

Spatio-temporal modelling of climate-sensitive disease risk: towards an early warning system for dengue in Brazil

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Abstract

This paper considers the potential for using seasonal climate forecasts in developing an early warning system for dengue fever epidemics in Brazil. In the first instance, a generalised linear model (GLM) is used to select climate and other covariates which are both readily available and prove significant in

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prediction of confirmed monthly dengue cases based on data collected across the whole of Brazil for the period January 2001 to December 2008 at the microregion level (typically consisting of one large city and several smaller municipalities). The covariates explored include temperature and precipitation data on a $2.5^\circ \times 2.5^\circ$ longitude-latitude grid with time lags relevant to dengue transmission, an El Niño Southern Oscillation index and other relevant socio-economic and environmental variables. A Negative-Binomial model formulation is adopted in this model selection to allow for extra-Poisson variation (overdispersion) in the observed dengue counts caused by unknown/unobserved confounding factors and possible correlations in these effects in both time and space. Subsequently, the selected global model is refined in the context of the South East region of Brazil where dengue predominates, by reverting to a Poisson framework and explicitly modelling the overdispersion through a combination of unstructured and spatio-temporal structured random effects. The resulting spatio-temporal hierarchical model (or GLMM - generalised linear mixed model) is implemented via a Bayesian framework using Markov Chain Monte Carlo (MCMC). Dengue predictions are found to be enhanced both spatially and temporally when using the GLMM and the Bayesian framework allows posterior predictive distributions for dengue cases to be derived which can be useful for developing a dengue alert system. Using this model, we conclude that seasonal climate forecasts could have potential value in helping to predict dengue incidence months in advance of an epidemic in South East Brazil.

Keywords: dengue fever, prediction, epidemic, spatio-temporal model, seasonal climate forecasts

1. Introduction and motivation

The early identification of an epidemic of infectious disease is an important first step towards implementing effective interventions to control the disease and reducing mortality and morbidity in human populations (Kuhn et al., 2005). However, often an epidemic is under way before the authorities are notified and control measures are put in place. In this paper we assess the potential for using seasonal climate forecasts to provide early warnings of future increased and geographically specific risk of dengue fever in Brazil.

Dengue fever and its more severe form (dengue hemorrhagic fever) is one of the most important emerging tropical diseases at the beginning of the 21st century in terms of morbidity and mortality (Gubler, 2002, Guzman and Kouri, 2003). Dengue is an acute viral disease characterised by fever, headache, muscle and joint pains, rash, nausea, and vomiting, while dengue haemorrhagic fever is a potentially deadly complication that in severe cases, can cause circulatory failure. Dengue viruses are transmitted by the bite of infected *Aedes* females, in particular *Aedes aegypti*, an urban mosquito with widespread distribution in tropical cities. Field survivability of *Aedes aegypti* and patterns of dengue transmission are influenced by many factors including, but not limited to, climate which influences mosquito biology and interactions between the mosquito vector and dengue virus (Kuno, 1995; Scott et al., 2000; Sanchez et al., 2006). In many regions, epidemic dengue transmission is seasonal in response to variability in temperature and rainfall. There have been recent concerns of a worldwide spread of dengue fever because of climate changes that could favour an expansion of the transmission area.

25 In Brazil, the greatest incidence of cases occur from January to May when
26 the climate is warmest and most humid (Braga and Valle, 2007). Three of
27 the four dengue virus serotypes have spread throughout Brazil, where re-
28 ported dengue cases in the last decade represent about 60% of dengue cases
29 reported in the Americas as a whole (Nogueira et al., 2007a). Dengue epi-
30 demics impact heavily on the national health services. There is no specific
31 treatment for dengue, but appropriate medical care frequently saves the lives
32 of patients with the more serious dengue haemorrhagic fever. A major epi-
33 demic occurred in Brazil in 2008, with 764 040 reported cases (January to
34 September) including 3 848 cases of hemorrhagic fever and 213 deaths ¹. In
35 Rio de Janeiro, military field hospitals were opened during the 2008 outbreak
36 to help to ease the pressure on emergency rooms packed with people suffering
37 from dengue ².

38 The current monitoring system in Brazil relies on observing dengue incidence
39 in December/January to estimate epidemic potential late in the austral sum-
40 mer. However, this does not provide a quantitative measure or much pre-
41 dictive lead time. The greater the lead time available for forecasting disease
42 risk, the greater the opportunity for effective disease risk intervention, al-
43 though long term predictions often involve larger errors. Myers et al. (2000)
44 suggested that epidemic forecasting is most useful to health services when
45 case numbers are predicted two to six months ahead. This would allow time
46 for the allocation of resources to interventions such as preparing health care

¹<http://portal.saude.gov.br/saude/>

²<http://news.bbc.co.uk/1/hi/world/americas/7324000.stm>

47 services for increased numbers of dengue patients and educating populations
48 to eliminate mosquito breeding sites i.e. by regularly emptying water that
49 accumulates in discarded refuse, tyres and domestic water storage containers,
50 commonplace in urban slums/favelas found in some areas of Brazil.

51 As seasonal climate forecasts predict seasonal or monthly average tempera-
52 ture and precipitation (and other variables) for the forthcoming months/season
53 in both time and space, they could potentially be used in a national dengue
54 early warning system (EWS) for Brazil to aid epidemic planning months in
55 advance. EWS based on seasonal climate forecasts have been developed to
56 predict malaria incidence, for example in Botswana (Thomson et al., 2006),
57 but there has been limited progress in developing EWS for dengue fever.
58 Therefore, the use of seasonal climate forecasts with lead times of one month
59 or more within a dengue EWS is a research area in need of exploration.

60 Before assessing the viability of using seasonal climate forecasts in a dengue
61 prediction model, a model driven by observed climate variables with time
62 lags relevant to dengue transmission, issued at the same resolution as the
63 climate forecasts, must first be evaluated. If a significant relationship is
64 identified between observed climate and dengue in Brazil, the use of forecast
65 climate for dengue prediction purposes could be valuable. The remainder of
66 this paper focuses on the viability of using observed climate variables in a
67 spatio-temporal dengue prediction model.

68 In Section 2 we outline some of the key processes involved in dengue trans-
69 mission and describe the data used in the statistical modelling. Section 3
70 documents the exploratory data analysis and model selection process to find

71 which monthly climate variables and time lags are statistically significant
72 for modelling dengue incidence in Brazil, using a negative-binomial gener-
73 alised linear model (GLM) to allow for overdispersion. In section 4 we fo-
74 cus on the South East of Brazil where dengue predominates, and refine the
75 previously selected Brazilian global model by reverting to a Poisson formu-
76 lation and explicitly including spatially unstructured and spatio-temporal
77 structured random effects via a Bayesian framework to account for unob-
78 served/confounding factors. Section 5 then assesses the ability of the refined
79 model to issue dengue epidemic warnings for the peak dengue season in 2008
80 when a serious epidemic occurred. The final section discusses future ideas
81 for research and summarises the main findings of the paper.

82 **2. Dengue transmission**

83 A number of complex factors are related to dengue transmission, in partic-
84 ular population growth and unplanned urbanization, resulting in substan-
85 dard housing, inadequate water, sewerage and waste management systems
86 which allow mosquito reproduction. Poverty and health inequality are be-
87 hind almost all of these factors (Gubler, 2002). Given favourable climatic
88 conditions for development of the dengue-carrying mosquito, the urban envi-
89 ronment plays a major role in determining transmission rates. Rainfall may
90 influence the filling of containers out in the open (e.g. old tyres) which cre-
91 ate potential breeding sites for the mosquito. More importantly, the breed-
92 ing of mosquitoes depends on temperature, humidity, the mosquitoes' life
93 expectancy, life-long fecundity, biting activity and virus incubation (Favier

94 et al., 2005). Several previous studies have examined the link between cli-
95 mate and dengue. In many tropical countries, a positive association between
96 rainfall and dengue incidence have been documented (Li et al., 1985; Moore
97 et al., 1978; Gould et al., 1970). However, a significant relationship was not
98 found for other regions (Eamchan et al., 1989, Goth et al., 1987 Kuno, 1995).
99 Some authors have found that time-lagged climate variables of up to two or
100 three months have a statistically significant association with dengue (Li et al.,
101 1985; Schreiber, 2001; Wu et al., 2007). Precipitation and temperature os-
102 cillations over large parts of Latin America and the Caribbean are strongly
103 influenced by changes in Pacific sea surface temperatures (SST) as part of
104 the El Niño Southern Oscillation (ENSO) (Glantz, 2001) and these in turn
105 can influence vector competence and survivorship. Several studies have also
106 used some index of ENSO to model dengue (Brunkard et al., 2008; Cazelles
107 et al., 2005; Gagnon et al., 2001; Hales et al., 1999). Therefore the inclusion
108 of covariates based on the urban environment, climate (e.g. temperature,
109 precipitation, Pacific SST) and their lagged effects appear to be potentially
110 important components of a climate informed dengue prediction model.

111 Dengue fever data (counts of confirmed cases per month) from January 2001
112 - December 2008 (96 months) were obtained at municipality level (5651 mu-
113 nicipalities) from SINAN DATASUS - an Information System for Notifiable
114 Diseases, established by the Brazilian Ministry of Health³. A network of
115 laboratories, capable of diagnosing dengue infections, has been implemented
116 in all states. The network is responsible for confirmation of cases to support

³<http://dtr2004.saude.gov.br/sinanweb/novo/>

117 epidemiological surveillance (Nogueira et al., 2007b). However, this network
118 is not accessible to all municipalities. Dengue counts were aggregated to the
119 microregion level (558 microregions), where a microregion typically consists
120 of one large city and several smaller municipalities. This alleviates problems
121 of misreporting due to variation in the availability of health services and
122 epidemiological facilities at the municipality level. Figure 1a shows dengue
123 counts for this period grouped into the 5 main regions of Brazil (Figure 1b)
124 and Figure 1c shows the total dengue cases in each microregion for the period
125 January 2001-December 2008. Dengue is most prevalent in the South East.
126 Two major epidemics occurred in the late austral summer of 2002 and 2008,
127 while considerably less dengue occurred in 2004 and 2005. There is very little
128 dengue in South Brazil and the North West Amazon.

