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3 Detecting space-time clusters of dengue fever in Panama after adjusting for vector
4 surveillance data

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25 Abstract – 206 words

26 Long term surveillance of vectors and arboviruses is an integral aspect of disease prevention and
27 control systems in countries affected by increasing risk. Yet, little effort has been made to adjust space-
28 time risk estimation by integrating disease case counts with vector surveillance data, which may result in
29 inaccurate risk projection when several vector species are present, and little is known about their likely
30 role in local transmission. Here, we integrate 13 years of dengue case surveillance and associated *Aedes*
31 occurrence data across 462 localities in 63 districts to estimate the risk of infection in the Republic of
32 Panama. Our space-time modelling approach detected the presence of five clusters, which varied by
33 duration, relative risk, and spatial extent after incorporating vector species as covariates. Dengue
34 prevalence (n = 49,910) was predicted by the presence of resident *Aedes aegypti* alone, while all other
35 covariates exhibited insignificant statistical relationships with it, including the presence and absence of
36 invasive *Aedes albopictus*. Furthermore, the *Ae. aegypti* model contained the highest number of districts
37 with more dengue cases than would be expected given baseline population levels. This implies that
38 arbovirus case surveillance coupled with entomological surveillance can affect cluster detection and risk
39 estimation, improving efforts to understand outbreak dynamics at national scales.

40

41 Author Summary

42 Dengue cases have increased in tropical regions worldwide owing to climate change,
43 urbanization, and globalization facilitating the spread of *Aedes* mosquito vectors. National surveillance
44 programs monitor trends in dengue fever and inform the public about epidemiological scenarios where
45 outbreak preventive actions are most needed. Yet, most estimations of dengue risk so far derive only
46 from disease case data, ignoring *Aedes* occurrence as a key aspect of dengue transmission dynamic.
47 Here we illustrate how incorporating vector presence and absence as a model covariate can considerably
48 alter the characteristics of space-time cluster estimations of dengue cases. We further show that *Ae.*

49 *aegypti* has likely been a greater driver of dengue infection in high risk districts of Panama than *Ae.*
50 *albopictus*, and provide a discussion of possible public health implications of both spatial and non-
51 spatial model outcomes.

52 **Text Word Count: 3658**

53 **Introduction**

54 Dengue fever, a disease transmitted to humans by *Aedes* mosquitoes, is endemic to 128
55 countries, with 3.9 billion people considered at-risk [1]. Dengue fever cases have increased dramatically
56 worldwide throughout the previous several decades [2], likely a result of climate change [3],
57 urbanization [4], globalization [5], and the spread of the invasive *Aedes albopictus* [6]. As a result of
58 both recent and historical risk, many countries employ national surveillance programs to monitor trends
59 in dengue fever and inform local health authorities to the places and times where preventative practices
60 are most required. However, despite the commonality of these programs and unforeseen cost of cutting
61 them [7], surveillance budgets are often limited [8,9], restricting the scope and quality of the work. This
62 is concerning in developing regions such as Central America, where the burden of disease is high [1]
63 and per capita public health expenditure is among the lowest of any region of the world [10].

64 Surveillance of both viruses and vectors is an essential component of integrated disease
65 management programs that can be used to determine risk changes in space and time, thus providing the
66 evidence for more targeted prevention and control interventions [11]. Nevertheless, with few exceptions,
67 it is rare for surveillance programs to concurrently monitor both arbovirus cases and vector populations
68 in the same locations and at regular intervals. Most projections of disease risk used to justify public
69 health actions are derived purely from disease case data, ignoring vector population dynamics, which is
70 key aspect of the vector transmission model. This is particularly concerning when more than one vector
71 species is present, and little is known about their likely role in local transmission, which may result in
72 inaccurate or incomplete risk projection or case clustering models.

73 The Republic of Panama has been monitoring dengue cases alongside vector presence through
74 the National Department of Epidemiology (NDE) since 1988, making it one of the most long-standing
75 and successful surveillance programs of its kind in Latin America. Of the two known dengue mosquito
76 vectors, *Ae. aegypti* is considered resident to Latin America and Panama since the 19th century, and the
77 primary source of transmission [11] while *Ae. albopictus*, considered a secondary vector, has been
78 spreading throughout the region ever since it got introduced in Panama in 2004 [12,13]. Widespread
79 extirpation of *Ae. aegypti* by a superior ecological competitor like *Ae. albopictus* has occurred
80 throughout the world in recent decades [14–16], with unknown consequences on arbovirus transmission
81 risk. Encompassing this period of growing interspecific competition among two vector species,
82 Panama’s surveillance system is particularly unique and potentially useful to modelling dengue
83 transmission risk while considering *Aedes* species interaction. Attaining a better understanding of
84 dengue outbreak dynamics over time may improve the capacity of public health authorities to combat
85 the spread of other arboviruses, such as Zika Virus and Chikungunya Virus.

86 Our overall aim is to examine the influence that concurrent dengue case surveillance and *Aedes*
87 species monitoring can have on cluster detection and relative risk estimation. In so doing, we describe
88 the results of 13 years of dengue fever and *Aedes* surveillance data, including two competing vector
89 species plus virus data originating from long-term cooperatively organized surveillance programs. We
90 further assess whether dengue prevalence can be attributed to district socioeconomic attributes. We
91 believe this is the first effort to adjust for vector presence and absence in a disease cluster detection
92 model, which we hope sheds light on the characteristics of space-time clusters and relative risk
93 estimation of dengue after *Aedes* species are used as model covariates.

94

95 **Methods**

96 **Dengue Data**

97 We utilized dengue prevalence data collected by the National Department of Epidemiology
98 (NDE), housed within the Panamanian Ministry of Health (MINSa). Systematic national surveillance of
99 dengue cases in Panama have been continuous since 1988. Suspected cases are defined by a patient with
100 a fever and one or more of the following symptoms: headache, retro orbital pain, myalgia, exanthema,
101 rash, vomiting, malaise, leukopenia, and jaundice. A confirmed case is defined as a suspected case with
102 a positive dengue test, conducted using either viral isolation, reverse transcription polymerase chain
103 reaction (RT-PCR), IgM enzyme-linked immunosorbent assay platform (ELISA), or secondary IgG
104 ELISA. RT-PCR was established as the original standard by the National Reference Laboratory at the
105 Gorgas Memorial Institutes for Health Studies (ICGES) in 2003. Yet since 2009, MINSa established
106 national decentralization of serological confirmation of dengue using ELISA tests, which has improved
107 efficiency by allowing district health officials to confirm cases without needing to send samples to a
108 single central facility in Panama City. Data is recorded at the *Corregimiento*, or neighborhood, scale as
109 the number of confirmed cases in a given year at a given location. This is the lowest scale of data
110 granularity available, and thus, we do not have patient-level detail nor temporal detail at smaller units
111 than year.

