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► To cite this version:

Estrella Cruz, Ferdinand Salazar, Ariza Aguila, Jennifer Ramos, Richard E. Paul. Current and lagged associations of meteorological variables and *Aedes* mosquito indices with dengue incidence in the Philippines. 2024. pasteur-04667765v1

HAL Id: pasteur-04667765

<https://pasteur.hal.science/pasteur-04667765v1>

Preprint submitted on 25 Apr 2024 (v1), last revised 5 Aug 2024 (v2)

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1 **Title: Current and lagged associations of meteorological variables and *Aedes* mosquito**
2 **indices with dengue incidence in the Philippines**

3 Short title: Meteorological variables and mosquito indices for predicting dengue incidences.

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17

18

19 **Abstract**

20 **Background**

21 Dengue is an increasing health burden that has spread throughout the tropics and sub-tropics.
22 There is currently no effective vaccine and control is only possible through integrated vector
23 management. Early warning systems to alert potential dengue outbreaks are currently being
24 explored but despite showing promise are yet to come to fruition. This study addresses the
25 use of meteorological variables for predicting both entomological indices and dengue
26 incidences and assesses the added value of additionally using entomological indices for
27 predicting dengue incidences.

28 **Methodology/Principal Findings**

29 Entomological surveys were carried out monthly for 14 months in six sites spread across three
30 environmentally different cities of the Philippines. Meteorological and dengue data were
31 acquired. Non-linear generalized additive models were fitted to test associations with the
32 meteorological variables and both entomological indices and dengue cases. Rain and the
33 diurnal temperature range (DTR) contributed most to explaining the variation in both
34 entomological indices and number of dengue cases. DTR and minimum temperature also
35 explained variation in dengue cases occurring one and two months later. The number of adult
36 mosquitoes did associate with the number of dengue cases, but contributed no additional
37 value for predicting dengue cases.

38 **Conclusions/Significance**

39 The use of meteorological variables to predict future risk of dengue holds promise. The lack
40 of added value of using entomological indices confirms several previous studies and given the
41 onerous nature of obtaining such information, more effort should be placed on improving
42 meteorological information at a finer scale to evaluate efficacy in early warning of dengue
43 outbreaks.

44 **Author summary**

45 Dengue is a widespread mosquito-borne disease. Mosquitoes are sensitive to temperature
46 and rainfall and hence there have been efforts to identify such variables for predicting dengue
47 outbreaks. Several mosquito indices are measured routinely by national surveillance systems,
48 but which vary considerably in their success of predicting dengue outbreaks. This study
49 explored the current and lagged associations of meteorological variables with mosquito
50 indices and dengue incidence. Associations of mosquito indices with dengue were also
51 explored. Rain and the diurnal temperature range (DTR) contributed most to explaining the
52 variation in both entomological indices and number of dengue cases. DTR and minimum
53 temperature also explained variation in dengue cases occurring one and two months later.
54 Mosquito indices did not provide any additional predictive power of dengue incidences. Given
55 the onerous nature of measuring mosquito indices, advanced warning systems might be
56 improved using meteorological variables measured at finer scales than that traditionally
57 available.

58 **Introduction**

59 Dengue is a rapidly spreading mosquito-borne infectious disease caused by any of the
60 four serotypes of the dengue virus (DENV 1-4). Despite the known underestimation of its real
61 global burden [1], it is estimated that dengue incidence has increased 30-fold over the last few

62 decades [2]. The disease is endemic in over 100 countries and more than 3.5 billion people are
63 at risk of DENV infection [3,4]. Southeast Asia and the Western Pacific have historically been
64 and are still among the most affected places [5-8].The public health significance of dengue in
65 the Philippines has continued since its initial discovery in 1954 to date [9]. The exceptionally
66 high numbers of reported infections incidence and dengue-associated mortality cases in a
67 span of five years, from 2010 to 2014, claiming at least 812,525 victims and resulting in nearly
68 3,500 deaths, illustrates the high burden in the population.

69 Several environmental and socio-economic factors such as weather, urbanisation and
70 globalisation have been associated with the spread of dengue [10-14] and this spread depends
71 on the presence and abundance of the arthropod vector [15]. Moreover, in light of recent
72 anthropogenic environmental impact, there has been a growing concern over global climate
73 change as a potential factor increasing the risk of dengue through both the increased
74 distribution of the mosquito vector species and the increased capacity for the vector to
75 transmit the virus (the vectorial capacity) [16, 17].

76 DENV transmission is shaped by climatic conditions such as temperature and rainfall
77 [18]. *Aedes spp.* reproductive and feeding behaviours, as well as viability of the species,
78 depend, at least partly, on these environmental variables and thus have been widely studied.
79 Mosquito abundance is partially regulated by rainfall by providing breeding sites and
80 triggering egg hatching [19]. Temperature influences the life span of the mosquito vector and
81 has a direct effect on developmental and feeding rates [19-21]. In addition to this, DENV
82 replication inside the vector also increases in warmer temperatures [21, 22].

83 Having no fully effective vaccine to prevent infection, or drugs to treat the infection,
84 vector control is still the main strategy to prevent transmission of DENV. Vector monitoring

85 and surveillance is an evidence-based, analytic approach to better understand the mosquito
86 vector population dynamics and virus transmission. Combined with a community-based
87 strategy, which requires direct and immediate action in the community using Integrated
88 Vector Management practices and Communication for Behavioral Impact approaches, vector
89 surveillance offers the best defense against the vector and disease [23-25]. In urban settings,
90 the major vector species is *Aedes aegypti*, which has adapted to the peridomestic
91 environment, ovipositing in man-made artificial containers. Several *Aedes* indices, such as the
92 House, Container, Breteau and Pupal indices, have been proposed for monitoring strategies
93 to predict risk of dengue transmission. However, to date there is little consensus on the
94 appropriate threshold values to trigger a mosquito control response and their general utility
95 to avert an outbreak [26-30].

96 Identifying the factors that are implicated in DENV transmission and being able to
97 forecast the onset of dengue outbreaks in endemic areas would provide the opportunity to
98 be prepared and implement timely responses to decrease the burden of dengue in human
99 populations. Efforts have been made to predict the incidence of infection using meteorological
100 data [31, 32]. However, our understanding remains poor over the relative contributions of
101 meteorological variables to these indices in the context of urban settings where the
102 microenvironment and the abundance of artificial oviposition sites impact mosquito
103 abundance [17]. While other prevention and control measures for dengue are being
104 developed, understanding the relationship between the risk of disease and meteorological
105 factors in an urban setting for elaborating early warning systems remains of key interest.

106 The aim of this study was to expand the current knowledge on the associations between
107 different meteorological variables and both the *Aedes* indices and the incidence of dengue

108 and to identify the meteorological and mosquito indices that provide advanced warning of
109 dengue outbreaks in three representative cities in the Philippines.

110

111 **Methods**

112 ***Study sites (Figure 1)***

113 The study was carried out in six barangays, of which two were in each of the three study cities,
114 Manila and Muntinlupa on the major island of Luzon and Puerto Princesa on Palawan island.
115 In the highly densely populated area of Manila, two barangays were selected: Sampaloc,
116 Manila ($14^{\circ} 36' 39.708''\text{N } 120^{\circ} 59' 46.4496''\text{E}$) covering 7.90 km^2 with a population of 388,305
117 and Tambunting, Santa Cruz District, Manila ($14^{\circ}37'46.3''\text{N } 120^{\circ}59'01.5''\text{E}$) covering 3.07 km^2
118 with a population of 126,735. In the more recently urbanized and less dense city of
119 Muntinlupa, two barangays were selected: Cupang ([14°25'53.4"N 121°2'55"E](#)) covering 5.37
120 km^2 with a population of 57,013 inhabitants and Putatan ([14°23'54.12"N 121°2'10.96"E](#))
121 covering 6.75 km^2 with a population of 99,725. On the island of Palawan, which has a much
122 lower degree of urbanization and population density, two urban barangays were chosen
123 within Puerto Princesa, a coastal city covering $2,381 \text{ km}^2$ with a population of 307,079. Two
124 selected barangays were: San Miguel ($09^{\circ}44'39.48''\text{N } 118^{\circ}44'44.16''\text{E}$), considered an urban
125 barangay with a population of 21,157 and San Pedro ($09^{\circ}45'19.44''\text{N } 118^{\circ}45'2.52''\text{E}$) a
126 neighboring urban barangay with a population of 25,909.