129 Insert Figure 1 here

130 National cartographic data such as altitude and biome were obtained from
131 the Brazilian Institute for Geography and Statistics (IBGE)⁴. Census data
132 at the microregion level such as population, percentage of urban population,
133 and the percentage of households with a water supply provided by a network,
134 refuse collection and at least one bathroom, was obtained from an aggregated
135 database SIDRA maintained by IBGE. Each microregion belongs to an ad-
136 ministrative main region (1. North, 2. North East, 3. South, 4. South
137 East, 5. Central West) and a biome (1. Amazon Rainforest, 2. Caatinga, 3.
138 Cerrado, 4. Atlantic Rainforest, 5. Pampa, 6. Pantanal). A spatial variable

⁴<http://www.sidra.ibge.gov.br/>

139 named zone was defined according to the 6 biomes but by also subdividing
140 the Atlantic Rainforest biome into 3 areas (North, South East and South)
141 according to different climatic regimes. For example, south of the Tropic of
142 Capricorn (23.5°S) the climate is more temperate and humid, while in the
143 North East portion of the Atlantic Rainforest the climate is relatively warmer.
144 Therefore 8 zones are defined for which climatic, geographical and ecologi-
145 cal conditions are homogeneous. In a modelling context, zone is treated as
146 a categorical variable, or factor. Figure 2 shows the spatial distribution of
147 altitude and urban population in Brazil and the location of the geographical
148 zones (Figure 2a, b and c). Figures 2d, e and f illustrate the relationship be-
149 tween these covariates and standardised morbidity ratio (SMR) for the given
150 time period where, for a microregion i , the SMR is defined as the ratio of
151 observed (y_i) to expected (e_i) dengue cases in the time period. The expected
152 cases e_i in each microregion are calculated as the population at risk (p_i) mul-
153 tiplied by the global dengue detection rate over the whole of Brazil for the
154 time period ($e_i = p_i \times \sum y_i / \sum p_i$). Altitude has a statistically significant
155 negative relationship with dengue SMR (as altitude increases, dengue counts
156 decrease) and percentage of urban population had a statistically significant
157 positive relationship, given a microregion with excess risk of dengue fever
158 (SMR > 1), as urban areas are ideal environments for mosquitoes and many
159 people living in close proximity create a human virus reservoir.

160 Insert Figure 2 here

161 Figure 3 illustrates that dengue has a strong annual cycle which differs with
162 geographical zone. The spatially varying dengue annual cycle is included in

163 the model specified in section 3, as an interaction between the categorical
164 variables zone and month. As only part of the cycle may be attributable to
165 climatic conditions, the inclusion of this interaction could account for other
166 confounding variables, such as seasonal population movements, leading to
167 differences in the annual cycle across zones.

168 Insert Figure 3 here

169 Observed gridded ($2.5^\circ \times 2.5^\circ$ latitude-longitude grid) monthly mean precipi-
170 tation data was obtained from the Global Precipitation Climatology Project
171 (GPCP) (Adler et al., 2003). Reanalysis monthly mean surface air temper-
172 ature data was obtained from the NCAR/NCEP Reanalysis (Kalnay et al.,
173 1996). These climatic variables are referred to as ‘observed’ climate for the
174 remainder of the text. Niño 3.4 is an index used to measure the strength
175 of El Niño and La Niña events (Barnston et al., 1997) and is defined as the
176 departure in monthly sea surface temperature from its long-term mean av-
177 eraged over the region (120°W - 170°W and 5°S - 5°N). A positive (negative)
178 index indicates El Niño (La Niña) conditions. A time series of the monthly
179 Niño 3.4 index was obtained from NOAA Climate Prediction Center⁵.

180 Microregion and gridded data were combined by assigning a grid point to
181 each microregion on the basis that the microregion is contained within the
182 grid square (see Fig. 4).

183 Insert Figure 4 here

⁵<http://www.cpc.ncep.noaa.gov/data/indices/sstoi.indices>

184 3. Model selection using a generalised linear model

185 Poisson models are widely used in the analysis of count data. However, it
186 is well established that observed count data e.g. disease cases, often dis-
187 play substantial extra-Poisson variation, or overdispersion (Lawless, 1987).
188 Overdispersion was evident in this dengue dataset. Fitting a Poisson gen-
189 eralised linear model (GLM) involving the full set of explanatory variables
190 described earlier results in a residual deviance more than a hundred times
191 larger than the residual degrees of freedom, implying that as the mean dengue
192 count increases, the variance increases at a much greater rate. In section 4
193 we will consider making explicit allowance for this overdispersion within the
194 Poisson framework via the inclusion of appropriate random effects, but for
195 model selection purposes within this section we accommodate overdispers-
196 sion implicitly by using the negative binomial distribution for the observed
197 counts, viz:

$$f(y; \mu, \theta) = \frac{\Gamma(y + \theta)}{\Gamma(\theta)y} \frac{\mu^y \theta^\theta}{(\mu + \theta)^{y+\theta}},$$

198 with mean μ , scale parameter θ and variance function $V(\mu) = \mu + \mu^2/\theta$. In
199 a GLM context the associated canonical link is $g(\mu) = \log(\mu)$.

200 In order to select which explanatory variables are important for modelling
201 dengue counts in Brazil for the 96 month time period (Jan 2001 - Dec 2008),
202 the negative binomial GLM described above was fitted using the **MASS**
203 package (Venables and Ripley, 2002) in R (R Development Core Team, 2008),

204 starting with a maximal model based on all of the covariates described in
 205 the previous section i.e. spatial covariates related to the urban environment,
 206 altitude, the annual cycle and interactions with geographical zone, observed
 207 climate variables with associated time lags (0-3 months) and the Niño 3.4
 208 index with time lags of up to 6 months. Exploratory analyses were then car-
 209 ried out using different subsets of variables to select an appropriate prediction
 210 model (e.g. examining model fit with and without climate information and
 211 with different interactions). These analyses were assisted by use of stepwise
 212 model selection algorithms based on the Akaike information criterion (AIC)
 213 which not only rewards goodness of fit, but also includes a penalty that dis-
 214 courages overfitting. The final most parsimonious model which emerged from
 215 the investigation is as follows:

$$\begin{aligned}
 y_{it} &\sim \text{NegBin}(\mu_{it}, \theta) \\
 \log(\mu_{it}) &= \log(e_i) + \alpha + \sum_j \beta_j x_{jit} + \sum_j \gamma_j w_{ji} + \sum_j \delta_j z_{jit},
 \end{aligned}$$

216 where y_{it} is dengue count for microregion $i = 1, \dots, 558$ and time $t =$
 217 $1, \dots, 96$, μ_{it} is the corresponding mean dengue count and θ is the scale
 218 parameter. The expected cases $e_i = p_i r$ are treated as an offset in the model
 219 based on the population p_i in microregion i and the overall average dengue
 220 rate per month r . The variables x_{jit} represent the selected climate influences:
 221 precipitation one month previous ($j = 1$), precipitation two months previous
 222 ($j = 2$), temperature one month previous ($j = 3$), temperature two months
 223 previous ($j = 4$) and Niño 3.4 six months previous ($j = 5$). The variables w_{ji}

224 are: altitude ($j = 1$) and percentage of urban population ($j = 2$). Finally,
225 z_{jit} is a series of factors reflecting zone, month and interaction between zone
226 and month.

227 All covariate coefficients were found to be significantly different from zero at
228 the $p = 0.001$ level. The estimated parameters and standard errors for the
229 climate variables included in the final model are listed in Table 1. Precipita-
230 tion and temperature with time lags of 1 and 2 months were found to be the
231 most statistically significant and are positively related to dengue as warm,
232 humid conditions promote mosquito development and rain water fills dis-
233 carded containers outdoors to create mosquito breeding sites in the months
234 preceding increased dengue incidence. The Niño 3.4 index is negatively re-
235 lated to dengue. This is because the major dengue epidemics in 2002 and
236 2008 in particular, were preceded by negative SST anomalies in the Niño 3.4
237 region. The scale parameter θ was estimated to be 0.32 with standard error
238 0.002, confirming a mean variance relationship considerably different from
239 that of the Poisson (equal mean and variance), hence justifying the use of a
240 negative binomial rather than a Poisson GLM for model selection purposes.

241 One important aspect of such a model to a public health decision maker is its
242 ability to predict dengue during the peak dengue season from February-April
243 (FMA). In Figure 5, scatter plots with fitted loess curves show the relation-
244 ship between observed and predicted dengue using the GLM model for the
245 FMA season 2001-2008 for Brazil (Fig 5a) and the South East region where
246 dengue predominates (Fig 5b). Although the model clearly fails to capture
247 much of the variability in dengue counts in this season, there is an overall

Table 1: Parameter estimates for climate covariates.