112

113 **Vector Data**

114 We utilized vector data from the Vector Control Department (VCD) at MINSa. Systematic
115 entomological surveillance has occurred in Panama since 2000 in order to establish *Aedes* infestation
116 rates, and thus, areas of potential dengue transmission risk. Surveys of both *Ae. aegypti* and *Ae.*
117 *albopictus* are performed annually at the *Corregimiento*-scale and consist of solely larval surveillance.
118 Each year, a random block of houses is chosen and all houses in the block are searched for containers
119 holding *Aedes* larvae. The larvae are collected and allowed to mature to the fourth instar, at which point
120 they are taxonomically identified to species based on morphological keys [17]. The number of houses

121 positive for *Ae. aegypti*, *Ae. albopictus* or both are recorded in the raw datasets. However, because we
122 cannot confirm the number of houses in each block, we have transformed the data into a presence-
123 absence format in each *Corregimiento* rather than analyzing the number of positive houses.

124

125 **Data Analysis**

126 We conducted our analyses on dengue and vector data from 2005-2017, encompassing the period
127 in Panama when both *Ae. aegypti* and *Ae. albopictus* have been interacting. Overall, data was collapsed
128 from the original *Corregimiento* scale to the district scale. This is due to unreliable human population
129 estimates at scales smaller than the district. Population levels were required to compute prevalence rate
130 (x1000; PR), which was used as the dependent variable in the statistical analysis, rather than pure
131 number of cases, which does not consider the total number of potential virus hosts. Human population
132 data was gathered from the National Institute of Statistics and Census (INEC), which conducts a national
133 census every 10 years. We also gathered three socioeconomic metrics from INEC to use as covariates:
134 percentage of households with dirt floors, percentage of households without clean water, and percentage
135 of households without sanitary services. These covariates were chosen due to their relationship to
136 standing water, which may act as potential *Aedes* breeding habitat. Because the national census is only
137 conducted every ten years, we used the population levels from 2010 to calculate PR for data from 2005-
138 2017. While this is not ideal, and incurs inherent error in the year to year accuracy of the PR estimate,
139 there is no more frequent population estimate available. This is an unfortunately common situation,
140 especially in Central America, where no country conducts national population assessments more
141 frequently than every 10 years. The three socioeconomic variables are at their 2010 levels as well,
142 sourced from the same census as population.

143 We conducted two sets of analyses, non-spatial and spatial. The purpose of the spatial analyses
144 was exploratory, assessing the relationship between vector and virus in space and time. This was

145 conducted first, to establish a baseline understanding of how the addition of vector surveillance data
146 affects the estimation of the size and relative risk of case clusters. We followed the spatial modeling
147 with non-spatial statistical modelling, which served to test the hypotheses established by the spatial
148 models. Thus, the non-spatial models essentially serve to identify the significant covariates that can be
149 adjusted for in the spatial model

150 For the spatial analyses, we utilize discrete Poisson space-time modelling STSS [18], which
151 systematically moves cylindrical search windows across the geographic and temporal space to detect
152 space-time clusters. Essentially, STSS determines if the observed disease cases in a particular region
153 and time period exceed the expected cases under baseline conditions. In vector-borne disease research,
154 STSS have been used to examine outbreaks of dengue [19–21], chikungunya [22], malaria [23,24],
155 Chagas [25], and West Nile [26,27], for example. STSS have also been used to examine the co-
156 circulation of dengue and chikungunya in Colombia [28].

157 The cylinders are centered on the centroids of the Panamanian districts while the base of a
158 cylinder is defined as the spatial scan, and the height of a cylinder represents the temporal scan. The
159 number of observed and expected dengue cases are computed for each cylinder. Conceptually, a vast
160 number of cylinders of various space-time dimensions are generated until an upper bound is reached,
161 while each cylinder is a potential cluster. For this study, the maximum spatial scan was set to 25% of
162 the total population in Panama, while the maximum temporal scan was set to 4 years. A Poisson-based
163 likelihood ratio is calculated for each cylinder, which is proportional to $(n/\mu)^n [(N-n)/(N-\mu)]^{N-n}$
164 [29]. For the parameters, μ is the expected number of dengue cases in a cylinder, and n is the total
165 observed dengue cases in the cylinder. The expected number of dengue cases is computed by
166 multiplying the fraction of population that lives within the cylinder (p) by the total number of cases in
167 Panama (C) divided by the total population (P), that is: $E[c] = p * C / P$ - The cylinder with the highest
168 likelihood ratio is the most likely space-time cluster. To evaluate the statistical significance of the

169 candidate space-time clusters, 999 Monte Carlo simulations are performed under the null hypothesis that
170 there are no significant clusters. Subsequently, we report secondary space-time clusters with a p-value
171 less than 0.05.

172 For this study, we ran four STSS models: (1) dengue cases only; (2) dengue cases controlled for
173 the presence and absence of *Ae. aegypti* and/or *Ae. albopictus* (i.e. absence of both species, *Ae. aegypti*
174 presence, *A. albopictus* presence, and presence of both species); (3) dengue cases controlled for *Ae.*
175 *aegypti* presence/absence only; and (4) dengue cases controlled for *Ae. albopictus* presence/absence
176 only. For the covariate adjusted models, the expected number of dengue cases is defined the same way
177 for the non-adjusted model, but includes covariate category *i*. That is: $E[c] = \sum_i p_i * \frac{C_i}{P_i}$. In other words,
178 the adjusted STSS searches for clusters “above and beyond that which is expected due to these
179 covariates” (47). For each model, we also report the relative risk of prevalence in each district that
180 belongs to a space-time cluster, which is defined as $(c/e)/[(C - c)/(C - e)]$, where *c* is the total
181 observed dengue cases in a particular district; *e* is the expected cases in a district; and *C* is the total
182 observed dengue cases in the country of Panama. Clusters with a relative risk > 1 indicates that there
183 were more observed dengue cases than expected under baseline conditions. We created all maps in
184 ArcGIS [30].

185 In the non-spatial analyses we used generalized linear models (GLM; McCullagh & Nelder,
186 1972) with a log linkage to determine if dengue PR could be predicted by the presence of *Ae. albopictus*
187 alone, *Ae. aegypti* alone, the presence of both species, and the three socioeconomic attributes of the
188 district. In addition, we tested whether the presence of *Ae. aegypti* was negatively associated with the
189 occurrence of *Ae. albopictus*, which has been proposed by previous studies describing a pattern of
190 spatial displacement. GLMs are robust and capable of being applied to data without homogeneous
191 variance or normality. They have been utilized in a variety of studies on the public health implications of
192 *Aedes* mosquito ecology [32–34].

193

194 **Results**

195 From 2005-2017, there were a total of 49,910 cases of dengue fever in Panama, with 2009 and
196 2014 being the most severe at 6,941 and 7,423 cases respectively. These two years represented 28% of
197 the total dengue cases during the 13-year period. Additionally, at the start of the sample period, *Ae.*
198 *albopictus* was only present in 1 district, yet by 2017 had been found in 53 districts. It exhibited a
199 slightly increasing trajectory throughout time and has been present in the same number of districts as *Ae.*
200 *aegypti* since 2016. Surveillance of *Ae. aegypti* indicated fluctuating presence throughout the sample
201 period, with presence ranging from 48-57 districts (Fig 1).