127

128 **Figure 1. Study Sites**

129

130 ***Entomological, meteorological and dengue case data***

131 Entomological surveys were carried out monthly from November 2014 until December 2015,
132 thus 14 months duration. Dengue case data were available monthly from October 2014 until
133 December 2015. Meteorological data were available on a daily basis, provided by the
134 Philippine Atmospheric, Geophysical and Astronomical Services Administration (PAG-ASA)
135 from meteorological stations closest to the areas under study. Meteorological data included
136 rain, relative humidity and temperature. From these data the cumulative monthly rain (mm),
137 the monthly mean daily rain (mm), the monthly mean daily Relative Humidity (%), the monthly
138 mean daily minimum, maximum and mean temperatures (°C) and the monthly mean daily
139 Diurnal Temperature Range (DTR, °C) were calculated.

140 Mosquito indices: Immature mosquito life stages surveillance was conducted in 100
141 households per selected barangay wherein all water-holding containers were inspected for
142 presence of immature stages of mosquito. Larvae and pupae found in the containers were all
143 collected by pipetting. Specimens from each positive container were transferred in separate
144 ice plastic bags for transport to the laboratory for rearing and identification. The number of
145 water-holding containers (artificial or natural) with or without cover that were found indoors
146 or outdoors, together with the number of containers found positive for larvae and/or pupae
147 were recorded. The number of people who slept inside the house the previous night was also
148 noted. The following indices were used: the Container Index (CI, number of water-filled
149 containers positive for larvae or pupae), the House Index (HI, number of houses found positive
150 for larvae or pupae), the Breteau index (BI, the number of containers positive divided by the
151 number of houses visited), the Pupal Index (PI, the number of pupae divided by the number
152 of houses visited x 100), the number of pupa per person (PPI, the number of pupae divided by

153 the total population of the inspected households). In addition to these immature *Aedes* spp.
154 mosquito stage indices, adult mosquitoes were captured in the houses using a sweep net each
155 month. Adult mosquitoes were collected by circumnavigating the internal periphery of the
156 house from the front door to the different rooms while continually moving the net in a figure
157 of eight at 90° or at 180° targeting known resting places of adult mosquitoes. These areas
158 include areas under the beds, hanging clothes, under sink, comfort rooms, closet, dark cool
159 room of the house shoe racks, and outdoors such as vegetation, bushes, tree hook and plants.
160 Trapped mosquitoes were transferred to Styrofoam cups with the use of sucking tube. All
161 collected mosquitoes were identified morphologically to species in the laboratory. In addition
162 to the monthly adult *Aedes* spp. mosquito count, a cumulative two-monthly count was
163 calculated.

164 ***Statistical analyses***

165 To test the association of the meteorological variables with the entomological indices, a
166 Generalized Additive model (GAM) was fitted to account for any non-linearity in the
167 relationships. For indices concerning proportions (i.e. House Index and Container Index), a
168 logistic regression was fitted. For the indices concerning counts, a loglinear regression was
169 fitted. First all variables were fitted in a univariable analysis and those achieving a P-value less
170 than 0.25 were fitted in the multivariable analysis. Barangay was nested within City. The
171 multivariable analysis proceeded by step-wise elimination of non-significant variables until a
172 final adequate model containing only significant variables was achieved. Because many of the
173 variables were strongly correlated (i.e. the min, mean and max temperature variables), and
174 thus led to collinearity and potentially spurious non-significance, models were refitted with
175 removal and replacement to identify which of the variables were the most strongly associated
176 (based on % variance explained). For the analyses of the association of the meteorological

177 variables with the number of dengue cases, a similar approach was performed but including
178 the natural log of the population of each barangay as an offset. When using the entomological
179 indices as explanatory variables, the data were transformed either by using an arcsine
180 transformation for the proportion/percentage indices or by standardization for the count
181 indices (subtraction of the mean and division by the standard deviation). A dispersion
182 parameter was estimated to account for any over-dispersion of the data. All analyses were
183 conducted in Genstat version 22 [33].

184

185 **Results**

186 ***Description of city specific meteorological variables, dengue cases and mosquito catches***

187 Rainfall showed distinct seasonality, with the dry season from January to April and the peak
188 rainy season from July to October (Fig. S1). There was little variation among the three cities,
189 with the monthly mean of the daily rainfall varying from 0.014-14.35 mm in Muntinlupa, 0-
190 9.24 mm in Manila and 0-10.16 mm in Palawan. Relative humidity was consistently lower from
191 February to June in all three cities (Fig. S2). Palawan varied the least over the year (73.7-82.5%)
192 as compared to Manila (61.8-84.6%) or Muntinlupa (65.8-81.0%). Maximum temperatures
193 reached a peak from April to June (Maximum 35°C in Manila, 34-35°C in Muntinlupa and 32-
194 33°C in Palawan) (Fig. S3). Year round temperatures varied little with minimum temperatures
195 oscillating around 24-27°C and mean temperatures around 25-31°C (Fig. S4 and Fig. S5).
196 Temperatures varied little across the three cities but were generally less variable in Palawan
197 as compared to Manila and Muntinlupa. The same was seen for the Diurnal Temperature
198 Range with a peak from March to June (8-9°C) and higher values in Manila and Muntinlupa
199 than Palawan (6-9°C vs. 6-8°C) (Fig. S6).

200 Over the study period, dengue cases were concentrated from July-December 2015. Overall,
201 there were 343 and 369 in Tambunting and Sampaloc (Manila), respectively, 76 and 240 in
202 Cupang and Putatan (Muntinlupa), respectively and 188 and 110 in San Miguel and San Pedro
203 (Palawan). Dengue Incidence rates (IR) per 10,000 individuals were initially low (0-5.2 / 10000)
204 until July when an epidemic occurred, notably in San Miguel, Palawan, with IRs ranging from
205 9.0-28.4 / 10000 (Figure 2).

206

207 **Figure 2.** Dengue Incidence Rate per 10,000 individuals in the six study sites.

208

209 Overall 85.4% of the immature mosquito stages were *Aedes aegypti*, 12.3% *Aedes albopictus*
210 and 2.4% *Culex* or other genus spp. In the Luzon study sites (Manila and Muntinlupa), 96.8%
211 were *Ae. aegypti*, 1.9% were *Ae. albopictus* and 1.4% *Culex* or other genus spp. In the two
212 Palawan study sites, 79.5% were *Ae. aegypti*, 17.5% *Ae. albopictus* and 2.9% *Culex* or other
213 genus spp. For the adult mosquito catches, 50.5% were *Ae. aegypti*, 0.2% *Ae. albopictus* and
214 49.3% *Culex* or other genus spp. For the subsequent calculation of mosquito indices, only
215 *Aedes* spp. numbers were used. Because of the differing relative abundance of *Ae. albopictus*
216 in Palawan, for the association of mosquito indices with weather variables we first analyzed
217 all the sites together and then the two Palawan and four Luzon sites alone.