Observed Climate	Coefficient estimate	Standard error	Prob> $ z $
Precipitation lag 1	0.018	0.0037	5.12×10^{-4}
Precipitation lag 2	0.022	0.0036	6.45×10^{-11}
Temperature lag 1	0.091	0.0093	2×10^{-16}
Temperature lag 2	0.161	0.0093	2×10^{-16}
Niño 3.4 lag 6	-0.204	0.0119	2×10^{-16}

248 positive association between observed and predicted counts at both the na-
 249 tional and regional level. The influence of the climate variables in the model
 250 predictions is demonstrated in Figure 6a which shows the time series of total
 251 observed dengue cases for the FMA season, predicted dengue using a GLM
 252 without any climate information (dotted line) and with climate information
 253 (dashed line). The climate variables are the only source of temporal infor-
 254 mation in the model, therefore by not including them the same prediction is
 255 produced for every month/season of each year. By including climate infor-
 256 mation, some of the temporal variability is captured albeit with limited skill.
 257 Figure 6c illustrates how the GLM predicts dengue for the FMA season in
 258 2008. In some areas, the predicted dengue level corresponds to the observed
 259 level, for example, in coastal margins of the South East region (see Fig 6b).
 260 However, low levels of dengue are overestimated in the South and the model
 261 fails to reproduce the variability in dengue cases across the Amazon. When
 262 we focus in at the region level (South East) and microregion level (Rio de
 263 Janeiro) for which dengue early warnings would be most useful, time series of

264 dengue for the FMA season 2001-2008 show that the climate informed GLM
265 fails to reproduce the dengue epidemic in 2002 and the increase in dengue
266 from 2006-2007 (Fig 7a and b).

267 Insert Figure 5 here

268 Insert Figure 6 here

269 Insert Figure 7 here

270 This GLM clearly fails to capture much of the temporal variability in dengue
271 counts, which may be attributable to factors such as population immunity
272 to the dominant circulating serotype or specific health interventions and vec-
273 tor control measures. However, information regarding these aspects of the
274 disease system are not readily available. Therefore, the use of unstructured
275 random effects may be valuable to allow for unobserved latent structures
276 in the model (McCulloch and Searle, 2004), for example, to capture the
277 impact of unknown/unobserved confounding factors, such as the introduc-
278 tion of a new dengue serotype in a certain area of Brazil. Also, by using a
279 GLM independence is assumed in both time and space and neither of these
280 assumptions may be valid. There could be strong temporal correlation ef-
281 fects within some areas and there could also be spatial clustering effects in
282 neighbouring microregions. To allow for such latent effects and correlation
283 structures, the GLM is refined in the next section by reverting to a Poisson
284 framework but using a generalised linear mixed model (GLMM) which in-
285 cludes spatially unstructured and spatio-temporal structured random effects
286 in the linear predictor. This explicitly models the extra-Poisson variation or

287 overdispersion previously allowed for using the negative binomial.

288 We focus our analysis on the South East region of Brazil (see Figure 1a) where
289 dengue is most prevalent and there are a large number of densely populated
290 urban centres which could benefit from a climate informed dengue EWS.
291 This is also the region where the previously reported GLM predictions did
292 appear to capture some of the observed spatial variability in dengue counts
293 (see Figure 6c).

294 **4. Development of a generalised linear mixed model**

295 As described above, we now focus on the 160 microregions in South East
296 Brazil and return to a Poisson model for the dengue count data to develop a
297 GLMM that includes random effects in the linear predictor. One approach
298 to fitting such a model is to use a Bayesian framework. Markov Chain Monte
299 Carlo (MCMC) methods make Bayesian modelling of complex situations in-
300 volving many parameters a practical feasibility (see Gilks and Spiegelhal-
301 ter (1996), Brooks (1998) for more details). One further advantage of the
302 Bayesian approach is that the associated MCMC sampling yields full poste-
303 rior predictive distributions which automatically incorporate all components
304 of variance at the different levels in the model. A full assessment of predic-
305 tion uncertainty is therefore more easily obtained with Bayesian estimation
306 than with the more traditional maximum likelihood approach.

307 The inclusion of random effects introduces an extra source of variability (a
308 latent effect) into the model to capture the impact of unknown/unobserved

309 confounding factors. For example, serotype introduction, which can vary
 310 spatially and temporally. Unstructured random effects can help account for
 311 overdispersion in the distribution of dengue counts y_i , however, this does not
 312 allow for explicit spatial dependence between y_i . This dependence can be
 313 included by adding a spatially structured random effect. A typical choice for
 314 a spatially structured prior is a conditional intrinsic Gaussian autoregressive
 315 model (CAR) (see Besag et al., 1995);

$$\nu_i | \nu_{j \neq i} \sim N \left(\frac{\sum_{j \neq i} a_{ij} \nu_j}{\sum_{j \neq i} a_{ij}}, \frac{\sigma_\nu^2}{\sum_{j \neq i} a_{ij}} \right),$$

316 where a_{ij} are adjacency weights for the microregions, here taken to be simple
 317 binary values: $a_{ij} = 1$ if microregion i has a common boundary with mi-
 318 croregion j , $a_{ij} = 0$ otherwise. The hyperparameter σ_ν controls the strength
 319 of the local spatial dependence. As the CAR is improper, a ‘sum to zero’
 320 constraint is applied to ν_i and it is then advisable to take a uniform flat prior
 321 for the intercept α (see model specification below).

322 Models to predict vector-borne disease may include an autoregressive time
 323 series component (e.g. Gomez-Elipe et al., 2007), based on the idea that
 324 the current value of the time series y_{it} can be explained as a function of
 325 past values. Accordingly, a first order autoregressive temporal effect ω_t was
 326 included in the model, where t is calendar month and ω_1 (August) is set
 327 equal to zero in the model specification to avoid identifiability problems.

328 Therefore the spatio-temporal GLMM adopted is given by:

$$\begin{aligned}
y_{it} &\sim \text{Pois}(\mu_{it}) \\
\log(\mu_{it}) &= \log(e_i) + \alpha + \sum_j \beta_j x_{jit} + \sum_j \gamma_j w_{ji} + \phi_i + \nu_i + \omega_t \\
\alpha &\sim \text{U}(-\infty, +\infty) \\
\phi_i &\sim \text{N}(0, \sigma_\phi^2) \\
\nu_i &\sim \text{CAR}(\sigma_\nu^2) \\
\omega_1 &= 0, \omega_t \sim \text{N}(\omega_{t-1}, \sigma_\omega^2), \quad t = 2, \dots, 12.
\end{aligned}$$

329 Independent diffuse Gaussian priors (mean 0, precision 1×10^{-6}) were taken
330 for β_j ($j = 1, \dots, 5$) and γ_j ($j = 1, 2$), whilst independent gamma hyperpri-
331 ors with equal shape and inverse scale parameter (0.01) were used for the
332 precisions ($\tau_\phi = 1/\sigma_\phi^2$, $\tau_\nu = 1/\sigma_\nu^2$, $\tau_\omega = 1/\sigma_\omega^2$) of the priors for the spatially
333 unstructured ϕ_i and spatially structured ν_i random effects, ($i = 1, \dots, 160$),
334 and the temporally autocorrelated random effects ω_t ($t = 2, \dots, 12$).

335 This model was fit with WinBUGS⁶ software, using two parallel MCMC
336 chains, each of length 25,000 with a burn-in of 20,000 and thinning of 10
337 to obtain samples from $P(\alpha, \boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\phi}, \boldsymbol{\nu}, \boldsymbol{\omega}, \tau_\phi, \tau_\nu, \tau_\omega | \mathbf{y})$. As mentioned earlier,
338 the explanatory variables x_{jit} ($j = 1, \dots, 5$) and w_{ji} ($j = 1, 2$) are as before,
339 however, all covariates are now standardised to zero mean and unit variance
340 to aid convergence. This model is fit at the region level, therefore the zone
341 factor is omitted as there is little variation in zone type in the South East
342 region, and any geographic differences between microregions are captured by

⁶<http://www.mrc-bsu.cam.ac.uk/bugs/>

343 the spatial random effects. Satisfactory convergence was confirmed using a
344 range of standard criteria (Gelman et al., 2004). Posterior distributions for
345 each parameter associated with the climate covariates in the model are given
346 in Figure 8 (with posterior means in parentheses). The climate parameters
347 are all significantly different from zero and the sign of the association between
348 dengue and each climate variable is consistent with the results from the GLM
349 fit (Table 1).

350 Insert Figure 8 here

351 A posterior predictive distribution can be obtained for each microregion by
352 drawing random samples from a Poisson distribution with mean equal to the
353 MCMC samples from the model fit. The mean of the posterior predictive
354 distribution for all microregions in the South-East region were obtained for
355 the peak dengue season FMA. In Figure 9 a scatter plot with fitted loess curve
356 shows the relationship between observed and predicted dengue using the
357 GLMM model for the FMA season 2001-2008. When compared to predicted
358 values from the GLM (see Fig 5b), the loess curve has shifted towards the
359 45° line and more of the variability in dengue cases has been captured by the
360 prediction model. Figure 10 illustrates the spatial distribution of observed
361 (Fig 10a), and predicted dengue for FMA season 2008 using both the GLM
362 (Fig 10b) and GLMM (Fig 10c). While the GLM predicted medium levels of
363 dengue across much of the region, the GLMM captures more of the observed
364 variation. When compared with Figure 7, Figure 11 shows how the addition
365 of random effects to the model has improved dengue predictions for both the
366 South East as a whole (Fig. 11a) and for the microregion Rio de Janeiro

367 (Fig. 11b), particularly for the 2008 epidemic.

