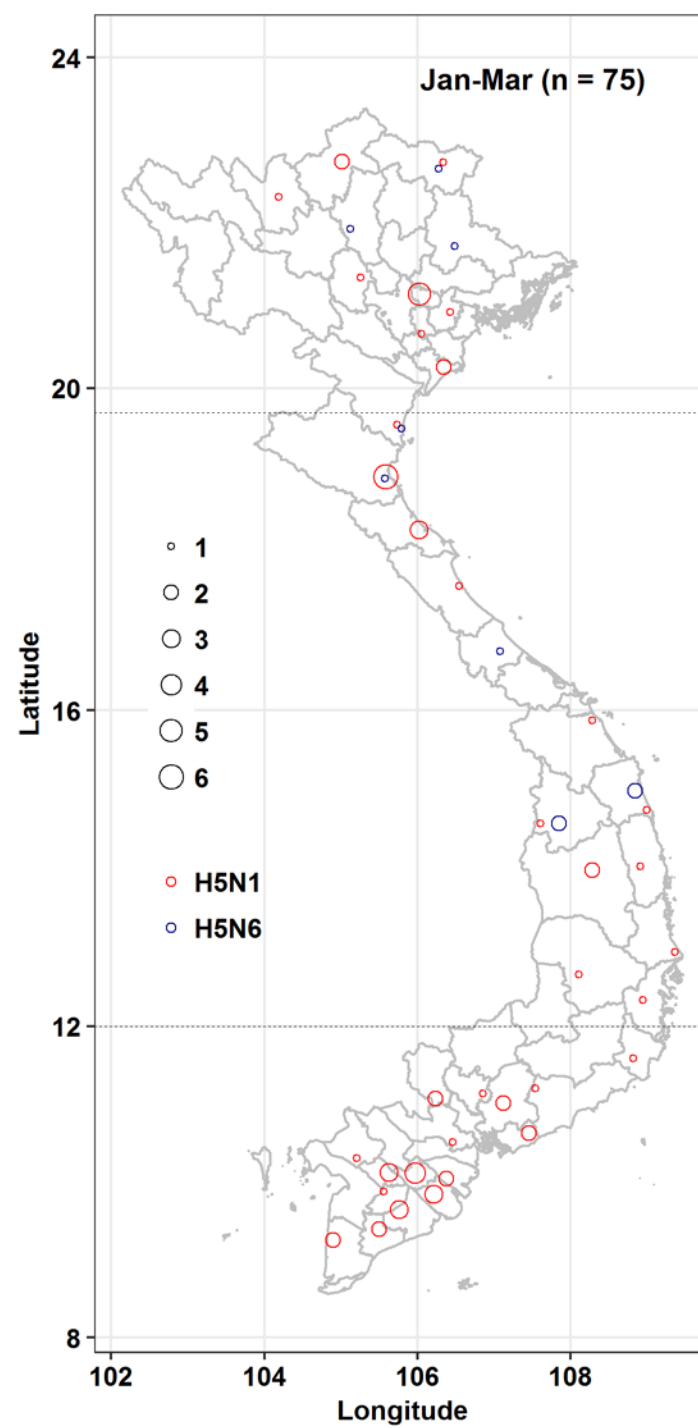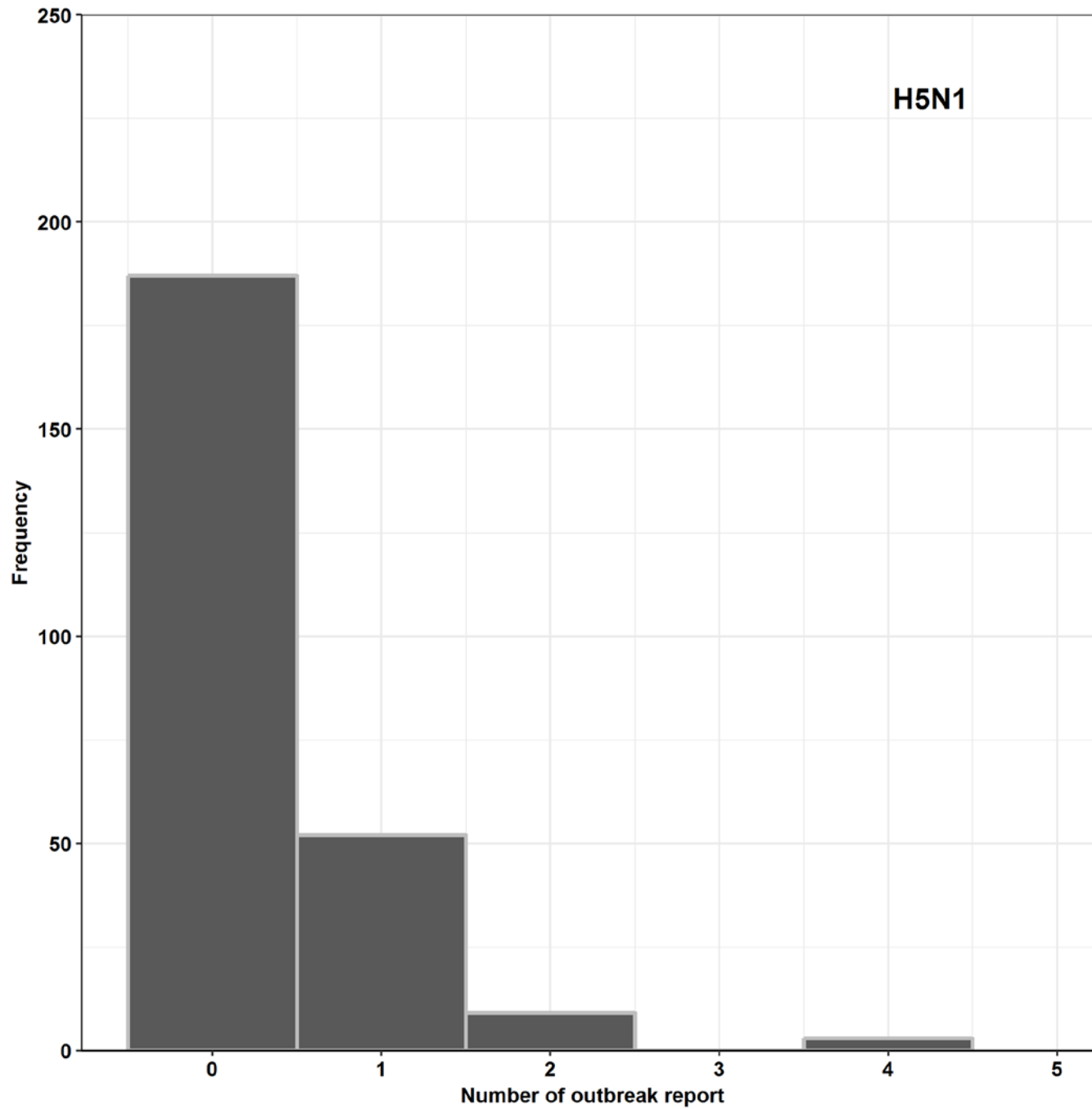
S. Fig. 2A.
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