218 ***Association of meteorological variables with mosquito indices***

219 The House indices (HI) were very high, reaching 50% in some sites in the months following the
220 onset of the rains in July (Mean Rain Figure S1 & House Index Fig. S7). Indices were highest in
221 San Pedro and San Miguel in Palawan and Putatan in Muntinlupa, the latter being

222 exceptionally high as compared to the other sites during the dry season, reaching 20%.
223 Association analyses revealed that in addition to the variation explained by location (27.2%
224 variance explained), meteorological variables explained 57.4% of the observed variation in HI
225 (Table 1). Cumulative monthly rainfall and mean daily rainfall showed the same relationship
226 with HI, where HI increased gradually before reaching a plateau at ~150mm for Cumulative
227 monthly rain and ~5mm for mean daily rain per month (See Supplementary Figure S8 for Fitted
228 plot of HI against Cumulative Rain). The monthly mean of the Diurnal Temperature range
229 exhibited an increase in HI to a peak at 6-6.5°C before a subsequent decline (Figure 3).

230

231 **Figure 3.** The fitted logistic regression of the House Index (here shown as a proportion) against
232 the Diurnal Temperature range. The red line shows the fitted model in the GAM.

233

234 **Table 1.** Association of meteorological variables with Mosquito indices.

		P value	variance explained (%)
House Index	Cumulative Rain (mm)	<.001	13.37
	Mean DTR (°C)	<.001	20.71
	Mean Rain (mm)	<.001	15.10
	Mean RH (%)	<.001	5.01
	Min. Temp. (°C)	0.01	3.22
Container Index	Cumulative Rain (mm)	<.001	15.25
	Mean DTR (°C)	<.001	20.19
	Mean Rain (mm)	<.001	6.45
	Mean RH (%)	0.001	5.39

	Min. Temp. (°C)	<i>0.016</i>	3.34
Breteau Index	Cumulative Rain (mm)	<.001	14.94
	Mean DTR (°C)	<.001	25.16
	Mean Rain (mm)	<.001	14.57
	Mean RH (%)	0.001	4.14
Pupal Index	Min. Temp. (°C)	0.002	3.82
	Cumulative Rain (mm)	<i>0.009</i>	6.90
	Mean DTR (°C)	<.001	17.38
	Mean Rain (mm)	<i>0.009</i>	6.85
	Mean RH (%)	<i>0.007</i>	7.30
	Min. Temp. (°C)	<i>0.011</i>	6.61
Pupa per person	Max. Temp. (°C)	<i>0.043</i>	3.58
	Cumulative Rain (mm)	<i>0.007</i>	6.94
	Mean DTR (°C)	<.001	18.03
	Mean Rain (mm)	<i>0.013</i>	6.14
	Mean RH (%)	0.006	7.19
	Min. Temp. (°C)	<i>0.01</i>	6.44
Adults	Max. Temp. (°C)	<i>0.033</i>	3.78
	Cumulative Rain (mm)	<.001	36.26
	Mean DTR (°C)	0.006	4.76
	Mean Rain (mm)	0.006	4.82
	Mean RH (%)	<.001	7.22
	Min. Temp. (°C)	<.001	14.42
	Max. Temp. (°C)	0.003	4.52

235 P values in italics are those above the Bonferroni corrected P threshold for multiple tests (7
 236 meteorological variables, plus one multivariable analyses, thus 8 models per index; P=0.0063).

237

238 Container indices (CI) were substantially lower, generally less than 5%, except reaching a
239 maximum of 17% in San Pedro following the rains (Figure S9). Once again, CIs were higher
240 following the rains in San Pedro, Palawan and during the dry season in Putatan, Muntinlupa.
241 The same relationships were observed with the meteorological variables as for HIs, explaining
242 50.6% of the variation in CIs (Table 1).

243 Breteau indices in the two sites in Manila never exceeded a $BI \geq 5$ (Figure S10). In Cupang,
244 Muntinlupa, $BI > 5$ occurred on three occasions but Putatan was consistently higher than 5 and
245 again showed aberrantly high values (10-23) during the dry months. Values in the two sites in
246 Palawan were consistently very high throughout the year except for the dry season months
247 (February to June); values reached over 100 in San Pedro and 9-23 in San Miguel during the
248 dengue epidemic period from July onwards in 2015. The same associations and relationships
249 with meteorological variables were observed, explaining 63% of the variation in BI (Table 1).

250 The Pupal and Pupa per person indices (PI and PPI) were highly variable ranging from 0 to over
251 100% (Figure S11 and Figure S12). With the exception of Putatan, which showed the
252 aberrantly high pupal indices in the dry season months, PIs were generally zero during the dry
253 season and then rapidly increased in the months following the rains. The same meteorological
254 associations were observed, albeit generally weaker than those observed for the HI, CI and BI.
255 However, these variables still explained 49% of the observed variation in PI and PPI (Table 1).

256 In contrast to these immature stage indices, adult *Aedes spp.* were less abundant in the two
257 Palawan sites and most abundant in Putatan, especially during the dry season (Figure S13).
258 The relationship of the meteorological variables with the number of adult *Aedes spp.*
259 mosquitoes also differed (Table 1). There was a strong association with Cumulative rain, with

260 progressively increasing numbers of *Aedes* spp. adults caught with increasing rain (Figure S14).
261 There was a distinct non-linear relationship with minimum temperature, with a peak at 25-
262 26°C (Figure S15). The strength of the relationships with the other meteorological variables
263 was much weaker, but combined overall explained 72% of the observed variation.

264 Analysis of the two sites on Palawan separately from the Luzon study sites revealed a similar
265 but simpler series of relationships with the meteorological variables. For HI, CI and Breteau,
266 Cumulative rain and DTR were significantly associated (Cumul. Rain: % variance explained
267 43.8%, 39.8% and 46.9% for HI, CI and Breteau respectively; DTR explained 13.1%, 14.2% and
268 17.3% of the variance for HI, CI and Breteau respectively). For the Pupal Index, Cumulative
269 rain and Relative Humidity explained 28.4% and 31.0% of the variance. For the PPI, Cumulative
270 rain, DTR and Relative Humidity explained 26.2%, 17.5% and 20.4% of the variance. Finally, for
271 the adults, Cumulative rain and DTR were significantly associated, explaining 44.3% and 27.2%
272 of the variance.

273 ***Association of meteorological variables with lagged mosquito indices***

274 The association analyses were then repeated for lag periods of one to four weeks. Monthly
275 values of the meteorological variables were thus calculated for the weeks preceding the
276 mosquito index counts. With the exception of the Pupal Index, lagged associations explained
277 less of the observed variation in the mosquito indices (Table S1). For the Pupal Index, variables
278 lagged by two weeks explained 52.9% of the variation as compared 48.6% for the unlagged
279 associations. In both cases there was a notable decrease in PI with increasing DTR (Figure S16)
280 and a significant increase in PI with increasing Cumulative rain (Figure S17).

281 ***Association of meteorological variables with dengue cases***

282 There were several associations of meteorological variables with the number of dengue cases
283 during the same month (Table 2). There was a gradual increase in the number of cases with
284 increasing rain (both Cumulative and monthly daily mean) (Figure 4) and Relative Humidity.
285 Dengue cases peaked at a maximum temperature of 32-33°C, a minimum temperature of 25-
286 26°C and a DTR of 6.5-7°C (Figure S18 for the association with DTR). Overall the meteorological
287 variables explained 60.4% in the variation of observed cases. Assessing the association with
288 dengue cases the following one or two months explained less of the variation (38.9% and
289 39.3% respectively) and the rain variables became non-significant. However, the associations
290 with DTR, RH and especially Minimum temperature remained significant and followed the
291 same form (Figure 5).