202

203 **Fig 1. Number of districts containing each *Aedes* species from 2005-2017.**

204

205 The results of our space-time modelling detected the presence of five clusters in each of the four
206 models, varying by cluster center and duration (Figs 2-5; Table 1). Incorporating covariates into the
207 models had considerable effects on the duration, relative risk (RR), and spatial extent of clusters (Table
208 2). The model adjusting for the presence of *Ae. aegypti* encompassed the greatest spatial range and
209 highest number of districts with a RR > 1, while the model adjusting for the presence of *Ae. albopictus*
210 encompassed the smallest spatial range and the lowest number of districts with a RR > 1. The duration
211 of the space-time clusters is notably different when adding the vector surveillance data to the model,
212 however, the one exception is cluster 1 for each model (most likely cluster). For example, the duration
213 of cluster 2 was 2015-2017 for the no covariate and *Ae. aegypti* model; while the *Ae. albopictus* and
214 *Aedes* (both) model reported a duration of only 1 year, which occurred six years earlier (2009).
215 Furthermore, cluster 2 was found in different geographic locations for the *Aedes* (both) and *Ae.*
216 *albopictus* models. This variation in duration of the clusters between the four models is a result of

217 adjusting for the presence of *Aedes* during the 13-year study period. In other words, the start, end, and
 218 duration of the clusters is substantially affected by the presence of one or more *Aedes* species. The
 219 relative risk may be higher if *Aedes* was found in a district during the entire duration of a space-time
 220 cluster. During the 13 years of our study period combined with the 63 districts containing data (13 * 63
 221 = 819), *Ae. aegypti* was present 690 times, *Ae. albopictus* was present 245 times, while both *Aedes*
 222 species were found in a district 224 times. As a result, the difference in species presence during the
 223 study period partly explains why the clusters for the *Ae. albopictus* model contained 19 less districts
 224 than the *Ae. aegypti* model, and 10 less districts than the model adjusting for both species.

225

226 **Table 1. Space-time dengue fever clusters.**

Cluster	Center of Cluster	Duration (years)	p-value	Observed	Expected	Relative Risk	Districts	Cluster Population
No covariates								
1	Balboa	2013-2015	p<0.01	5,846	1,270.83	5.1	5	368,341
2	Santa Maria	2015-2017	p<0.01	2,013	482.25	4.3	3	139,778
3	Colon	2009	p<0.01	1,402	237.54	6	1	206,553
4	Changuinola	2005-2007	p<0.01	1,734	394.85	4.5	2	114,445
5	Capira	2014	p<0.01	1,914	721.3	2.7	9	627,220
Adjusting for <i>Aedes</i> presence & absence								
1	Balboa	2013-2015	p<0.01	5,846	1,670.20	3.8	5	368,341
2	Baru	2009	p<0.01	2,019	408.4	5.1	11	492,942
3	Colon	2009	p<0.01	1,402	188.2	7.4	1	206,553
4	Calobre	2015-2017	p<0.01	2,120	511.5	4.1	4	162,315
5	Arraijan	2005-2006	p<0.01	1,923	608	3.2	1	220,779
Adjusting for <i>Ae. albopictus</i> presence & absence								
1	Balboa	2013-2015	p<0.01	5,846	1,636.70	3.9	5	368,341
2	Colon	2009	p<0.01	1,402	178.4	8	1	206,553
3	Changuinola	2005-2007	p<0.01	1,734	296.5	6	2	114,445
4	Santa Maria	2015-2017	p<0.01	2,013	445	4.6	3	139,778
5	Arraijan	2005-2006	p<0.01	1,923	591.4	3.3	1	220,779
Adjusting for <i>Ae. aegypti</i> presence & absence								

1	Balboa	2013-2015	p<0.01	5,846	1,318.90	4.9	5	368,341
2	Colobre	2015-2017	p<0.01	2,019	544.6	4	4	162,315
3	Colon	2009	p<0.01	1,402	247.2	5.8	1	206,553
4	Baru	2009	p<0.01	2,120	535.3	3.9	11	492,942
5	Capira	2014	p<0.01	1,923	745.9	3.1	10	652,859

227

228 **Table 2. Characteristics of each space-time model**

Model	Total number of districts	RR 0-1 (# of districts)	RR > 1 (# of districts)	Highest RR	Most observed cases
No covariates	20	9	11	Bocas Del Toro (5.2)	San Miguelito (13,109)
Both <i>Aedes</i> species	22	12	10	Santiago (2.9)	San Miguelito (13,109)
Only <i>Ae. albopictus</i>	12	4	8	Bocas del Toro (6.2)	San Miguelito (13,109)
Only <i>Ae. aegypti</i>	31	17	14	San Miguelito (3.3)	San Miguelito (13,109)

229

230 **Fig 2. Space-time clusters of dengue fever without adjusting for *Aedes* presence and absence in**
 231 **Panama (A); Relative risk for districts belonging to a significant space-time cluster (B). Map**
 232 **created using ArcGIS [30] and data from The Panamanian Ministry of Health.**

233

234 **Fig 3. Space-time clusters of dengue that adjusts for both *Aedes* species presence and absence in**
 235 **Panama (A); Relative risk for districts belonging to a significant space-time cluster (B). Map**
 236 **created using ArcGIS [30] and data from The Panamanian Ministry of Health.**

237

238 **Fig 4. Space-time clusters of dengue fever that adjusts for *Ae. albopictus* presence and absence in**
 239 **Panama (A); Relative risk for districts belonging to a significant space-time cluster (B). Map**
 240 **created using ArcGIS [30] and data from The Panamanian Ministry of Health.**

241

242 **Fig 5. Space-time clusters of dengue fever that adjusts for *Ae. aegypti* presence and absence in**
 243 **Panama (A); Relative risk for districts belonging to a significant space-time cluster (B). Map**
 244 **created using ArcGIS [30] and data from The Panamanian Ministry of Health.**

245

246 The results of our GLM indicate that dengue PR can be predicted by the presence of *Ae. aegypti*
 247 alone, with all other covariates exhibiting insignificant statistical relationships to PR ($P > 0.05$), with
 248 covariate selection employed. Thus, controlling for all other factors, districts with a presence of solely

249 *Ae. aegypti* exhibited an increase in adjusted PR of 1.0933 ($P = 0.001$). Additionally, the presence of *Ae.*
250 *albopictus* did not predict the presence of *Ae. aegypti* ($P > 0.05$).

251

252 **Discussion**

253 Our non-spatial statistical testing complements the space-time models, highlighting the likely
254 role of *Ae. aegypti* in dengue transmission dynamics across Panama as well as the need to incorporate
255 vector data into systematic dengue risk projections. In the model where *Ae. aegypti* presence and
256 absence was accounted for, more than double the number of districts were contained in clusters than the
257 model where *Ae. albopictus* presence and absence was accounted for. The *Ae. aegypti* model also
258 contained the highest number of districts with a relative risk > 1 , indicating more dengue cases than
259 would be expected given baseline population levels. Findings are further supported by our determination
260 that *Ae. aegypti* is the only predictor of dengue PR in the non-spatial model, which holds important
261 implications for the understanding of dengue transmission dynamics in the changing landscape of vector
262 ecology. As an invasive species that has systematically replaced *Ae. aegypti* throughout numerous
263 regions in its endemic range [14], *Ae. albopictus* has been spreading throughout Panama for the previous
264 13 years [12,13]. Our results illustrate that it has not been a key driver of dengue prevalence throughout
265 its time occurring in the country, but that more importantly, there is reason to believe that dengue rates
266 may decrease as the species further proliferates, extirpating *Ae. aegypti* from its resident range within
267 Panama. Globally, while *Ae. albopictus* has been implicated in several small outbreaks [35], the majority
268 of dengue serotypes are thought to be transmitted by *Ae. aegypti*, due to its preference for both
269 urbanized habitat [16,36] and human hosts [37,38].