368 Insert Figure 9 here

369 Insert Figure 10 here

370 Insert Figure 11 here

371 **5. Probabilistic epidemic prediction**

372 The specified Bayesian hierarchical model can also be used to predict the
373 probability of dengue exceeding a pre-defined epidemic threshold in each mi-
374 croregion. As the GLMM here provides a posterior predictive distribution
375 for each microregion (rather than a point estimate), the probability of ex-
376 ceeding an epidemic threshold can be calculated and the decision to trigger
377 an alert can be based on the probability of exceeding the threshold being
378 greater than a specified alert level, (e.g. probability of exceedance $\geq 90\%$).
379 Many epidemic detection algorithms have been investigated to detect epi-
380 demics (Cullen et al., 1984; Hay et al., 2002; Teklehaimanot et al., 2004). As
381 an example, we consider the event of dengue exceeding an epidemic threshold
382 of the mean plus one standard deviation for each microregion in South East
383 Brazil in FMA 2008. The epidemic threshold is based on the dengue counts
384 in the FMA season for the previous seven years (FMA 2001-2007). We can
385 assess the ability of the GLMM to predict ‘dengue epidemics’ across South
386 East Brazil during the FMA season in 2008 using a contingency table (see
387 Table 2). Observed dengue counts for the 3-month season were compared

388 with model predictions where the probability of an epidemic exceeded an
 389 alert threshold chosen to be 90%.

Table 2: Contingency table for observed dengue exceeding epidemic threshold (mean plus one standard deviation) and probability of predicted dengue exceeding alert threshold ($\geq 90\%$) for the 160 microregions.

		Observed		
		Yes	No	Total
Predicted probability $\geq 90\%$	Yes	a=29	b=9	38
	No	c=19	d=103	122
Total		48	112	160

390 The contingency table provides information on the overall predictive skill
 391 of the warning system. The proportion correct, defined as the proportion
 392 of the 160 microregions for which the prediction correctly anticipated the
 393 subsequent epidemic or non-epidemic $(a + d/a + b + c + d)$, was 83%. The
 394 hit rate (the proportion of epidemics that were correctly predicted $a/a + c$)
 395 was 60%. Conversely, the false alarm rate (the proportion of epidemics that
 396 were predicted but did not occur $b/b + d$) was 8%.

397 Figure 12 shows the posterior predictive distribution for the FMA season 2008
 398 for the microregion Linhares, found on the coastal region of Espírito Santo,
 399 where the probability of exceeding the epidemic threshold was found to be
 400 $\geq 90\%$, based on the epidemic threshold of mean plus one standard deviation
 401 derived from the distribution of dengue for the season FMA 2001-2007. A
 402 successful epidemic alert would have been issued for this microregion using

403 the GLMM with the given epidemic threshold and alert level. By lowering
404 the alert level below 90% the hit rate for the region increases but so does the
405 false alarm rate. In practice, the choice of epidemic threshold and alert level
406 should be selected by decision makers based on expert opinion and available
407 resources.

408 Insert Figure 12 here

409 **6. Discussion and Conclusion**

410 The preliminary modelling results in this paper indicate that climatic covari-
411 ates play a statistically significant role in the transmission of dengue fever.
412 Although climate information alone does not account for a large proportion
413 of the overall variation in dengue cases in Brazil, spatio-temporal climate in-
414 formation with the addition of spatio-temporal random effects do account for
415 some of this variability, particularly for the 2008 peak dengue season, when
416 a serious epidemic occurred. Therefore the inclusion of seasonal climate fore-
417 casts in a dengue EWS for Brazil is worth investigating. The next step would
418 be to assess the predictive validity of the model when replacing ‘observed’
419 with ‘hindcast’ (i.e. retrospective forecasts made for a historical period in
420 pseudo-operational mode) climate variables. ‘Hindcast’ precipitation, tem-
421 perature and Niño3.4 data are available from forecasting systems such as the
422 UK Met Office seasonal forecasting system (Graham et al., 2005) and the
423 European Centre for Medium Range Forecasts (ECMWF) System 3 (Ander-
424 son et al., 2007). These systems typically produce ensemble predictions with
425 lead times up to 6 months. By replacing ‘observed’ with ‘hindcast’ climate

426 variables in the above GLMM, a dengue prediction could be made 5 months
427 ahead of the dengue season of interest. For example, to predict dengue in-
428 cidence for March 2010, the model could be run in October 2009 using the
429 observed Niño 3.4 index for September 2009 (6 month lag), and precipitation
430 and temperature forecasts for January and February 2010 issued in October
431 2009. The reliability of a climate-based EWS will depend on the skill of the
432 forecasting system or multi-model combined and calibrated system such as
433 EUROBRISA (Coelho et al., 2006), in predicting seasonal climate conditions
434 for the region of interest.

435 Previous sections have highlighted the potential for incorporating climate
436 information into a spatio-temporal EWS for dengue in Brazil. However, be-
437 fore implementing such an operational system several technical issues need
438 to be considered. For example, the definition of epidemic thresholds by pub-
439 lic health decision makers. Thresholds should be designed to minimise false
440 alarms and false negatives (i.e. failing to predict that an epidemic will occur)
441 and should correspond with the epidemic response capabilities in specific lo-
442 cations. The spatial scale of the system affects the type of response activity
443 that could be implemented. For example, at the microregion level interven-
444 tions such as health care provisions may be possible. However, vector-control
445 efforts may be more difficult to target. Predictive output from an EWS needs
446 to be continuously monitored and evaluated over time and models should be
447 refitted as new dengue/climate data becomes available. Spatial demographic
448 data from the census (and interim projections) should also be updated when
449 necessary. In order to issue the most reliable epidemic predictions forecast
450 climate should be replaced with observed climate as time progresses towards

451 the peak epidemic season, so that updated epidemic alerts can be re-issued
452 to public health decision makers. However, time delays in obtaining and
453 collating real-time information for both confirmed dengue cases from SINAN
454 and climate forecasts and observations could hinder the ability to provide
455 warnings far enough in advance. Another important consideration is the dis-
456 semination and visualisation of early warnings of increased level of dengue
457 risk. It is vital to train public health decision makers on how to interpret
458 and use dengue risk forecasts, including awareness about forecast limitations
459 to avoid misinterpretation and/or over interpretation.

460 Developing a climate-based EWS for dengue using climate and disease in-
461 formation over such short time periods remains a major challenge. During
462 the study period, the Niño 3.4 index strongly influences the temporal signal
463 of predicted dengue. From June 2007, a moderate La Niña event developed,
464 which strengthened in early 2008. Was the dengue epidemic in 2008 influ-
465 enced by this La Niña event or was this a coincidence? ENSO may play a role
466 in synchronizing epidemics, however, periods between epidemics may also be
467 a function of herd immunity from previous epidemics, and these two cycles
468 (ENSO and herd immunity) may have coincided during the 2001-2008 study
469 period. Further investigation is needed to understand temperature and pre-
470 cipitation patterns associated with warm phase and cold phase ENSO for this
471 region in Brazil and to consider the possibility of a non-linear relationship be-
472 tween precipitation/temperature and dengue. The model parameterisation
473 would benefit from the inclusion of one or more past epidemics to address
474 these problems.

475 Despite this, it is hoped that this spatio-temporal dengue prediction model
476 is a step towards the development of a useful decision making tool for the
477 Brazilian health services. Such spatio-temporal models offer an opportunity
478 to balance global climate variables and local responses, e.g. the influence
479 of ENSO on dengue incidence is likely to occur unequally across the region
480 due to particular socio-economic local conditions. Another advantage of the
481 GLMM is the ability to address specific public health issues in terms of
482 probabilities. This model could be extended to other regions in the world
483 where climate-sensitive infectious diseases (e.g. cholera, malaria, leptospiro-
484 sis, plague) present a burden to public health infrastructure, particularly in
485 developing countries.

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624 **Figure captions**

625 Figure 1: (a) Monthly dengue fever counts (1 000 cases) for main regions of
626 Brazil from January 2001 to December 2008 (b) map to show main regions
627 of Brazil (c) map of total dengue cases in each microregion (558) in Brazil
628 for period January 2001 to December 2008.

629 Figure 2: Upper panel: spatial distribution of (a) altitude, (b) urban popu-
630 lation, (c) zones in Brazil. Lower panel: scatter plot and loess curve to show
631 relationship between dengue SMR and (d) altitude, (e) percentage of urban
632 population, (f) boxplots to show distribution of dengue SMR in each zone.
633 Note logarithmic y axes.

634 Figure 3: Annual cycle of dengue for 8 zones in Brazil, calculated for period
635 January 2001 to December 2008.

636 Figure 4: Map to show centroids of microregions in Brazil (circles) and $2.5^\circ \times$
637 2.5° climate grid (squares). Box indicates approximate location of South East
638 region for which GLMM is developed.

639 Figure 5: Scatter plot and loess curve (solid line) to show observed and
640 predicted dengue fever, using GLM model for 3 month season FMA 2001-
641 2008 for (a) Brazil and (b) South East region.

642 Figure 6: (a) time series of total observed dengue (solid line), GLM predicted
643 dengue without climate (dashed line) and GLM predicted dengue with cli-
644 mate (dotted line) for FMA season 2001-2008 in Brazil, maps to show sum of
645 (b) observed and (c) predicted dengue cases for microregions of Brazil, FMA

646 season 2008. Categories defined by quintiles of observed dengue for FMA
647 season 2008.

648 Figure 7: Time series of total observed dengue (solid line), GLM predicted
649 dengue without climate (dashed line) and GLM predicted dengue with cli-
650 mate (dotted line) for FMA season 2001-2008 for (a) South East (region
651 level) and (b) Rio de Janeiro (microregion level).