292

293 **Table 2** Association of meteorological variables with dengue cases.

	Variable	P value	variance explained (%)
Cases same month	Cumulative Rain (mm)	<.001	15.02
	Mean DTR (°C)	0.001	8.36
	Mean Rain (mm)	<.001	15.32
	Mean RH (%)	<i>0.01</i>	5.75
	Min. Temp. (°C)	<.001	11.54
	Max. Temp. (°C)	<i>0.012</i>	4.39
Cases 1 month later	Mean DTR (°C)	0.002	10.90
	Mean RH (%)	<i>0.018</i>	7.32
	Min. Temp. (°C)	<.001	20.63
Cases 2 months later	Mean DTR (°C)	0.001	11.38
	Mean RH (%)	0.003	9.68

Min. Temp. (°C) <.001 18.20

294 8 models per analysis. Bonferroni P value threshold $P=0.0063$. P values in italics are those
295 above this threshold.

296

297 **Figure 4.** Fitted model of the association between Cumulative rain and dengue cases in the
298 same month. Shown are the observed data (crosses) and the fitted model (red line).

299

300 **Figure 5.** Mean Daily Minimum Temperatures and the number of dengue cases one month
301 later

302

303 Analyzing the two Palawan sites independently of the four Luzon sites revealed a much
304 improved model fit, with Cumulative rain, DTR and Relative Humidity explaining 71.3% of the
305 variation in the number of dengue cases in the same month. Moreover, Cumulative rain, DTR
306 and Mean maximum temperatures explained 73.9% and 71.7% of the variation in cases one
307 and two months later respectively. The model fit for the association of the meteorological
308 variables with the number of dengue cases two months later is shown in Figure 6. 10.2% of
309 the variation was accounted for by the site (San Miguel vs. San Pedro). Likewise, when
310 analyzing the four sites on Luzon independently of Palawan gave a much improved model fit,
311 explaining 69.5%, 48.1% and 77.9% of the variation in dengue cases the same month and one
312 and two months later. Minimum temperatures and DTR contributed the most. The model fit
313 for the association of the meteorological variables with the number of dengue cases two

314 months later is shown in Figure 7. However, when analyzing Muntinlupa and Manila
315 separately, there was no improved model fit from when analyzing all four Luzon sites together.

316 **Figure 6** Fitted model of meteorological variables with the observed number of dengue cases
317 two months later in the two study sites on Palawan. Observed values shown by the blue line
318 and fitted values by the orange line. The X-axis is the observation month for each of the two
319 study sites starting from the beginning of the study until the end. Thus months 1 & 2 will be
320 the first observation months of San Miguel and San Pedro respectively and so forth.

321

322 **Figure 7** Fitted model of meteorological variables with the observed number of dengue cases
323 during the same month in Luzon. Observed values shown by the blue line and fitted values by
324 the orange line. The X-axis is the observation month for each of the two study sites starting
325 from the beginning of the study until the end. Thus months 1-4 will be the first observation
326 months of Cupang, Putatan, Sampaloc and Tambunting respectively and so forth.

327

328 ***Association of mosquito indices with dengue cases***

329 Whilst Container, House and Breteau indices and cumulative adult mosquitoes (over 2
330 months) were all associated with dengue cases in the same month in the univariable analyses,
331 only the latter was positively associated with dengue cases in the final multivariable analysis
332 ($t=3.32$, $P=0.001$), explaining 4.79% of the variation in the number of dengue cases (Figure
333 S19). There was an increased Relative Risk of 1.52 (95%CI 1.18-1.95) for every increase in one
334 mosquito in the standardized mosquito number, equivalent to a Relative Risk of 1.02 (95% CI
335 1.01-1.03) for every increase in one mosquito (unstandardized). This positive association was

336 lost when combined with the meteorological variables. There were no associations of
337 mosquito indices with dengue cases the following one or two months.

338

339 **Discussion**

340 Meteorological conditions can influence the spread of dengue through their impact on the
341 vector's life cycle and ability to transmit the virus. This study aimed to expand the knowledge
342 on the associations and their time lags between different meteorological variables and
343 mosquito indices on the one hand and dengue incidence on the other. This study also aimed
344 to assess the added value of incorporating the entomological indices in explaining variation in
345 dengue incidence.

346 There were several non-linear associations between meteorological variables and the
347 immature entomological indices, namely HI, CI, BI, PI and PPI. The most pertinent variables
348 were those associated with rain (whether cumulative or mean daily rain over the month) and
349 the DTR. These variables explained 49-63% of the variation in the immature indices. The rain
350 variables showed a distinct plateau, with increasing indices up a certain level of precipitation
351 but not beyond. Heavy rain has been suggested to result in a decrease in immature mosquito
352 indices by flushing out the immature stages, thus decreasing its population and ability to
353 transmit the disease [32, 34]. This study found no evidence of a decrease as might be expected
354 if excess rain lead to flushing of the oviposition sites. The plateauing out of the indices with
355 increasing rain might reflect a saturation in the number of available water-filled oviposition
356 sites. Although the number of potential containers increases with population density, a
357 modelling study on the relationship between human and mosquito densities has previously
358 suggested that water container number likely does not keep increasing after a given number

359 of humans is reached [35]. The non-linear relationship of immature indices with DTR is a well-
360 recognised phenomenon whereby larval developmental time and time to pupation is
361 impacted by higher DTR [36, 37]. Furthermore, Carrington et al. found that both small and
362 large DTRs can affect the population dynamics [38].

363 In contrast to the immature indices, the adult mosquito numbers were most strongly
364 influenced by minimum temperatures and Cumulative rain, with moderate effects of the other
365 meteorological variables. No plateau in adult mosquito numbers was observed with increasing
366 Cumulative rain, but which may reflect the weak correlation between immature and adult
367 numbers. The association with minimum temperature most likely reflects the more general
368 effects of temperature on adult longevity with peak survival rates occurring round 27°C and
369 increased mortality rates occurring above 32°C [39-41]. The temperature variables are all
370 highly correlated and thus the minimum temperature *per se* may not be the most biologically
371 important.

372 The absence of any improved model fitting when using entomological indices lagged by one
373 to four weeks after the meteorological variables suggests that the current month's weather is
374 that impacting the current month's mosquito numbers. It should be noted, however, that
375 although there was not an improved model fit, the meteorological variables did explain a
376 substantial amount of the observed variation, ranging up to 64% for a four week lag with adult
377 mosquitoes (as compared to 72% for the same month's weather). This relatively strong
378 association might be of value for an advanced warning index. In addition, the absence of
379 improved lag effects may also reflect the relatively low variation in the meteorological
380 variables over such a short time period and a longer time frame might be more informative,
381 especially with respect to the adult population density following the dry season.

382 Similarly to previous studies, most meteorological variables had a non-linear association with
383 the incidence of dengue [32, 42, 43]. Temperature fluctuations have an impact on the
384 mosquito's life span, development, reproduction rates, and feeding frequency, as well as the
385 speed of virus replication and extrinsic incubation rate [19, 44]. Low temperatures have been
386 associated with a decreased vector capacity, and here we clearly observed an accelerating risk
387 of dengue beyond a minimum temperature of $\sim 22^{\circ}\text{C}$. High temperatures have also been found
388 to be associated with decreased risk of dengue, generating a non-linear pattern [21, 32, 42,
389 45]. This is also observed in the present study, with a trend for decreased dengue incidence at
390 temperatures beyond 33°C . A suggestive decrease in dengue risk was also observed beyond
391 34°C in Guangzhou [46]. Previous estimates of threshold temperature values for increased risk
392 of dengue incidence, all from Guangzhou, China have identified values of ca. $18\text{-}23^{\circ}\text{C}$ and 22-
393 32°C for minimum and maximum temperature thresholds [46-48]. The values we found fall
394 within the same range.