270 Perhaps curious is the lack of association found with the other covariates, which included the
271 presence and absence of *Ae. albopictus*, coexistence of both species, and the three socioeconomic
272 variables. There have been a number of studies addressing the vector status and potential of *Ae.*

273 *albopictus*. While it is biologically capable of transmitting dengue fever [6], outbreaks that can be
274 directly attributed to this species are rare [35,39–41]. The lack of contribution of socioeconomic
275 variables is also interesting, given socioeconomic conditions have been found to influence vector
276 distribution [42–44]. However, no clear connection has been found between dengue risk and particular
277 socioeconomic conditions [45], thus supporting our results. Overall, based on our findings, we suggest
278 that vector surveillance results be incorporated into vector control planning. Specifically, focusing on
279 regions where *Ae. aegypti* still maintains a stronghold may be an effective way of combating dengue
280 outbreaks. Balboa, for example, was identified as a cluster in all four models and had a steady presence
281 of *Ae. aegypti* throughout the sample period as well as increasing presence of *Ae. albopictus* since 2006.
282 This district is relatively rural with approximately 2400 people spread across 400km² area. It is possible
283 that vector control efforts in Balboa are not as frequent or efficacious as in the more populated regions,
284 yet this hypothesis would require field testing to confirm. Another district, San Miguelito in
285 metropolitan Panama City, contained the most observed cases during our study period, despite being
286 only 49.9km². This district can be characterized by high density housing and residents of relatively low
287 socioeconomic status. The staggering number of cases should be a cause for concern, yet its small
288 geographic area may facilitate public health interventions such as vector control and community
289 education. Overall, now that the identification of high risk districts at the national scale has been
290 completed and informed by vector presence, the subsequent step of illustrating the comparative
291 characteristics of each district relative to dengue transmission risk can be undertaken. Understanding
292 what caused Balboa and San Miguelito to experience such high relative risk, for example, is the next
293 task necessary for adjusting public health interventions to effectively address the needs and conditions of
294 each district.

295 Despite the longevity of our data and thoroughness of the surveillance efforts, there are clear
296 considerations and limitations of our work which we would like to see addressed in future studies. First,

297 it is possible that the reported cases of dengue in certain districts are travel cases (seeking treatment in a
298 district different than actual residence), therefore, adjusting for the presence of *Aedes* can shed light on
299 the districts where an individual is more likely to get infected with dengue, not necessarily where all
300 total cases were recorded. The lack of population data for more than one year across such a lengthy
301 period is a considerable shortcoming of this work. While the frequency of a census in Panama is on par
302 with much of Latin America, this greatly impacts our ability to determine accurate prevalence rates year
303 to year. Since linear interpolation is often inaccurate for non-linear trends like population growth rate,
304 we would like to see more frequent population assessments conducted in regions where dengue is an
305 ongoing risk, and while we understand that resources may not easily allow for this, the role of national
306 census efforts in public health is often under-appreciated. Second, the cylindrical shape of the clusters
307 does not represent the true shape of the clusters, while it is possible to use irregular search windows [46–
308 48]. Third, the STSS reports the relative risk for the entire study period, while relative risk will likely
309 vary temporally. A final core limitation is the vector surveillance methods employed. Values are
310 reported as the number of houses containing larvae of each respective species. No information is given
311 on the number of houses surveyed, and thus we were forced to transform the data into presence and
312 absence. Had the total number of surveyed houses been reported, we would have been able to compute
313 each district's infestation rate, which would have provided a scaled and more nuanced independent
314 variable to compare to dengue PR.

315 Overall, it is key to recognize that adding vector surveillance data as a covariate changes the
316 location, duration, and relative risk of dengue case clusters. Although unadjusted cluster analysis is a
317 valuable tool for public health officials to identify high risk areas of vector-borne disease, our study
318 illustrates the role that incorporating relevant covariates can play in altering the model output. While this
319 has been demonstrated in cancer [49,50], this is the first use of covariates in space-time cluster detection
320 modelling of neglected tropical disease. With this comes potential to expand into other classes of

321 covariates. For example, in addition to vector surveillance data, we support the incorporation of
322 additional covariates such as vector genetic background, climate, vegetation, and land cover to dengue
323 cluster models. Furthermore, the differences reported for the clusters of dengue after adjusting for vector
324 presence merit further small-area studies to determine local-scale characteristics that may assist in
325 targeted intervention campaigns. Vector surveillance clearly provides valuable information in the
326 determination of virus case clusters, and thus should be conducted alongside virus surveillance so that it
327 may be included in modelling efforts. We intend for this exploratory study to inspire future
328 investigations into the vector status of *Ae. albopictus* as well as the role of vector surveillance in public
329 health planning efforts. We hope Panama's robust dengue surveillance program can stand as a model for
330 practitioners elsewhere, where current surveillance may be less thorough.