652 Figure 8: Kernel density estimates for marginal posterior distributions of pa-
653 rameters β_1, \dots, β_5 (posterior means in parentheses) associated with climate
654 variables: (a) precipitation lag 1, (b) precipitation lag 2, (c) temperature lag
655 1, (d) temperature lag 2 and (e) Niño 3.4 index lag 6 for South East Brazil.

656 Figure 9: Scatter plot and loess curve (solid line) to show observed and
657 predicted dengue fever using GLMM for 3 month season FMA 2001-2008 for
658 South East Brazil.

659 Figure 10: Maps to show (a) observed dengue, (b) predicted dengue using
660 GLM model and (c) predicted dengue using GLMM model for South East,
661 FMA season 2008. Categories defined by quintiles of observed dengue for
662 FMA season 2008.

663 Figure 11: Time series of total observed dengue (solid line) and predicted
664 dengue using GLMM (dashed line) for FMA season 2001-2008 for (a) South
665 East (region level) and (b) Rio de Janeiro (microregion level).

666 Figure 12: Kernel density estimate for posterior predictive distribution of
667 dengue, FMA 2008 for Linhares (19.4°S,40.1°W), a microregion in Espírito

668 Santo. Dashed vertical line indicates epidemic threshold of mean plus one
669 standard deviation based on FMA 2001-2007. Solid vertical line indicates
670 observed dengue count in FMA 2008.

Figure 1
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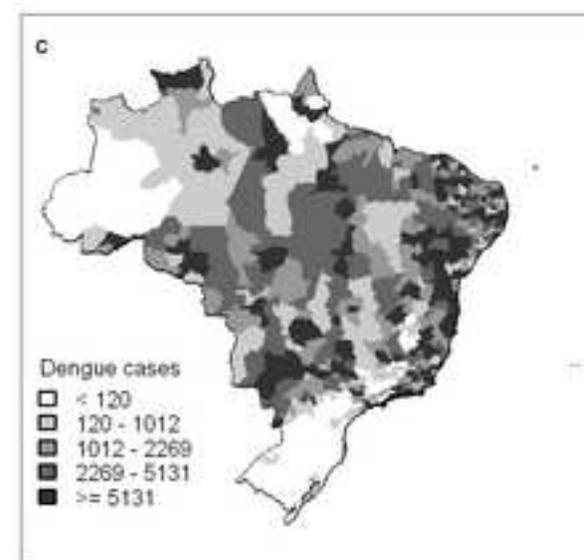
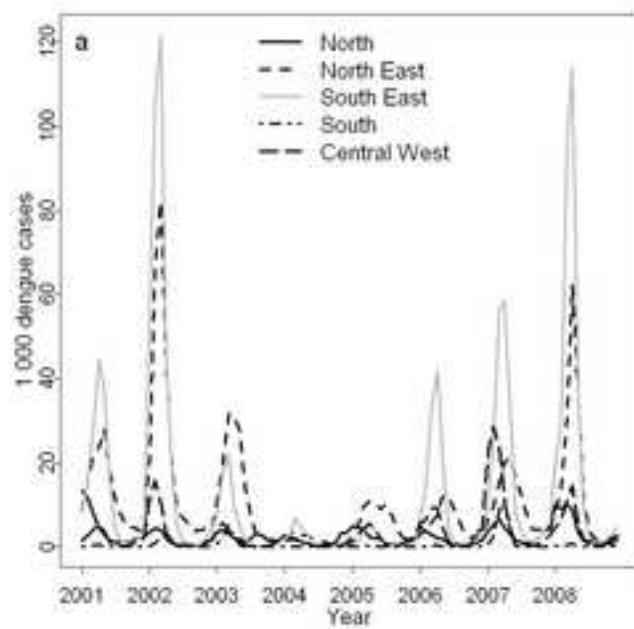


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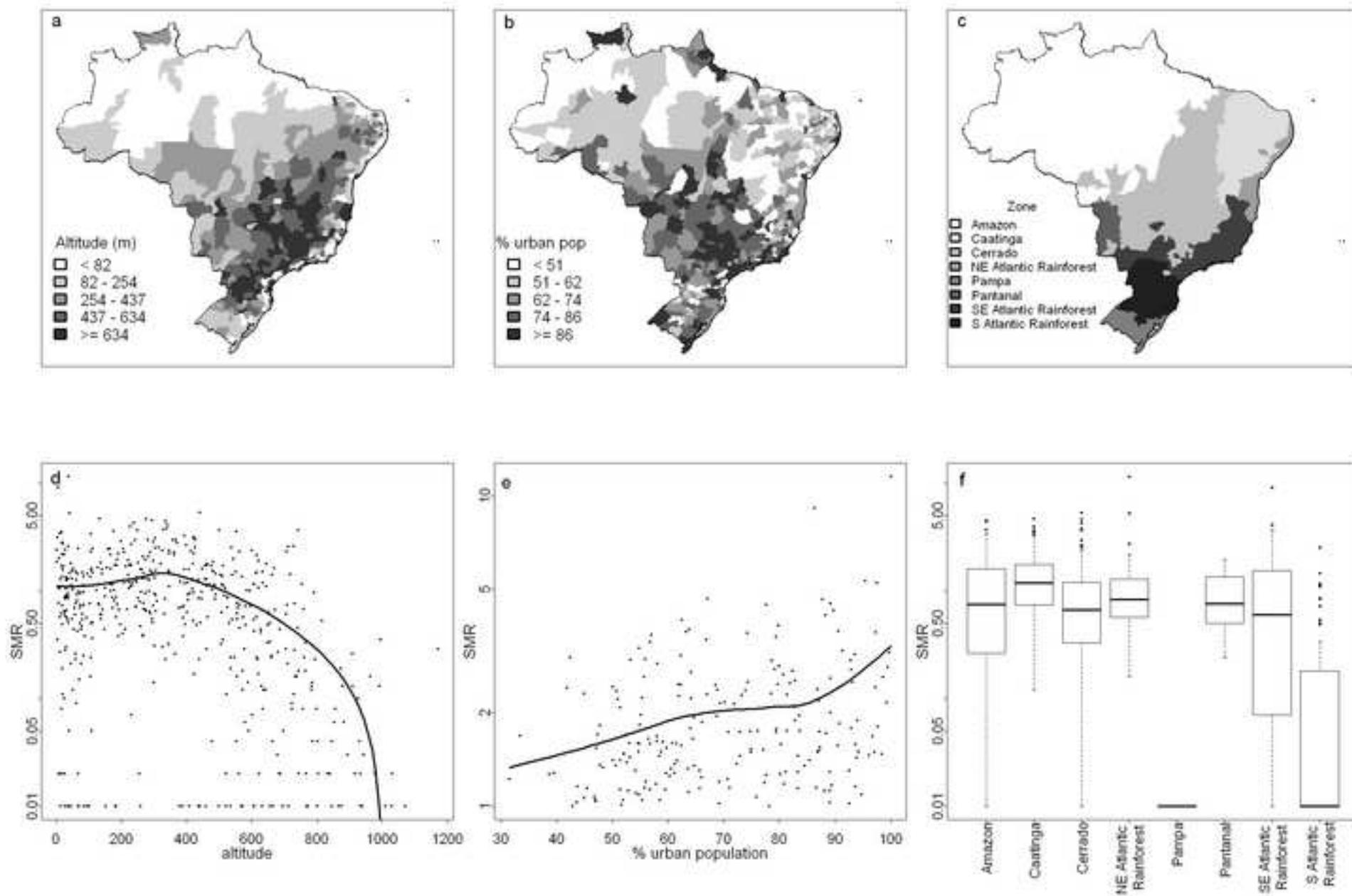


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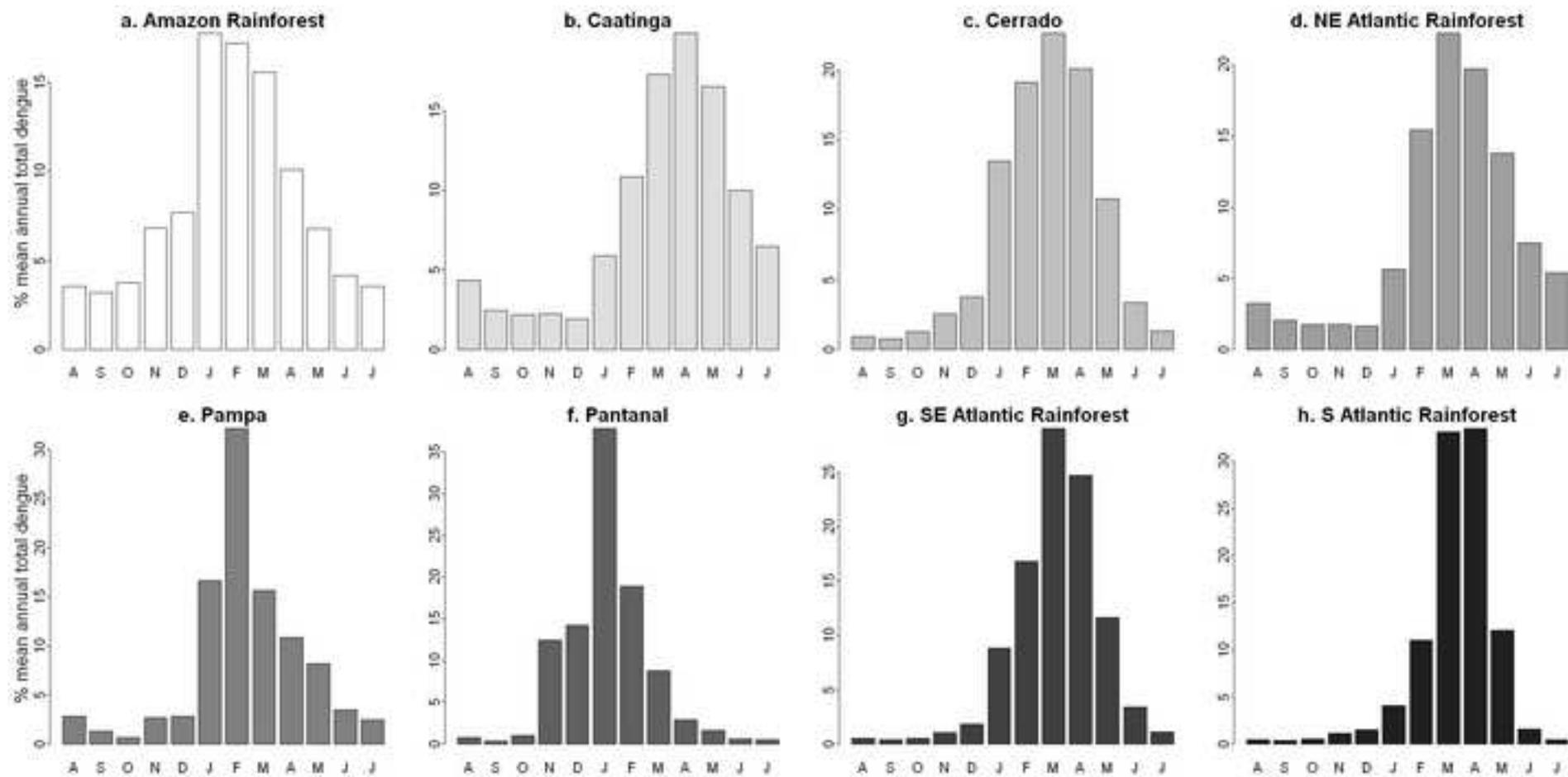