395 Lower diurnal temperature ranges have been associated with a higher spread of the dengue
396 [20]. Moreover, less temperature variation during the day can also coincide with an optimal
397 temperature mean for dengue transmission. A modelling approach found that decreased
398 temperature variation around the predicted optimal temperature ($\sim 29^{\circ}\text{C}$) increases the
399 chances of viral transmission [21]. This negative association between temperature variation
400 and dengue incidence was observed here and found only to lead to reduced risk at DTR above
401 6.5°C . Below this DTR, mean temperatures ranged from $27\text{-}29^{\circ}\text{C}$, suggesting an optimal
402 combination of temperatures for transmission.

403 Rainfall can increase dengue transmission, generating more abundant oviposition sites and
404 maintaining a sufficient relative humidity for adult mosquito survival [19]. A positive

405 association with cumulative rainfall was observed here, with incidence increasing with as little
406 as 100mm rainfall in a month. The similarity in the shape of the relationship of rain with adult
407 mosquitoes and rain with dengue cases would suggest that this latter is occurring through the
408 increase in adult mosquito numbers. This is supported by the observation of a positive
409 association of cumulated adult mosquito numbers and dengue incidence.

410 When analysing the study sites on the island of Palawan separately from those on Luzon led
411 to vastly improved model fit, especially for dengue cases occurring two months later. The
412 same occurred when analysing the Luzon sites separately from the Palawan sites, but no
413 added value was observed when analysing each city within Luzon separately. It is tempting to
414 hypothesise that the weather variables are differentially affecting the two *Aedes* species that
415 have differing relative abundances on the two islands with knock-on effects for explaining
416 variation in dengue incidence. That the significantly associated meteorological variables
417 remained over one to two months lag time is consistent with previous findings and potentially
418 useful for any advanced warning strategy [32, 42]. Such long delayed effects are biologically
419 plausible, reflecting the delay between amplification of the mosquito population, initial
420 spread and subsequent expansion of the viral population. DENV has a lifecycle taking a
421 minimum of 15 days, including a ~10 day extrinsic incubation period within the mosquito
422 following an infective bloodmeal and then a 4-10 day intrinsic incubation period following an
423 infectious bite on a human. Two months lag would thus correspond to a maximum of three
424 generations of viral transmission even with an adequate mosquito population density.
425 Furthermore, given that the majority of DENV infections are inapparent, the consequences of
426 expanding viral circulation identified through clinical cases would take longer [49].

427 There are several limitations to this study. Firstly, we only had 14 months dengue case data
428 upon which to base our analyses, but which was carried out in six sites on two environmentally
429 differing islands. Secondly, even though we had meteorological data from each of the cities,
430 we had no more specific information at the scale of each site and thus could not include a
431 spatial element in the analyses. Intra-annual spatial variation in incidence was observed, but
432 may more likely reflect the known clustered nature of dengue outbreaks and the impact of
433 herd immunity [50, 51]. Whilst meteorological variables likely vary at very local scales,
434 disentangling the relative roles of immunity, clustering and meteorology will require fine-scale
435 measures of serology, meteorology and case geolocalisation.

436 In conclusion, there have been increasing efforts to establish early warning and response
437 systems using meteorological information, but which although promising have often proven
438 country-specific [31, 32, 52]. The clear associations of meteorological variables and the
439 mosquito indices is encouraging and yet it seems that the link between such indices and
440 dengue incidence remains non-significant. Only adult mosquitoes showed any positive
441 association, but far weaker than when using meteorological variables. In short, given the
442 considerable effort required to obtain such entomological indices and their lack of any added
443 value for predicting dengue outbreaks, further emphasis on meteorological variables at a
444 more local scale might be a more promising route of investigation.

445

446 **Acknowledgements**

447

448 **References**

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604

605 **Supplementary Information captions**

606 **Figure S1** Mean Daily Rain (mm) by month in each of the three cities. Shown are means and
607 standard errors of the mean.

608 **Figure S2** Mean Daily Relative Humidity (%) by month in each of the three cities. Shown are
609 means and standard errors of the mean.

610 **Figure S3** Mean Daily Maximum Temperature (°C) by month in each of the three cities. Shown
611 are means and standard errors of the mean.

612 **Figure S4** Mean Daily Minimum Temperature (°C) by month in each of the three cities. Shown
613 are means and standard errors of the mean.

614 **Figure S5** Mean Daily Mean Temperature (°C) by month in each of the three cities. Shown are
615 means and standard errors of the mean.

616 **Figure S6** Mean Daily Diurnal Temperature Range (°C) by month in each of the three cities.
617 Shown are means and standard errors of the mean.

618 **Figure S7** House Indices per month in the six study sites. Shown are % and 95% Confidence
619 Intervals.

620 **Figure S8** Fitted logistic regression model of House Index (here given as a proportion) against
621 Cumulative Rain during the month. Red line shows the model output for the association of
622 cumulative rain with HI and the actual data are crosses.

623 **Figure S9** Container Indices per month in the six study sites. Shown are % and 95% Confidence
624 Intervals.

625 **Figure S10** Breteau Indices per month in the six study sites.

626 **Figure S11** Pupal Indices per month in the six study sites.

627 **Figure S12** Pupa per Person Indices per month in the six study sites.

628 **Figure S13** Number of adult Aedes spp. per month in the six study sites.

629 **Figure S14** The fitted loglinear regression of the number of adult Aedes spp. mosquitoes
630 against the monthly Cumulative rain. The red line shows the fitted model in the GAM.

631 **Figure S15** The fitted loglinear regression of the number of adult Aedes spp mosquitoes
632 against the monthly mean minimum temperature. The red line shows the fitted model in the
633 GAM.

634 **Figure S16** The fitted loglinear regression of the lagged 2 week Pupal Index against the
635 monthly mean Diurnal Temperature range. The red line shows the fitted model in the GAM.

636 **Figure S17** The fitted loglinear regression of the lagged 2 week Pupal Index against the
637 monthly cumulative rain. The red line shows the fitted model in the GAM.

638 **Figure S18** The fitted loglinear regression of the mean Diurnal temperature range against the
639 number of dengue cases the same month. The red line shows the fitted model in the GAM.

640 **Figure S19** The fitted loglinear regression of the standardized cumulative adult mosquitoes
641 against the number of dengue cases the same month. The red line shows the fitted model in
642 the GAM.

643 **Table S1** Association of meteorological variables with lagged mosquito indices. For each index
644 we do 4 (lag weeks) x7 (meteorological variables) univariable analyses plus 1 multi per lag
645 week so 29. Bonferroni correction P value = 0.0017. P values in italics are those above this P
646 value threshold.