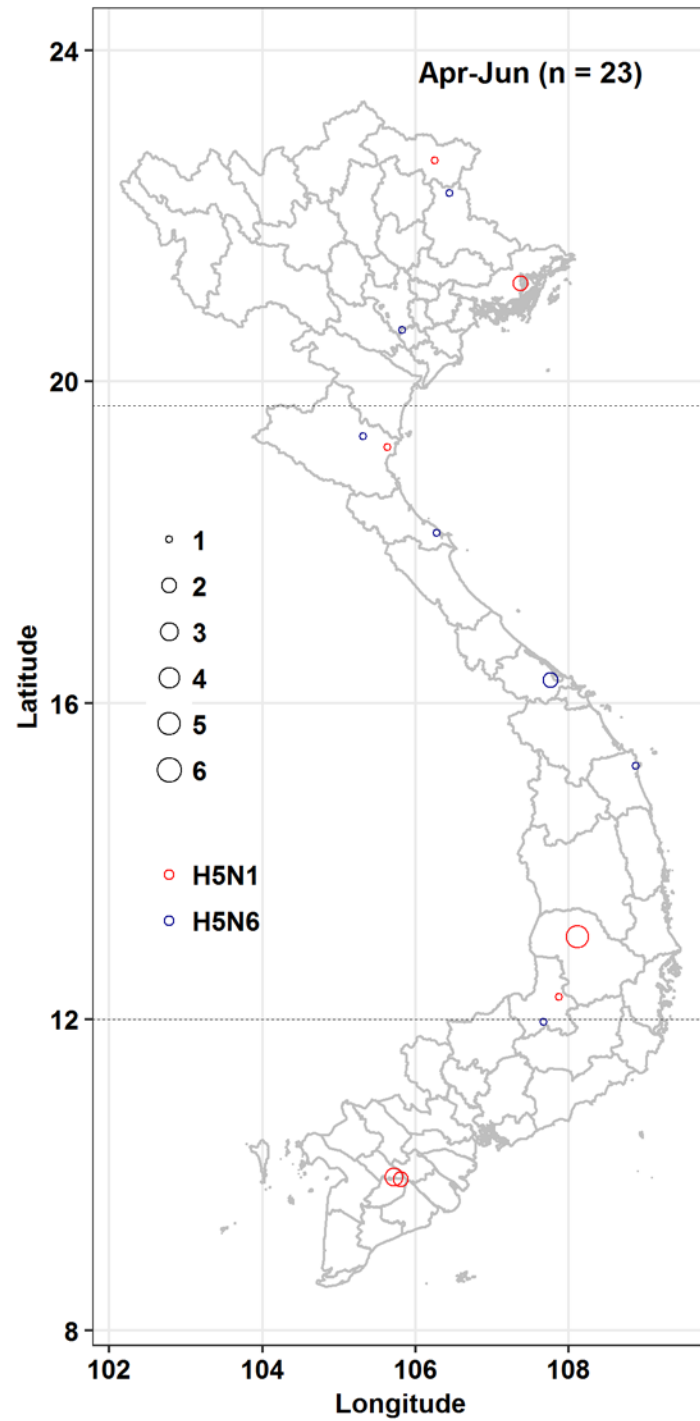
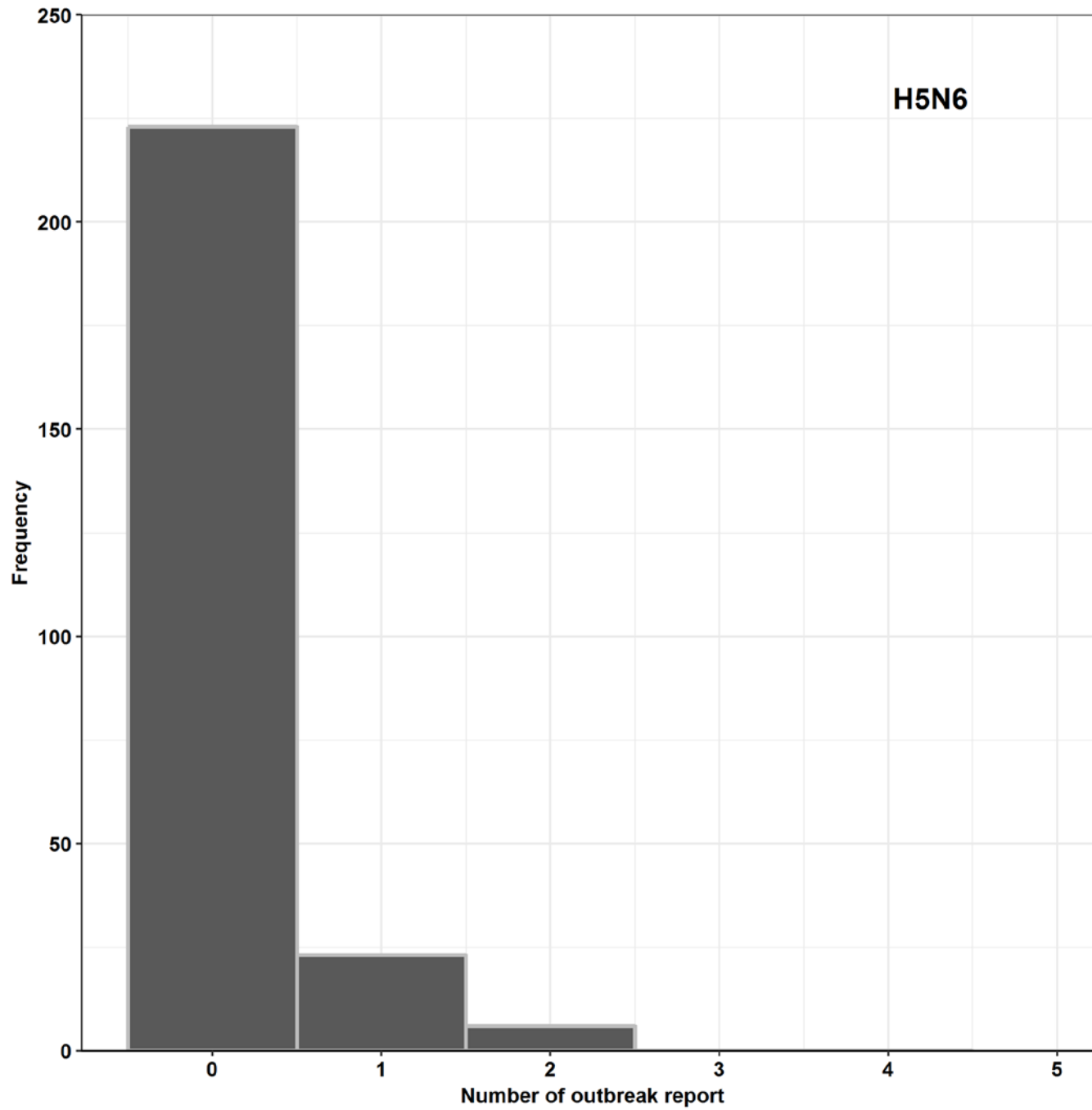**S. Fig. 2B.**