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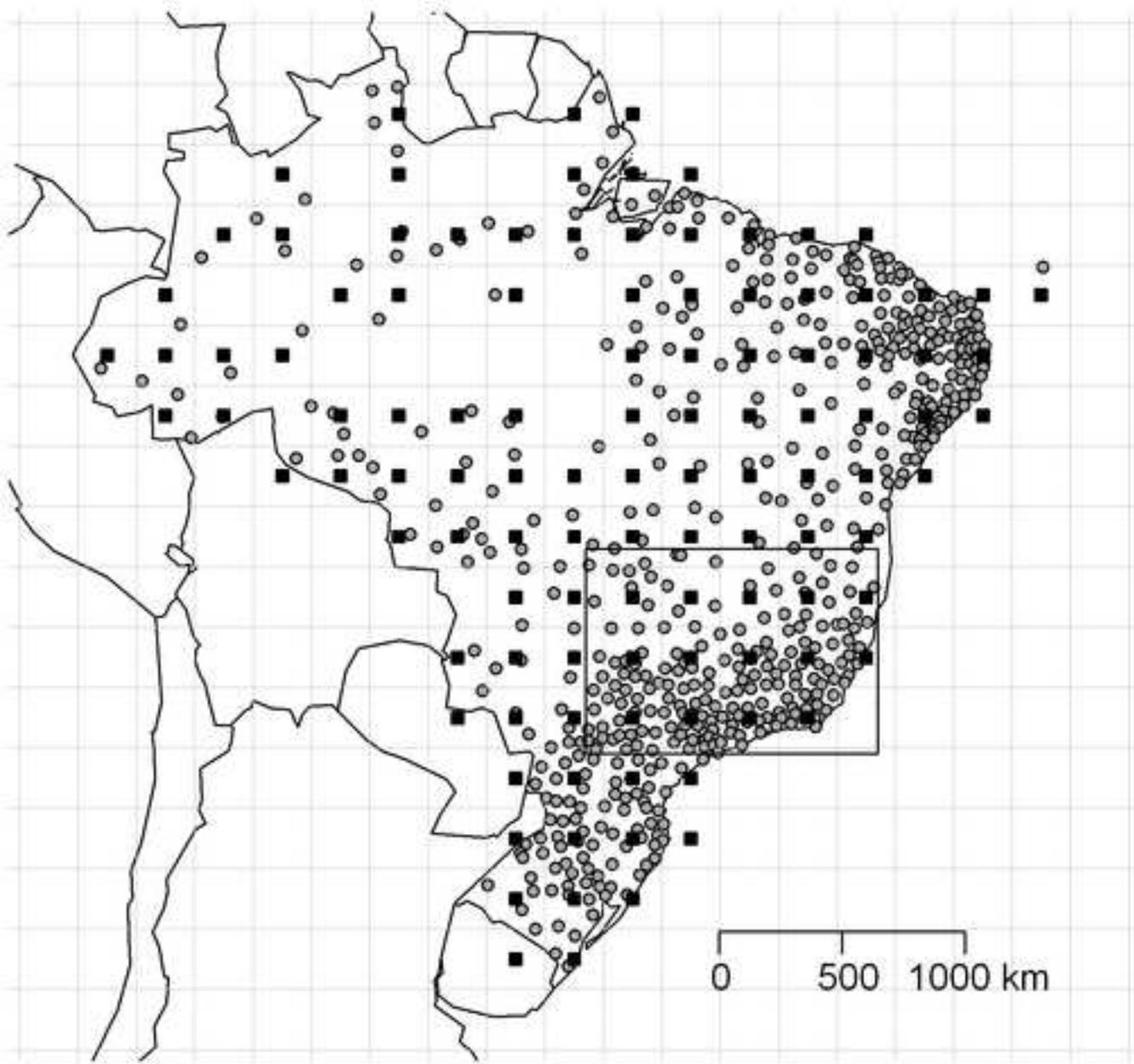


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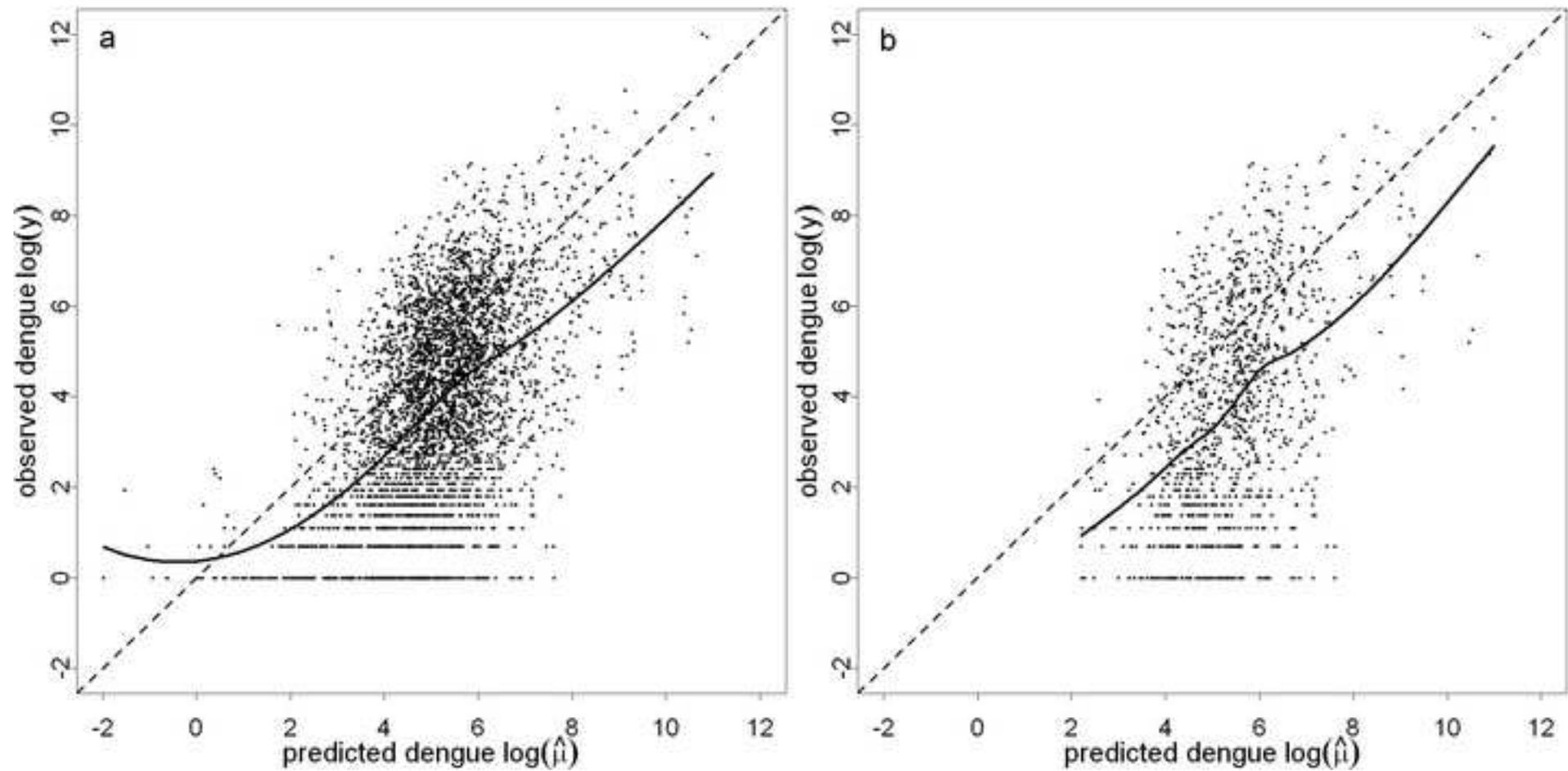