647

648 **Data reporting:** Data are freely available on Figshare private link:
649 <https://figshare.com/s/0c5efc295eac6a3f09b5> and doi: [10.6084/m9.figshare.23978448](https://doi.org/10.6084/m9.figshare.23978448)

650



Legend



Figure 1

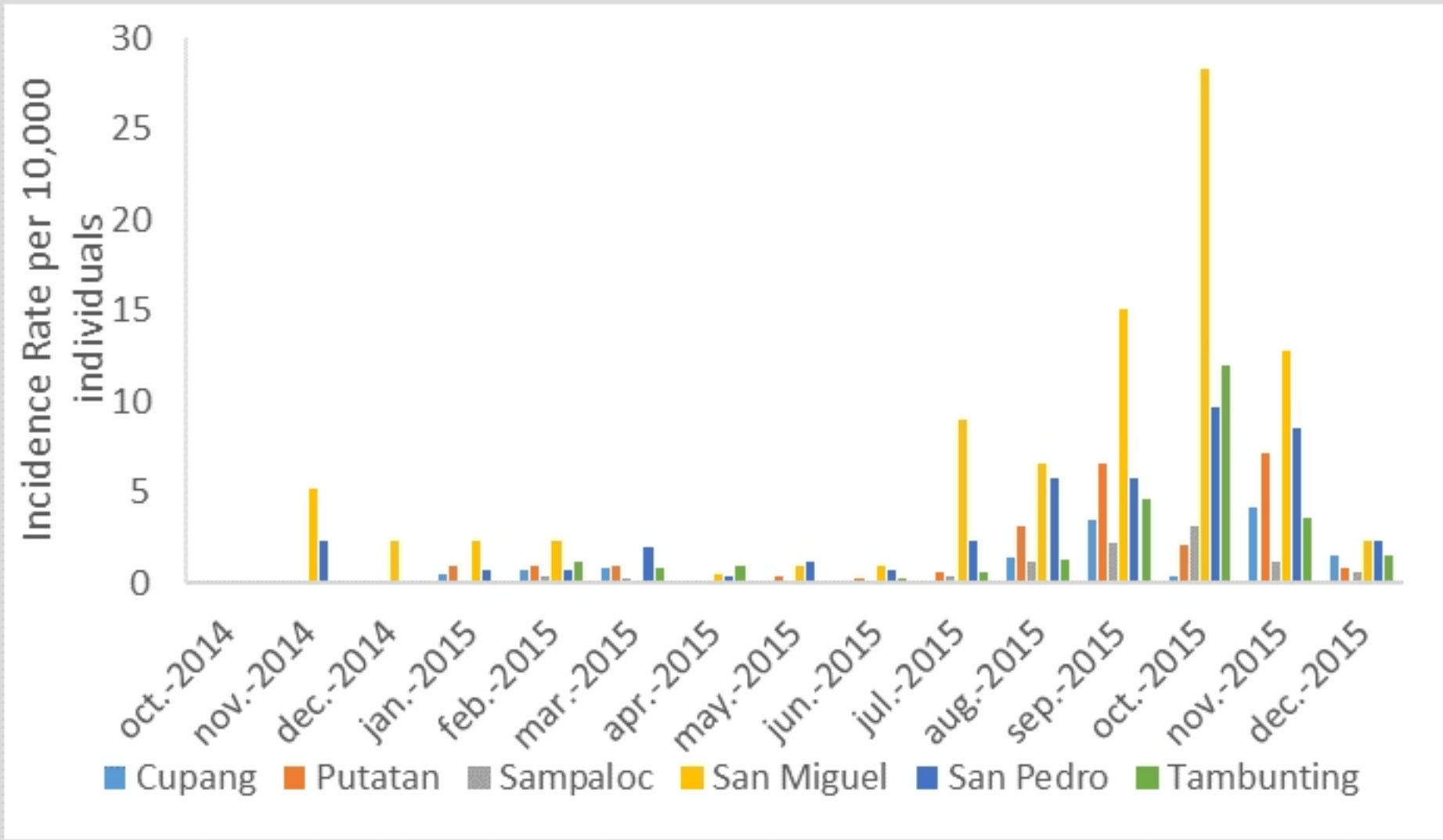


Figure 2

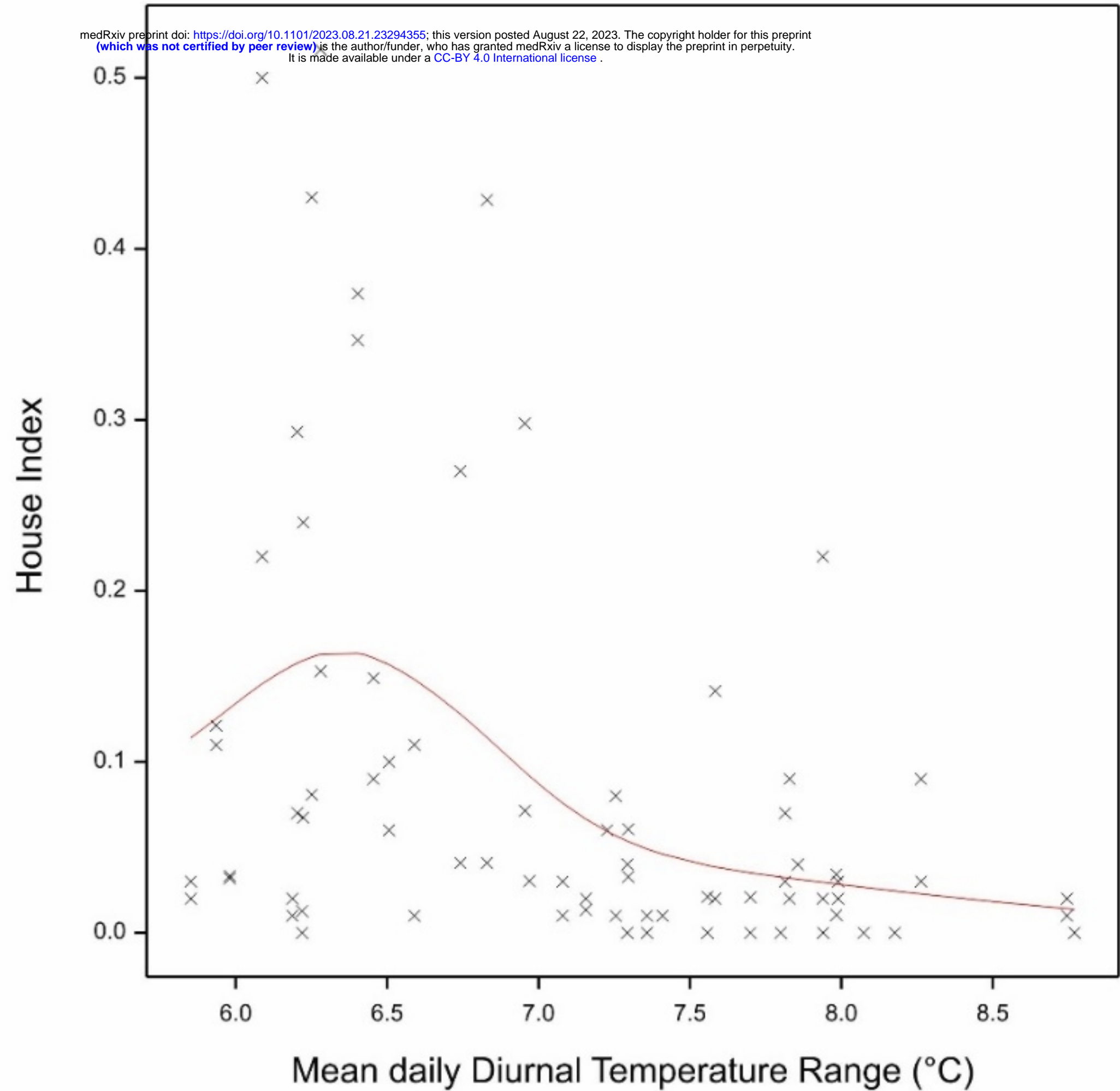


Figure 3

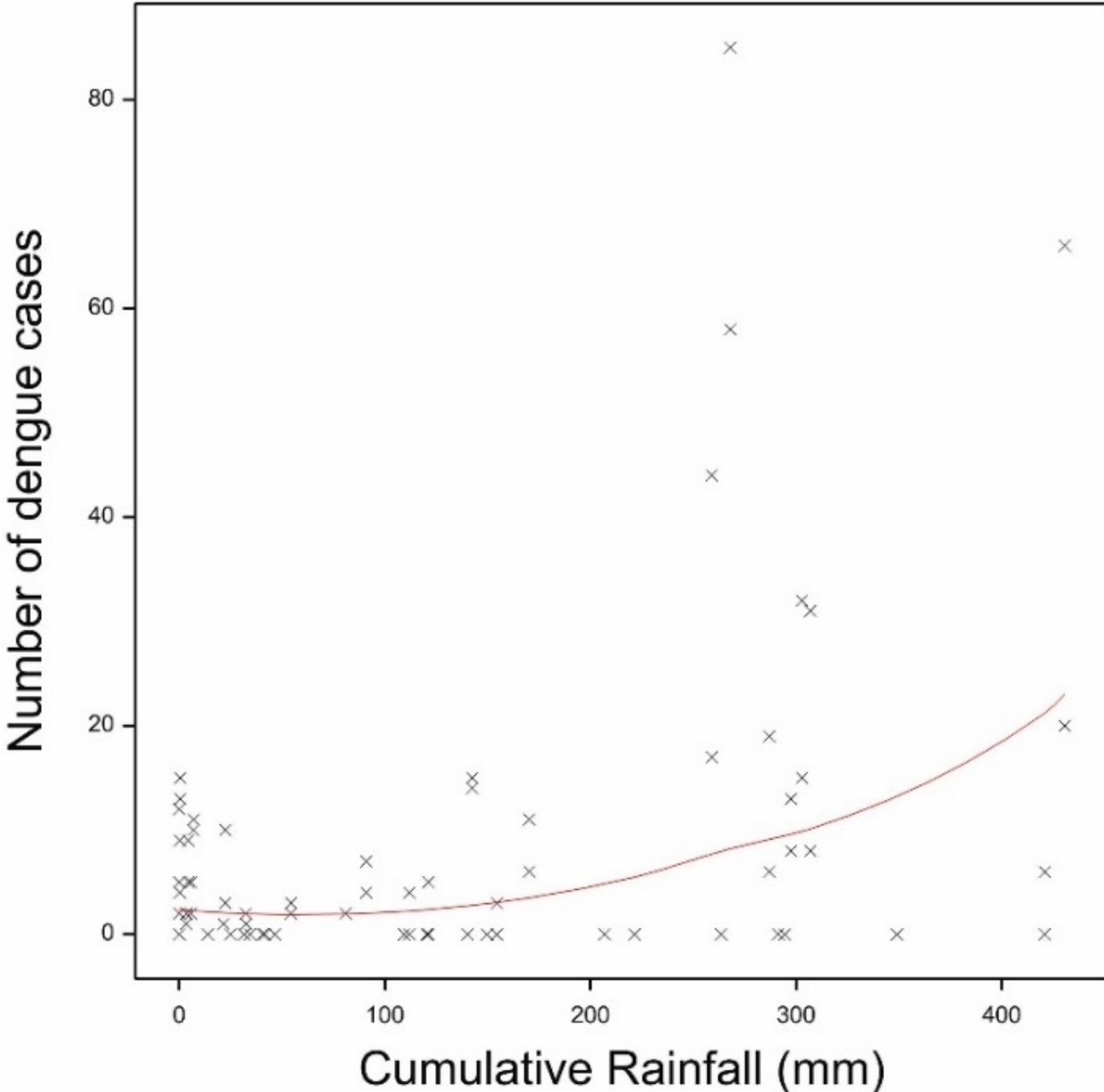