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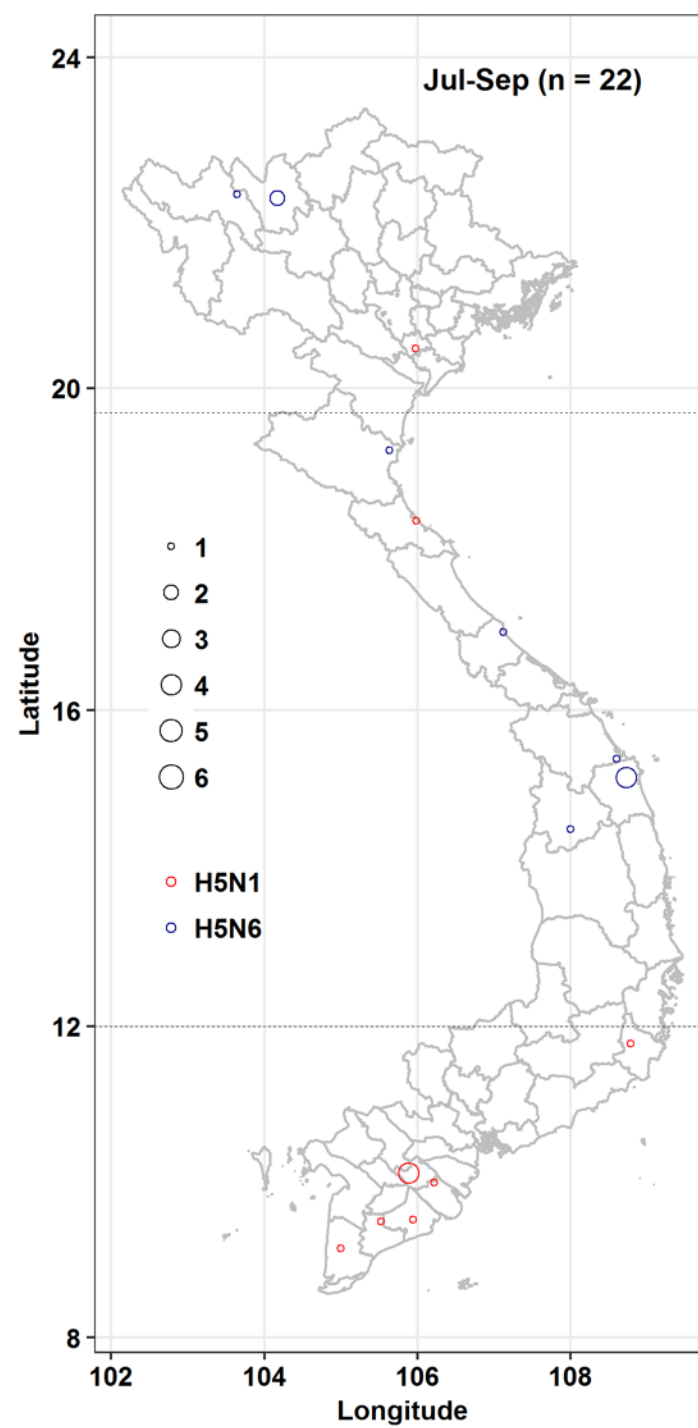
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