1 Modeling the relative role of human mobility, land-use and climate factors on dengue outbreak
2 emergence in Sri Lanka
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6 Ying Zhang[1,2], Jefferson Riera[3], Kayla Ostrow[1], Sauleh Siddiqui[1,4], Harendra de Silva[5], Sahotra Sarkar[6],
7 Lakkumar Fernando[7], Lauren Gardner[8,1*]
8
9 [1]Department of Civil Engineering, Johns Hopkins University, Baltimore, MD 21218, USA
10
11 [2]Department of Earth and Planetary Sciences, Johns Hopkins University, Baltimore, MD 21218, USA
12
13 [3]Department of Environmental Health and Engineering, Johns Hopkins University, Baltimore, MD 21205,
14 USA
15
16 [4]Department of Applied Mathematics and Statistics, Johns Hopkins University, Baltimore, MD 21218,
17 USA
18
19 [5]Department of Pediatrics, University of Colombo, Colombo, 00900, Sri Lanka
20
21 [6]Department of Philosophy, Department of Integrative Biology, University of Texas at Austin
22 Austin, TX, 78712
23
24 [7]Centre for Clinical Management of Dengue and Dengue Haemorrhagic Fever, Negombo, 11500, Sri Lanka
25
26 [8]School of Civil and Environmental Engineering, University of New South Wales (UNSW) Sydney,
27 Sydney, NSW, 2052 Australia
28
29 [*]Corresponding Author: l.gardner@unsw.edu.au, (+61 (02) 9385 5562)
30
31
32 Email of other authors:
33 Ying Zhang: ying.zhang@jhu.edu
34 Jefferson Riera: jriera1@jhu.edu
35 Kayla Ostrow: kostrow5@jhu.edu
36 Sauleh Siddiqui: siddiqui@jhu.edu
37 Harendra de Silva: harendra51@gmail.com
38 Sahotra Sarkar: sarkar@austin.utexas.edu
39 Lakkumar Fernando: lakkumar@gmail.com
40

41   **Abstract**

42   We present a statistical modeling framework to evaluate the spatial-temporal dynamics of the 2016-2017
43   dengue outbreak in the Negombo region of Sri Lanka as a function of human mobility, land-use, and
44   climate patterns. The analysis was conducted at a 1 km × 1 km spatial resolution and a weekly temporal
45   resolution. Our results indicate human mobility to be a significantly stronger indicator for local outbreak
46   clusters than land-use or climate variables, thus highlighting the potential value of using travel data to
47   target vector control within a region. The minimum daily temperature was identified as the most
48   influential climate variable on dengue cases in the region; while among the set of land-use patterns
49   considered, urban areas were found to be most prone to dengue outbreak, followed by areas with stagnant
50   water and coastal areas. The results are shown to be robust across spatial resolutions. In addition to
51   illustrating the relative relationship between various potential risk factors for dengue outbreaks, the results
52   of our study can be used to predict where and when new cases of dengue are likely to occur within a
53   region, and thus help more effectively and innovatively, plan for disease surveillance and vector control.

54
55   Keywords: dengue; outbreaks; risk factors; human mobility; climate; land-use; spatial-temporal dynamics;
56   statistical modeling, Sri Lanka

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1. Introduction

Dengue is a mosquito-borne viral disease that infects approximately 390 million people globally every year, particularly in tropical and subtropical countries (1, 2). The high number of infections combined with the lack, as yet, of an effective vaccine has made dengue a notorious public health problem (2, 3).

Dengue spreads through the bite of infected *Ades* mosquitoes, especially *Aedes aegypti*– the primary vector, with an estimated 15 to 17-day delay between the primary and secondary human infections (4). Dengue outbreak control is a challenge for policy makers because *Aedes aegypti* mosquitoes are well adapted to high density urban environments and actively feed during the day (5-7), thus presenting an elevated risk to humans. Urban settings provide an ideal habitat for *Aedes aegypti* breeding due to an abundance of discarded trash bags, plastic bottles, tires, and other containers that enable the formation of stagnant shallow water surfaces after precipitation (8). Urban regions in developing countries are particularly vulnerable due to a lack of indoor plumbing infrastructure that, in conjunction with a lack of air-conditioning, results in higher human-mosquito exposure rates during the day. Additionally, because of the daytime feeding behaviors of *Aedes aegypti*, common vector control measures that work for night-biting mosquitoes, such as bed nets, fail to effectively control dengue transmission. Given these challenges, there is a need to better understand and predict dengue outbreaks and transmission risk within urban regions in developing countries so that vector control and surveillance resources can be optimally allocated.

Previous studies highlighted human mobility as a critical factor for dengue transmission (9-15), which contrasts the more minor role travel plays in the spread of vector-borne diseases transmitted by night-biting mosquitoes (15). While *Aedes aegypti* mosquitoes have a hard time dispersing geographically across large areas because they rarely travel more than 400m from where they emerge as adults (16-19), humans regularly travel much longer distances on a daily basis. As new dengue cases and clusters are regularly reported kilometers apart, it is likely that human mobility play a critical role in the spread of dengue outbreaks, *i.e.,* infected humans introduce dengue into new mosquito populations at their trip ends. As an example, Vazquez-Prokopec, Montgomery (12) studied the pattern of dengue transmission using location-based contact tracing on infected dengue patients during a dengue outbreak centered at Cairns, Australia. They collected locations that the patients frequently traveled to during the daytime and 2-4 weeks prior to the onset of symptoms through phone interviews. The contact locations with a proximity of 100 meters and a separation of 20 days were spatial-temporally linked into pairs and then chains to identify the plausible sites of dengue virus transmission. They showed that the complex pattern of dengue transmission was primarily driven by human mobility, and that targeted residual spaying could potentially reduce the probability of dengue transmission up to 96%. Their study highlights the importance of understanding dengue transmission patterns to optimize the allocation of dengue prevention and vector-control measures.