Figure 4

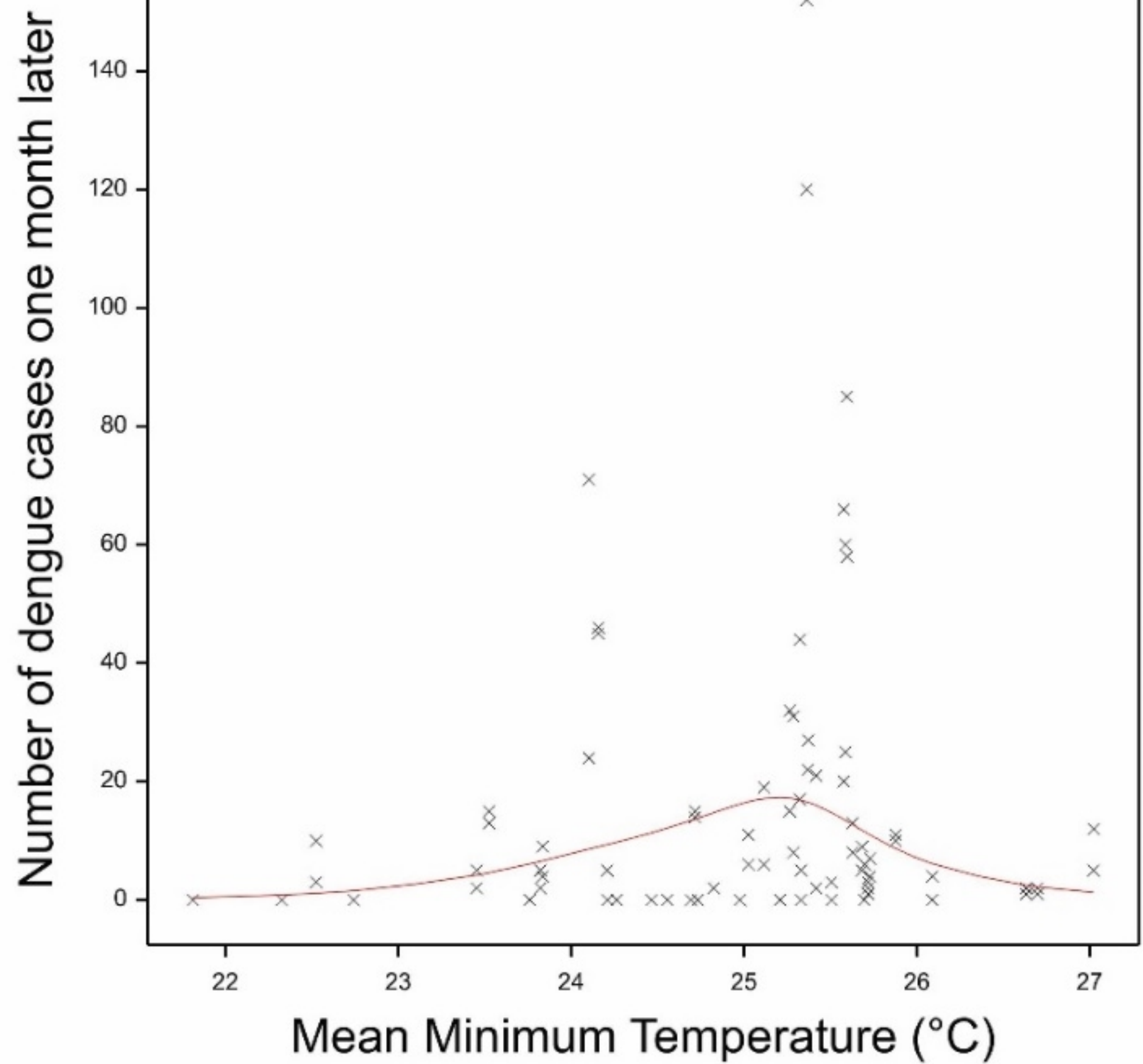


Figure 5

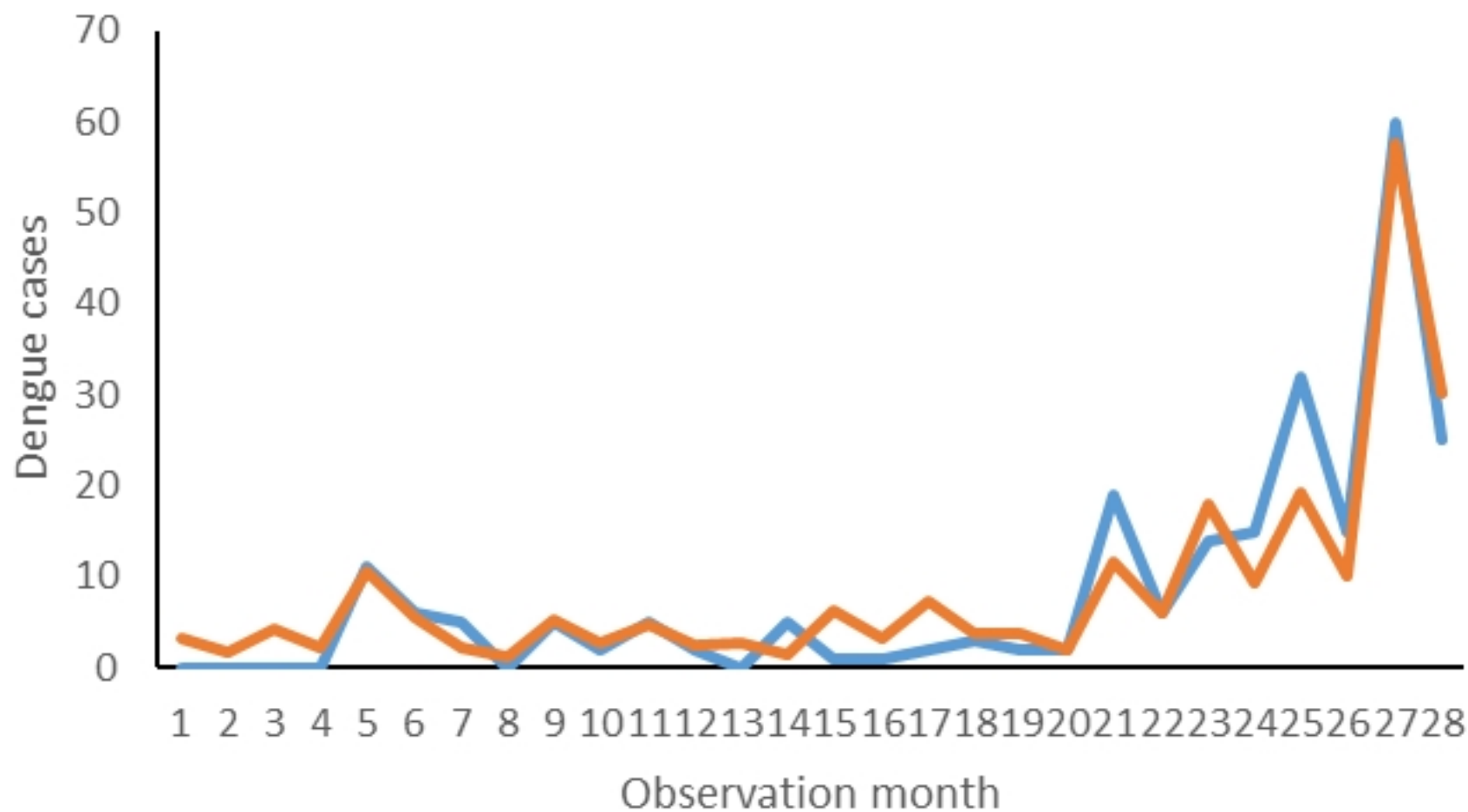


Figure 6

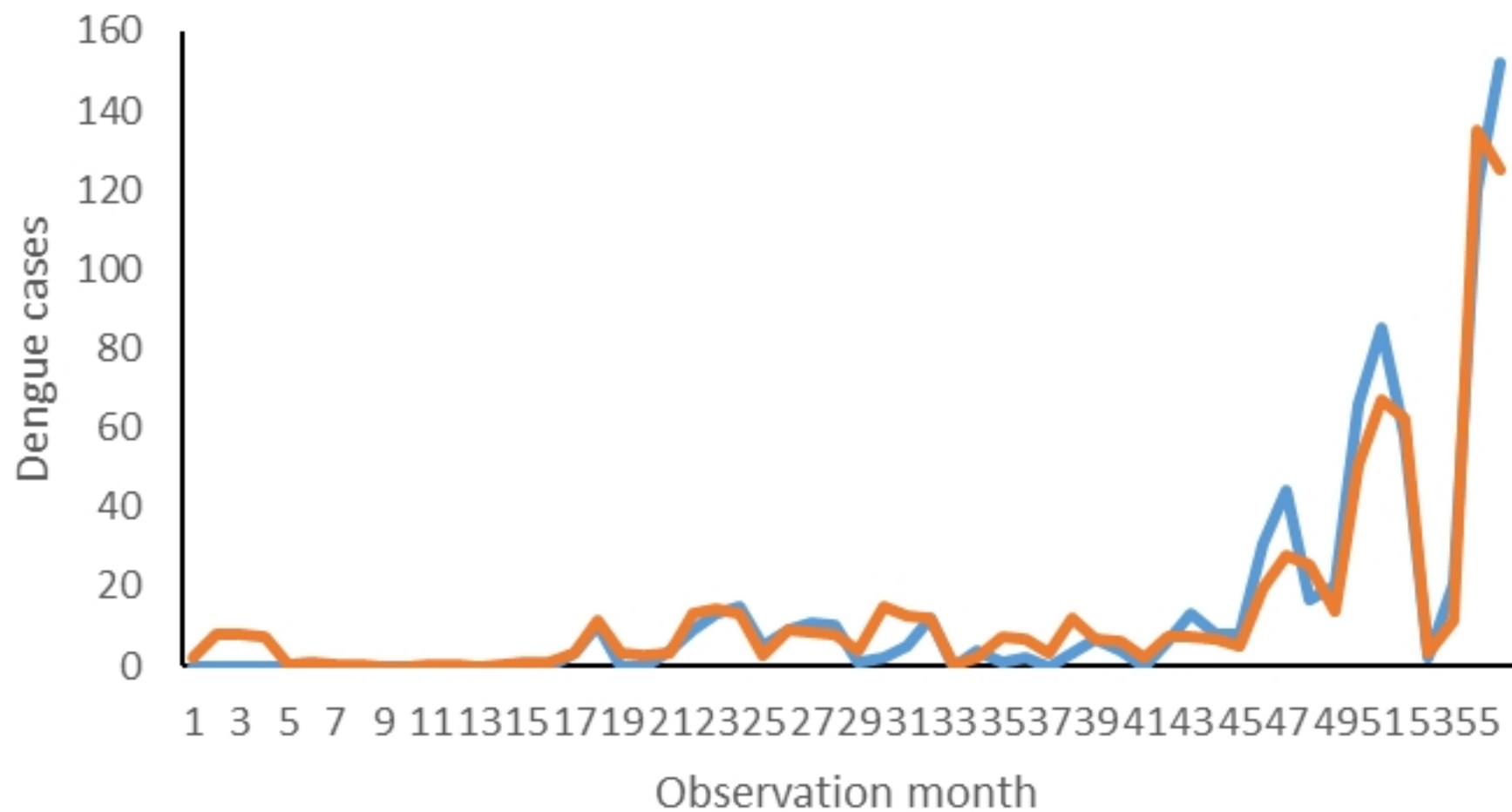


Figure 7