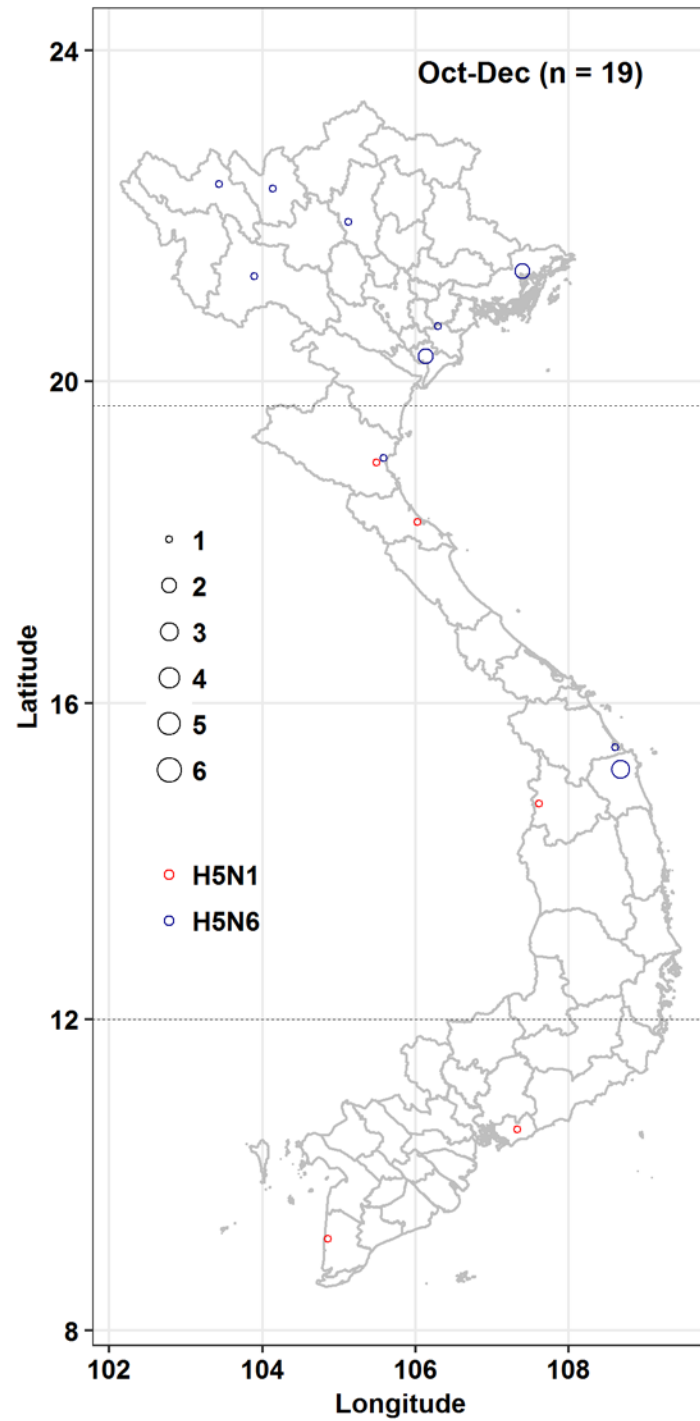
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Nguyen *et al.*,

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

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