331

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340

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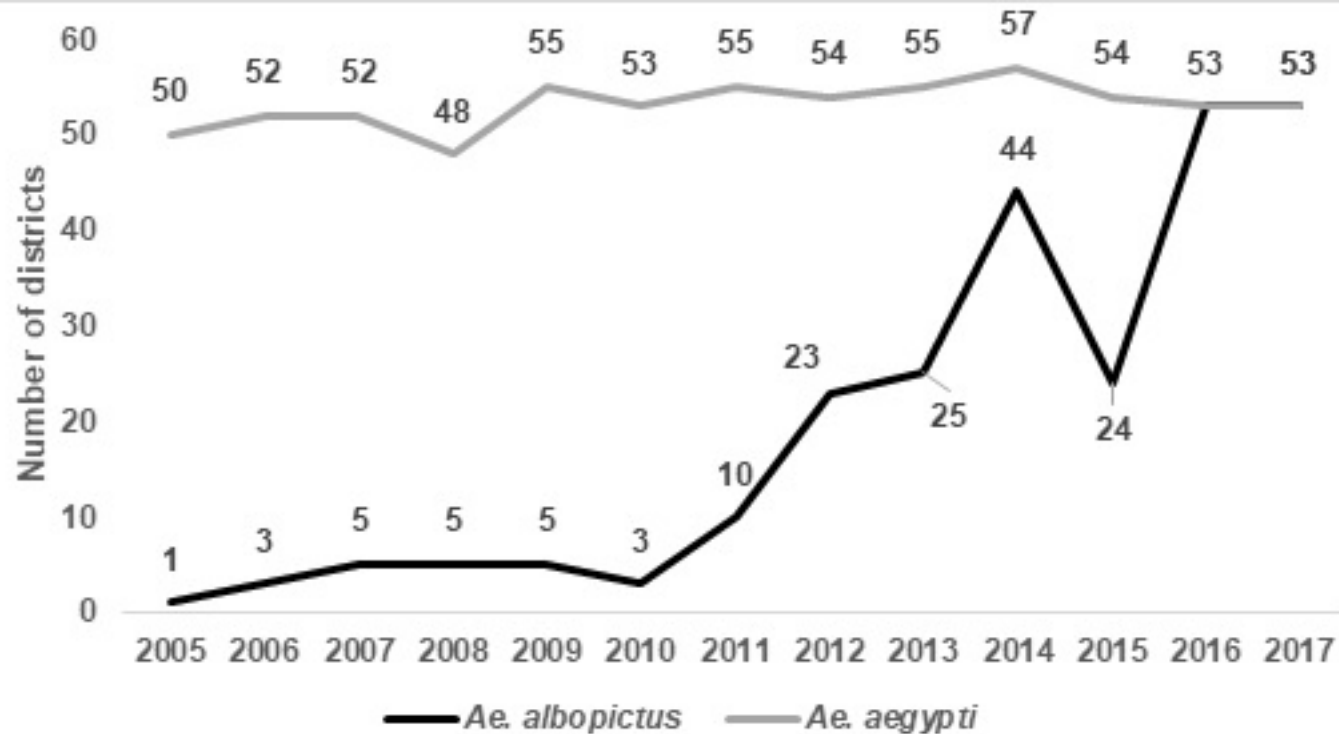
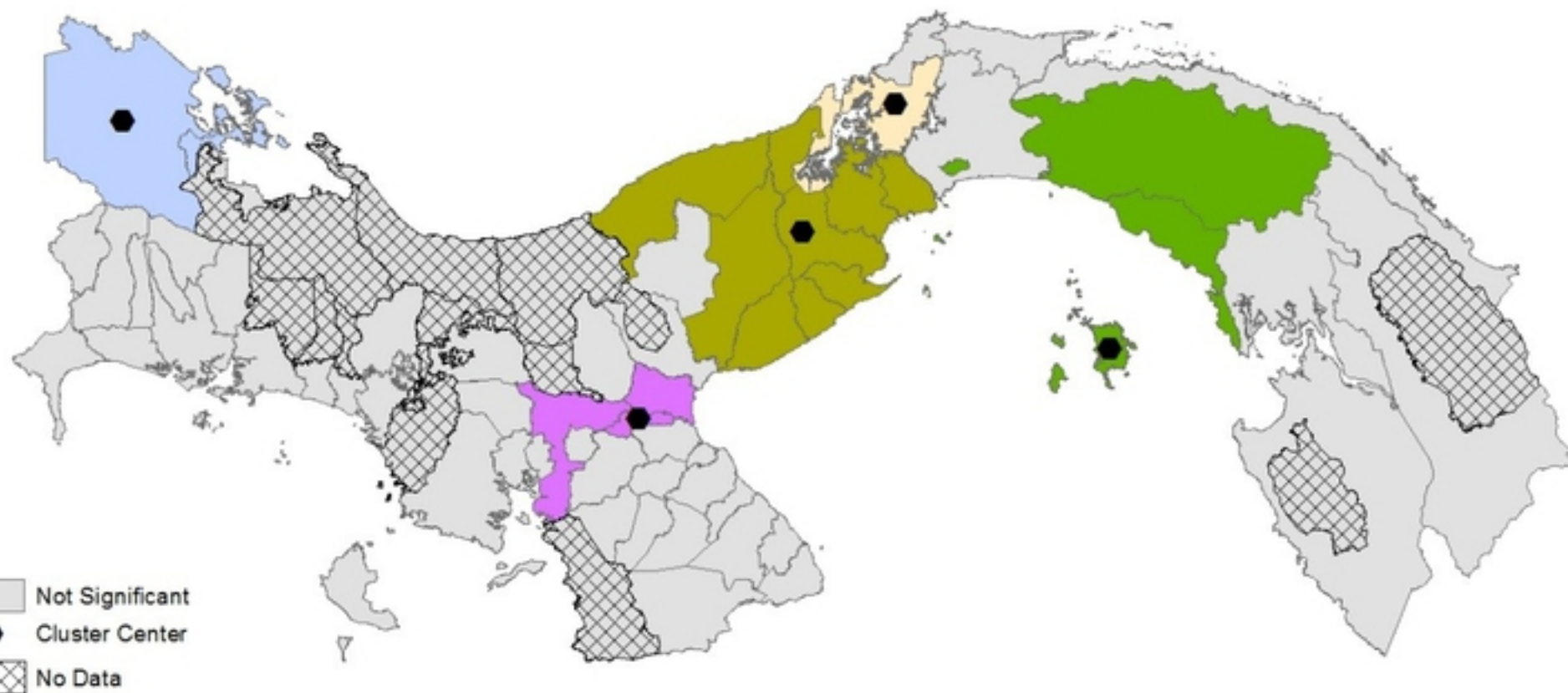
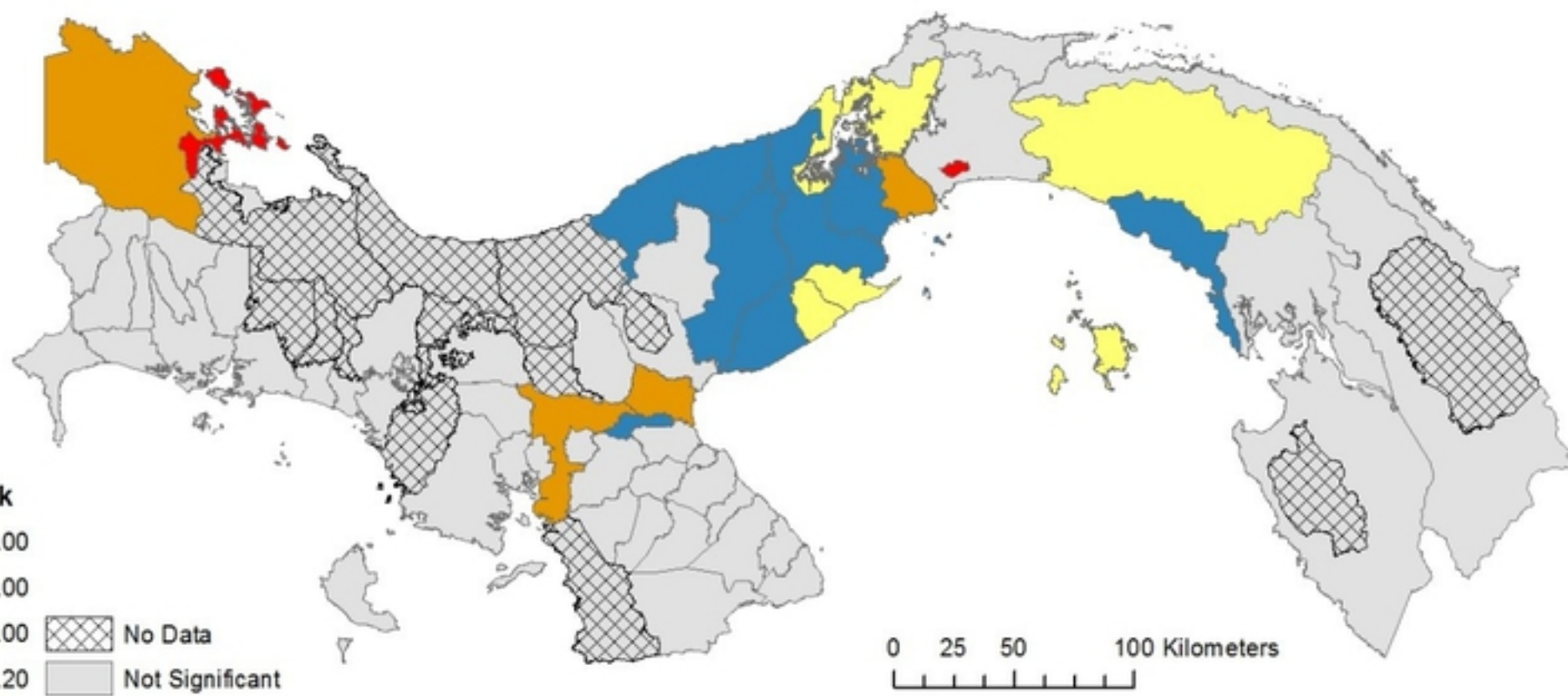