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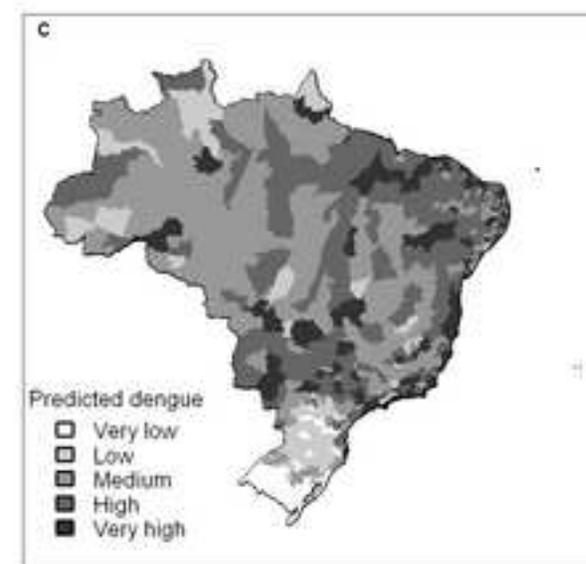
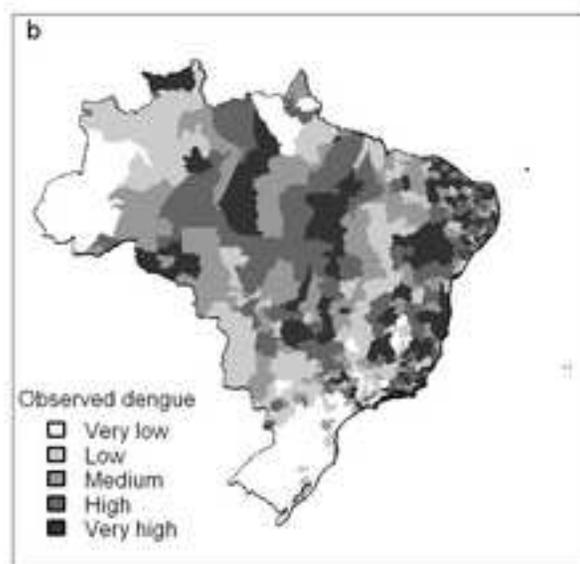
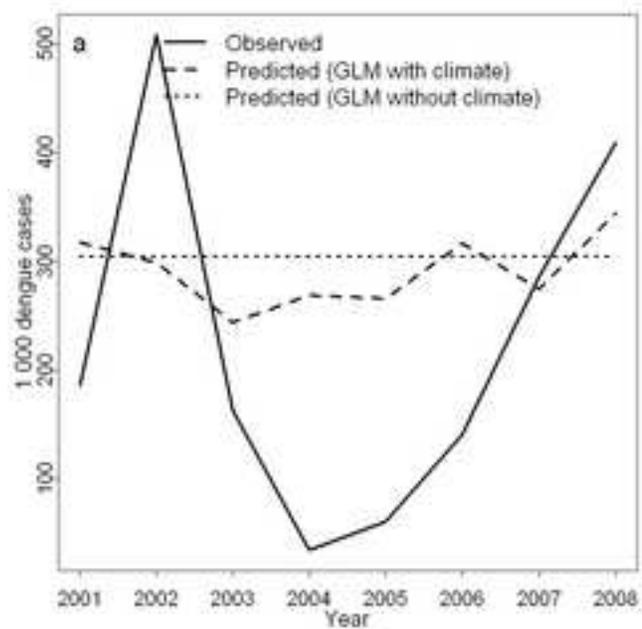


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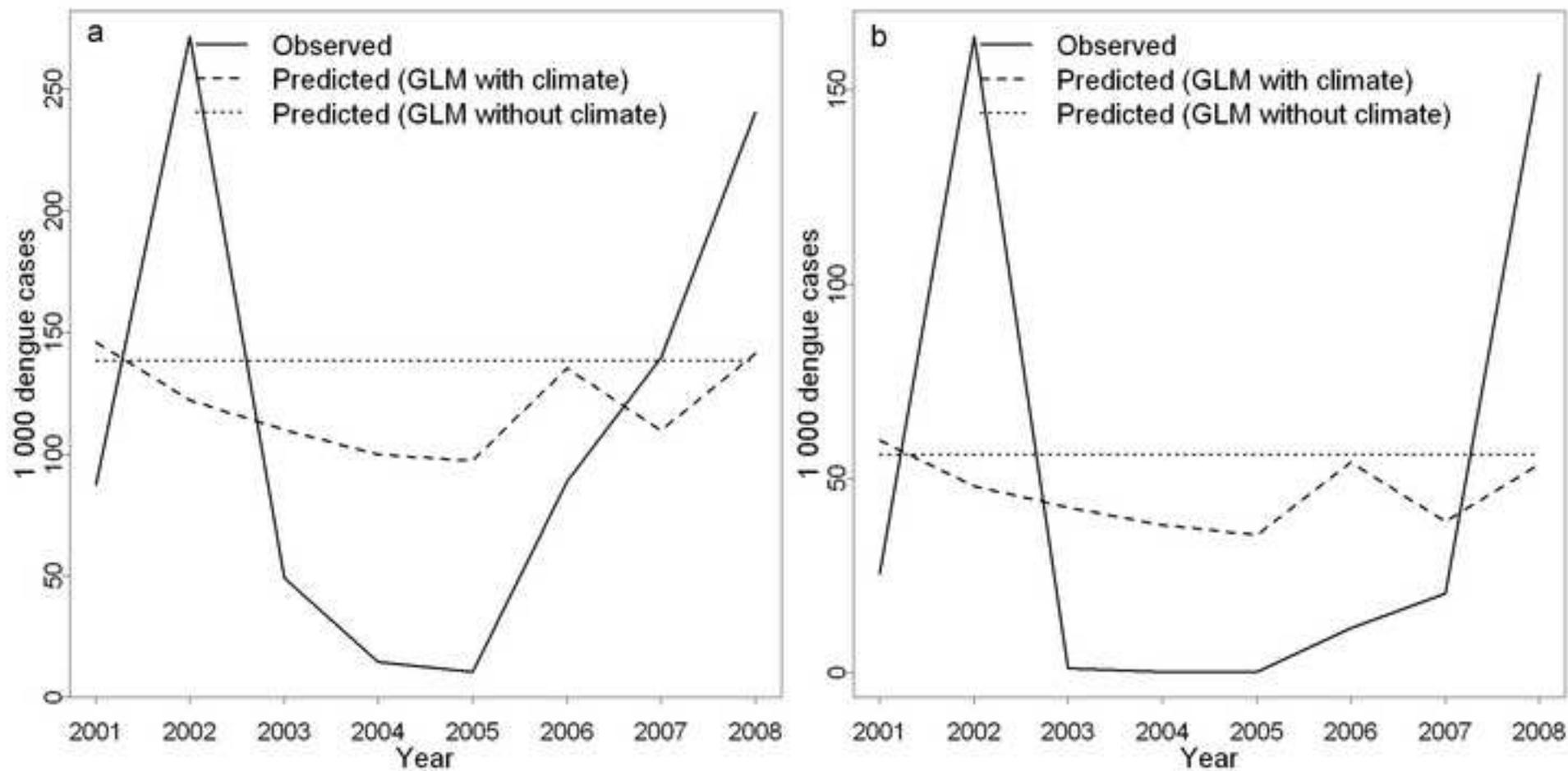


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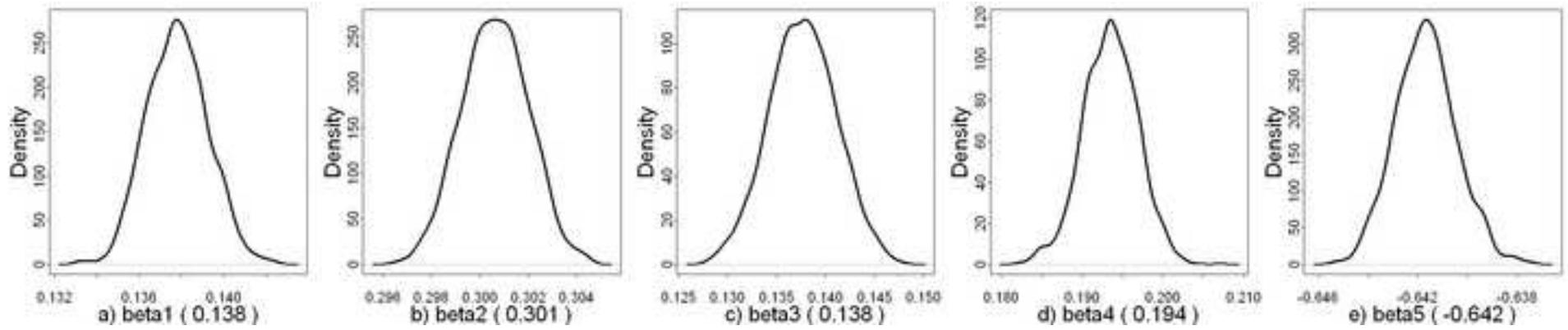


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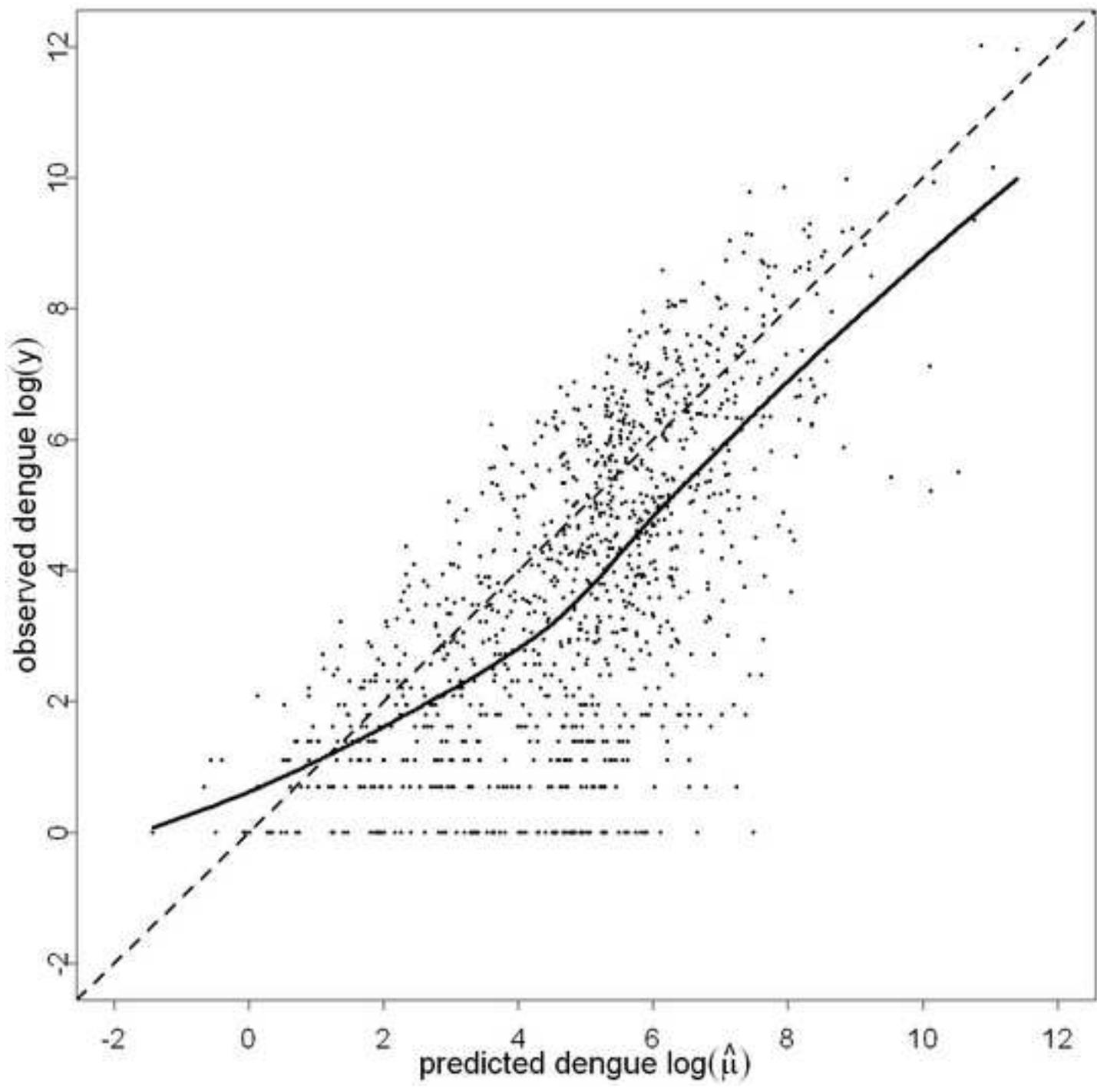


Figure 10

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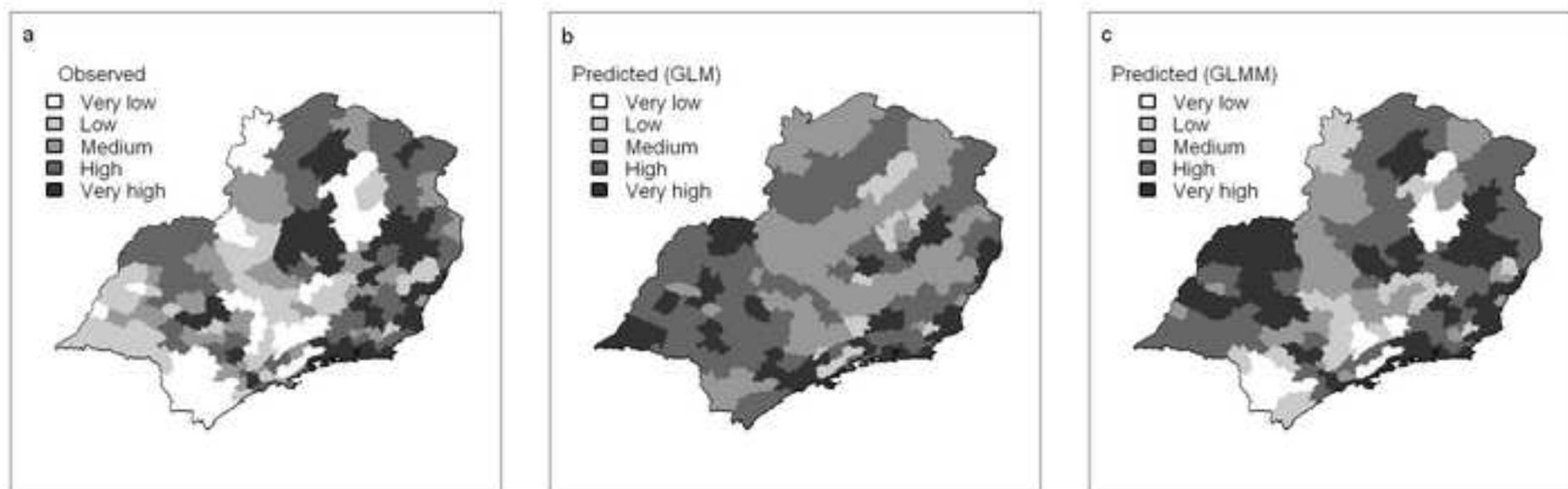


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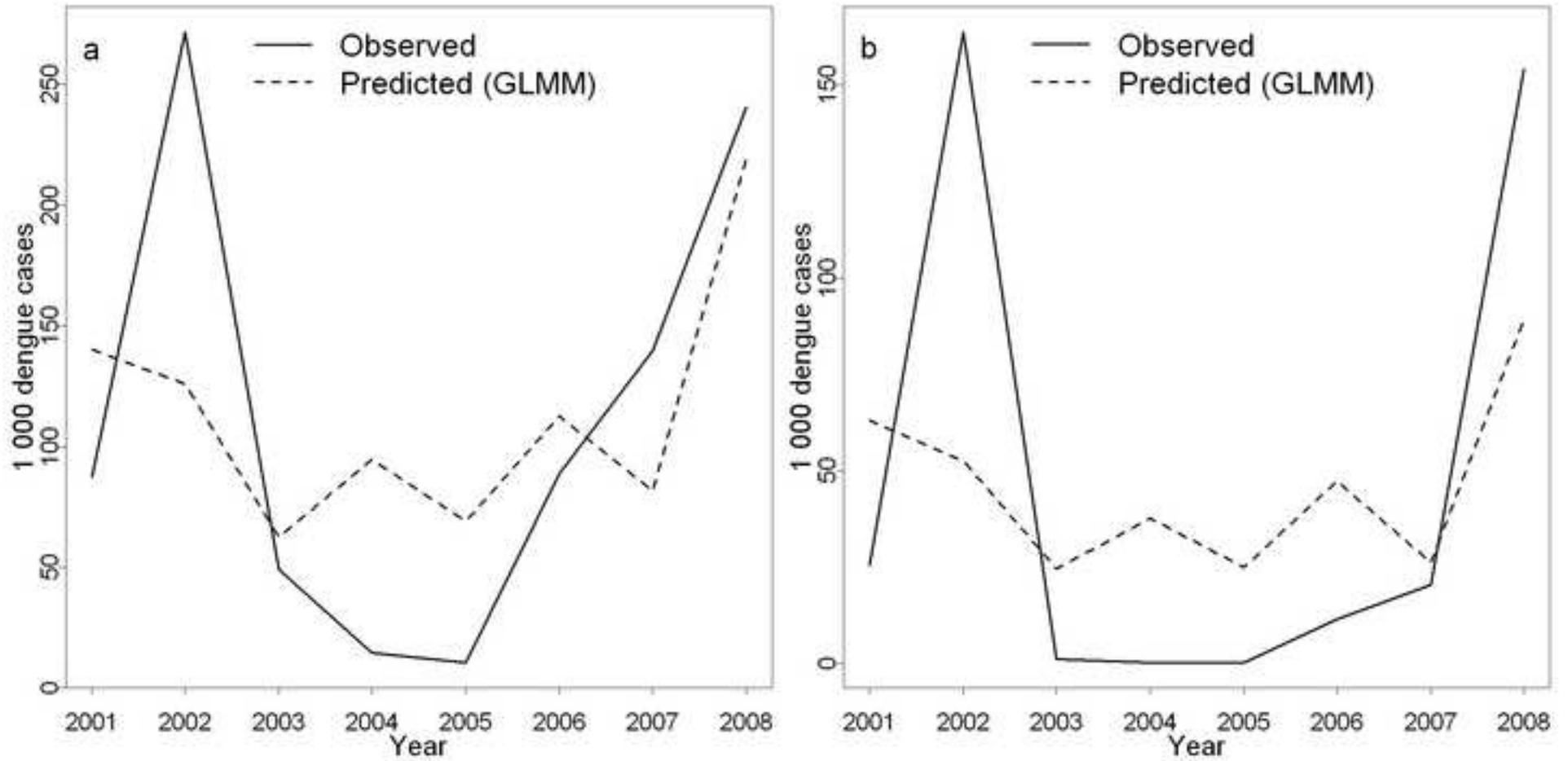


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