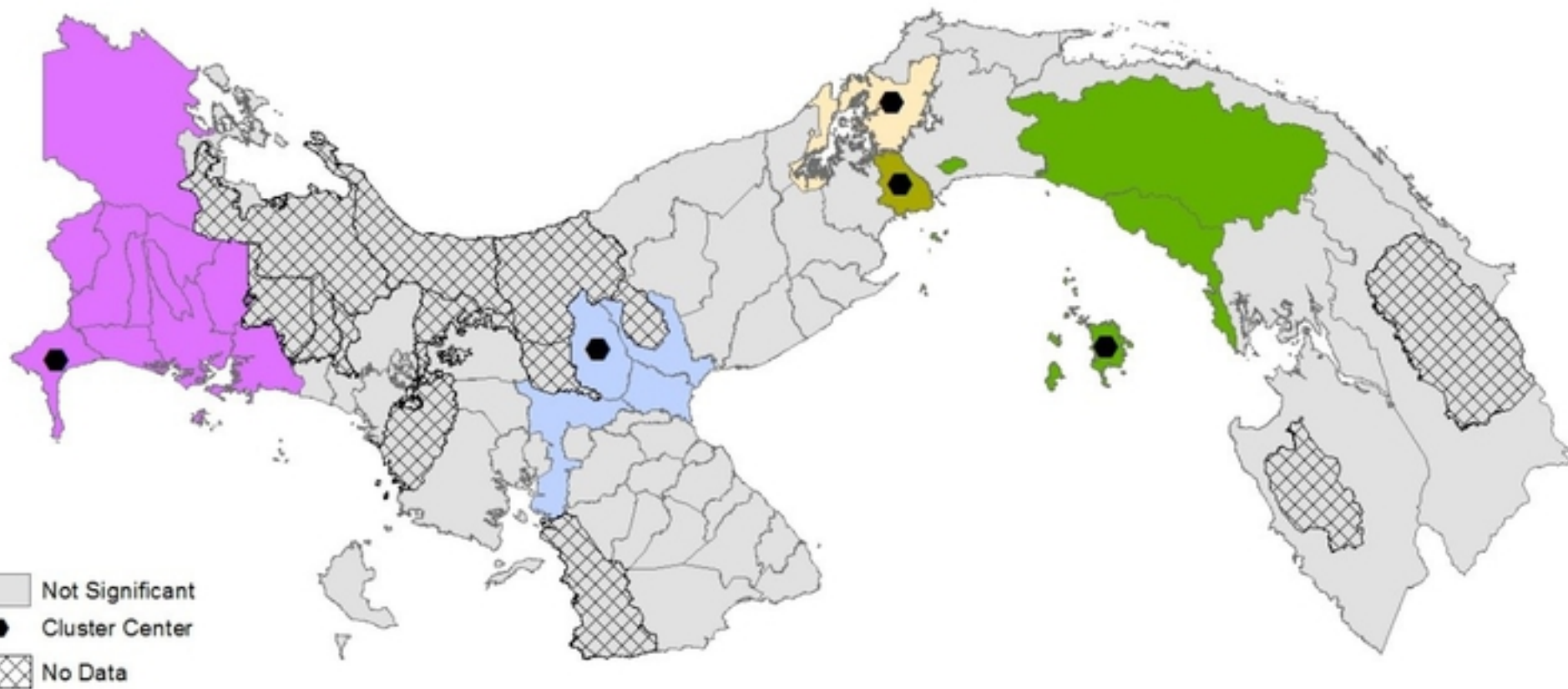
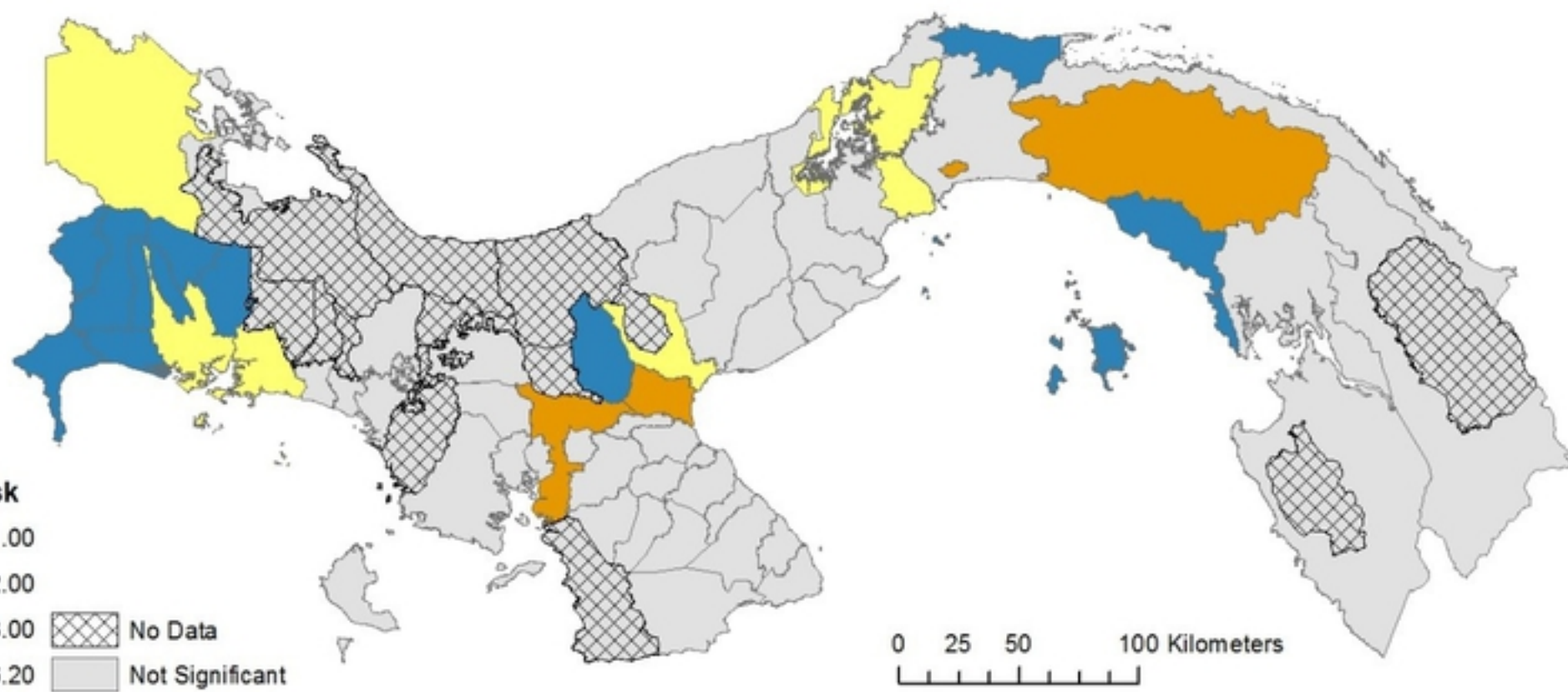
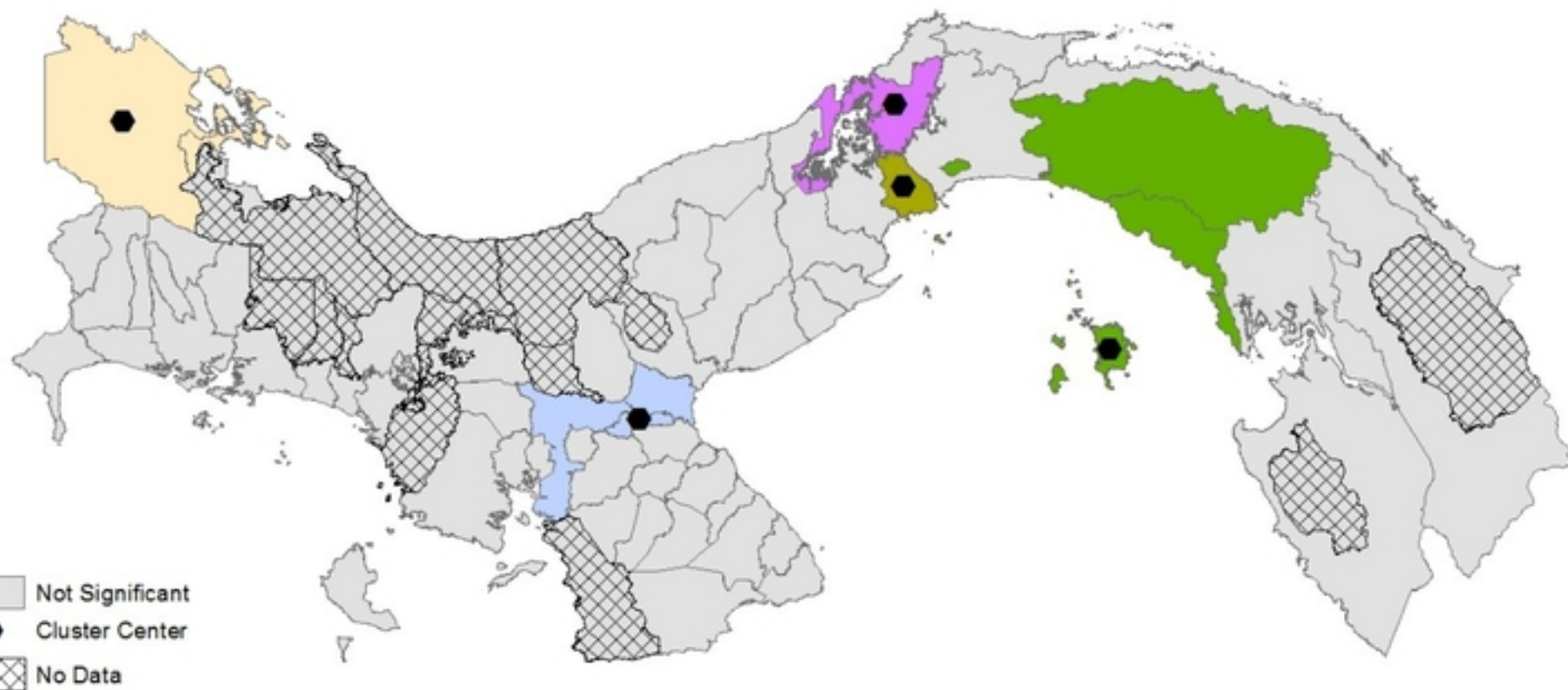


Figure 1

A**B****Figure 2**

A**B****Figure 3**

A



B

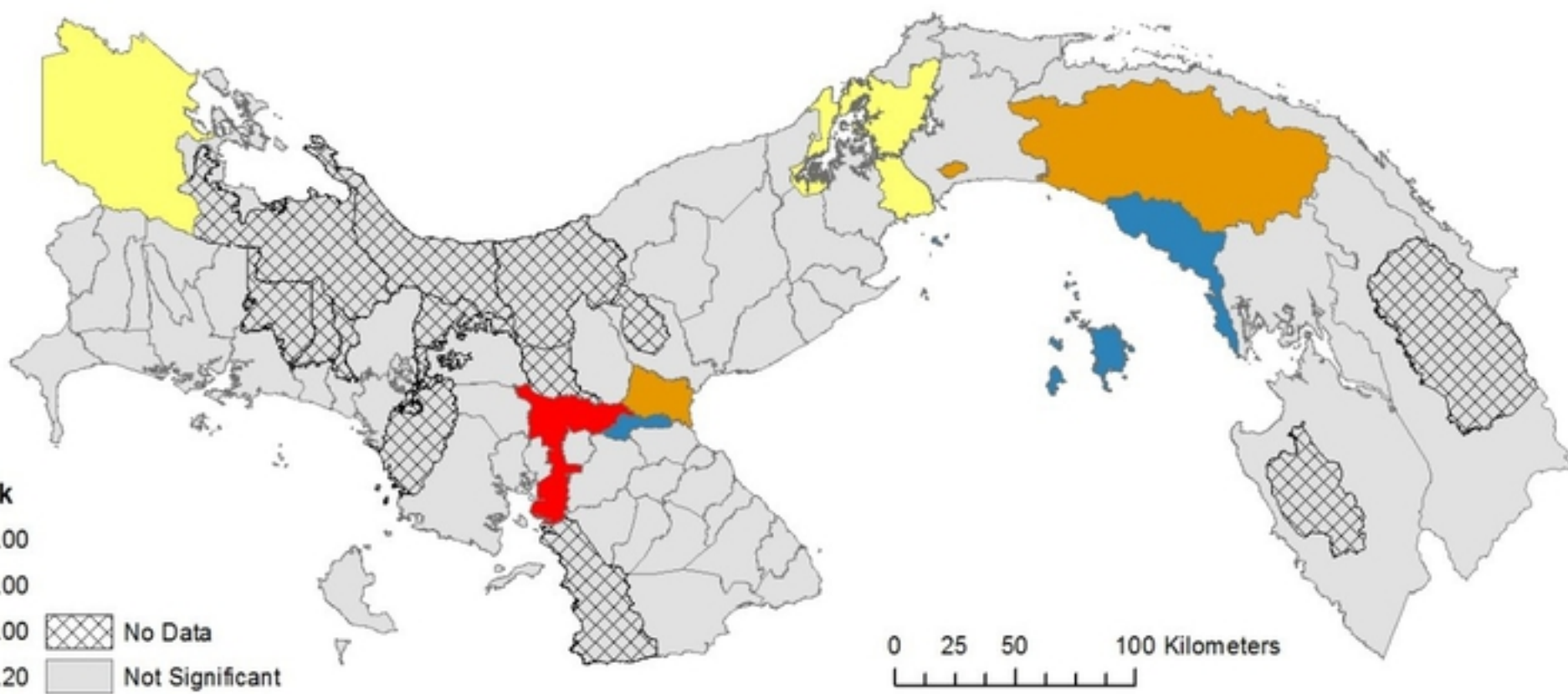
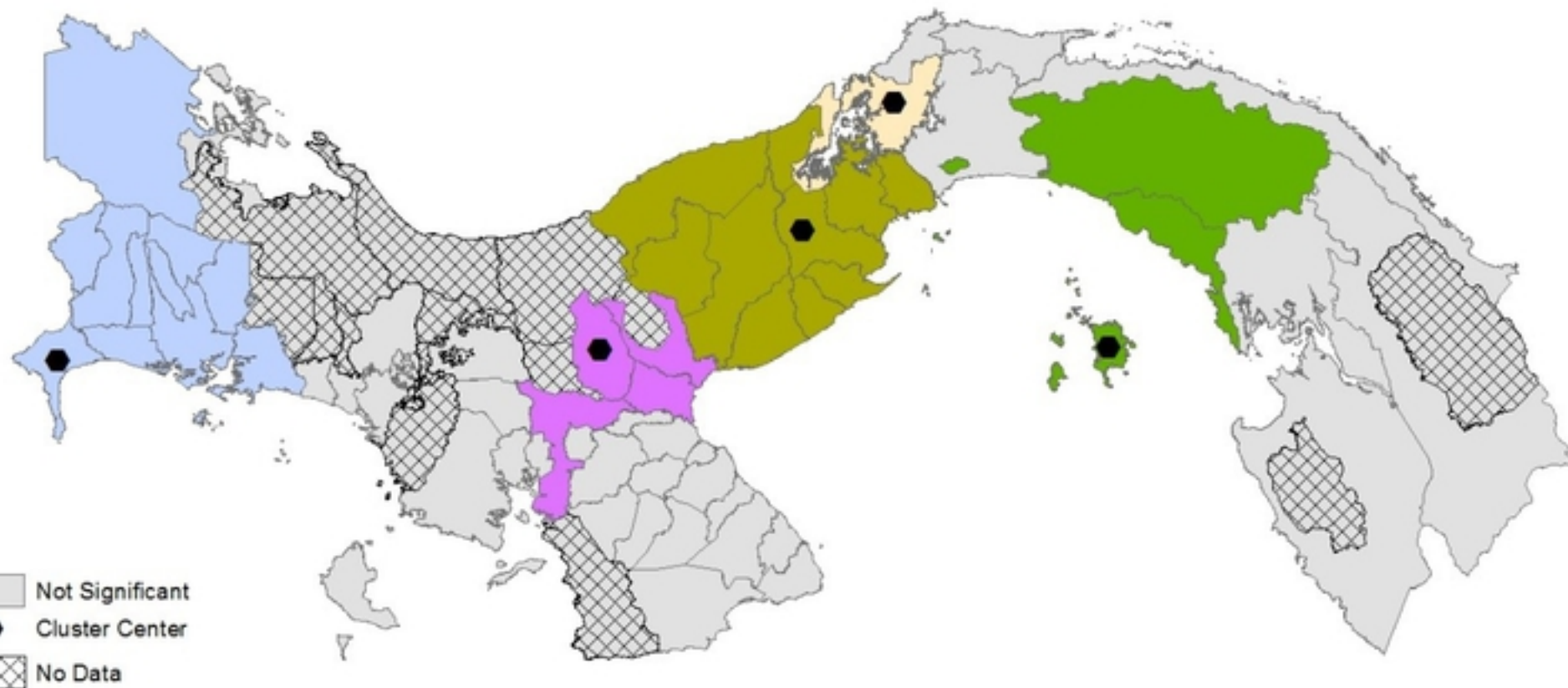


Figure 4

A



B

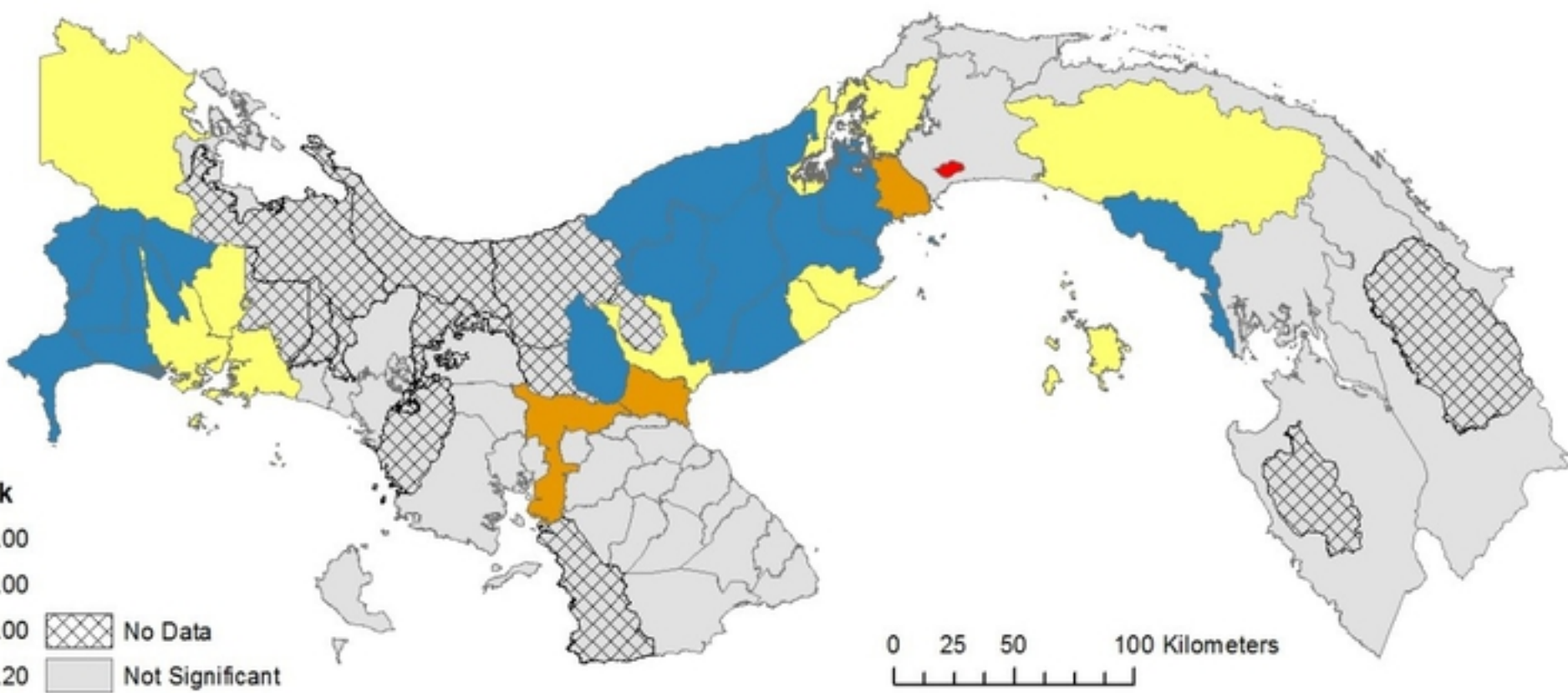


Figure 5