In addition to human mobility, recent studies have pointed to a strong association between climate conditions and dengue outbreaks at various locations and across different temporal resolutions (8, 20-24). Precipitation, mean temperature and temperature fluctuation were revealed to affect the population dynamics of *Aedes aegypti* mosquitoes and the dengue virus extrinsic incubation period (25-29). Specifically, a suitable average temperature and moderate temperature fluctuations are often favorable for dengue transmission (25), while an increase in precipitation is strongly associated with the onset of a dengue outbreak (22). Humidity, a combined effect of precipitation and temperature, is also a common climate index to evaluate the environmental capacity for dengue emergence (20, 21, 30, 31). Wesolowski, Qureshi (13) accounted for both climate and mobility in a study of dengue virus transmission over a large dengue outbreak period in Pakistan. They developed an epidemiological model that included temperature and relative humidity as input parameters for mosquito dynamics, as well as biting rate to capture the interactions between human and mosquito hosts. Human mobility was captured using mobile phone data

110 of ~40 million subscribers to estimate the spatially explicit travel volume, albeit not differentiating
111 infected and non-infected people. They showed that the emergence of dengue epidemics in a new region
112 could be predicted using aggregated travel patterns from endemic areas in combination with the
113 developed epidemiological model. While climatic factors were found to be significant for prediction, this
114 was in part due to the large study region, *i.e*., country level, which has variable climatic suitability for the
115 mosquito vector. The study region considered in our work is much smaller and has minimal climactic
116 variability, thus alternative methods are required to distinguish site-specific risk.

118 Land-use patterns — indicators of human activities and potential breeding habitats — have also been
119 linked to dengue outbreaks (32-37). Previous studies investigated the effect of land-use patterns on the
120 spread of dengue and found that human settlements, water bodies, and mixed horticulture are the top three
121 associated land-use patterns for dengue emergence in Malaysia (35). In another study (36), areas
122 surrounded by rice paddies and marshes/swamps were associated with a significantly higher population of
123 dengue vectors during the rainy season in Thailand. Orchards (which often contain artificial water
124 containers) and irrigation fields have also been shown to play an important role in dengue infections;
125 however, their role varies given different local conditions. Sometimes, land-use type can be a proxy for
126 other features, such as socio-economic factors, which may have a contradictory effect on dengue
127 infections (37).

129 In this study, we present a statistical modeling framework to evaluate the relative role of human travel
130 patterns, climate conditions, and land-use patterns on dengue outbreak dynamics in Negombo, Sri Lanka
131 (Figure 1). With more than 80,000 dengue cases including 215 deaths reported nationally in less than
132 seven months at the beginning of 2017, the recent dengue outbreak in Sri Lanka increased the number of
133 reported cases by 4.3 times compared to the average number over 2010-2016 (38). The region of
134 Negombo, located in the Western province, experienced the greatest number of dengue cases in the
135 country; approximately 45% of the cases nationwide by July 2017 (Figure 1). We applied a mixed-effects
136 model, where the mobility data bridges the time-varying, spatially-invariant climate variables and the
137 rasterized spatially explicit, time-invariant population and land-use variables, to capture the
138 spatial-temporal dynamics of dengue transmission. Our model framework differs from previous studies
139 that simulated the transmission process (12, 13, 39), and instead focuses on estimating the timing and
140 location of new case introductions though a non-process based statistical model. Specifically, we focus on
141 modeling the home locations of (newly infected) dengue patients, and assume dengue is introduced in
142 new areas by infected individuals who travel to the area. This assumption is consistent with previous
143 studies that have shown visits to a household by infected people determines the infection risk in that
144 household (11). In addition, the study was conducted at a fine-grained spatial and temporal resolution —
145 1 km × 1 km spatially and one week temporally — providing an improved understanding of the role of
146 mobility in the spread of dengue. While previous work studied the impact of mobility (12, 13), climate (8,
147 20, 22, 25), and land-use (35-37) separately on dengue, the authors are unaware of any existing study that
148 considers these factors within a single integrated framework. Thus, previous studies have been unable to
149 quantify the relative contribution of each factor on the spatial-temporal patterns of dengue transmission as
150 we do. The results from our study indicate that mobility is a much more significant predictor of new
151 dengue case clusters compared with land-use and climate data alone. Furthermore, the case study in Sri
152 Lanka provides critical insights into effective application of dengue prevention and vector control
153 measures in developing regions.

Landuse Cover Class
- Homesteads
- RockS
- BuiltUp
- Marsh
- Rubber
- Coconut
- OthAg
- Scrubland
- FlwWtr
- Other
- Sea
- Forest
- Paddy
- StWtr
- Climate Station

Dengue Cases
- 0 - 500
- 500 - 1000
- 1000 - 1500
- 1500 - 2000
- 2000 - 2500
- 2500 - 3000
- 3000 - 3500
- 3500 - 4000
- 4000 - 4500
- 4500 - 5000
- 5000 - 5500
- 5500 - 6000
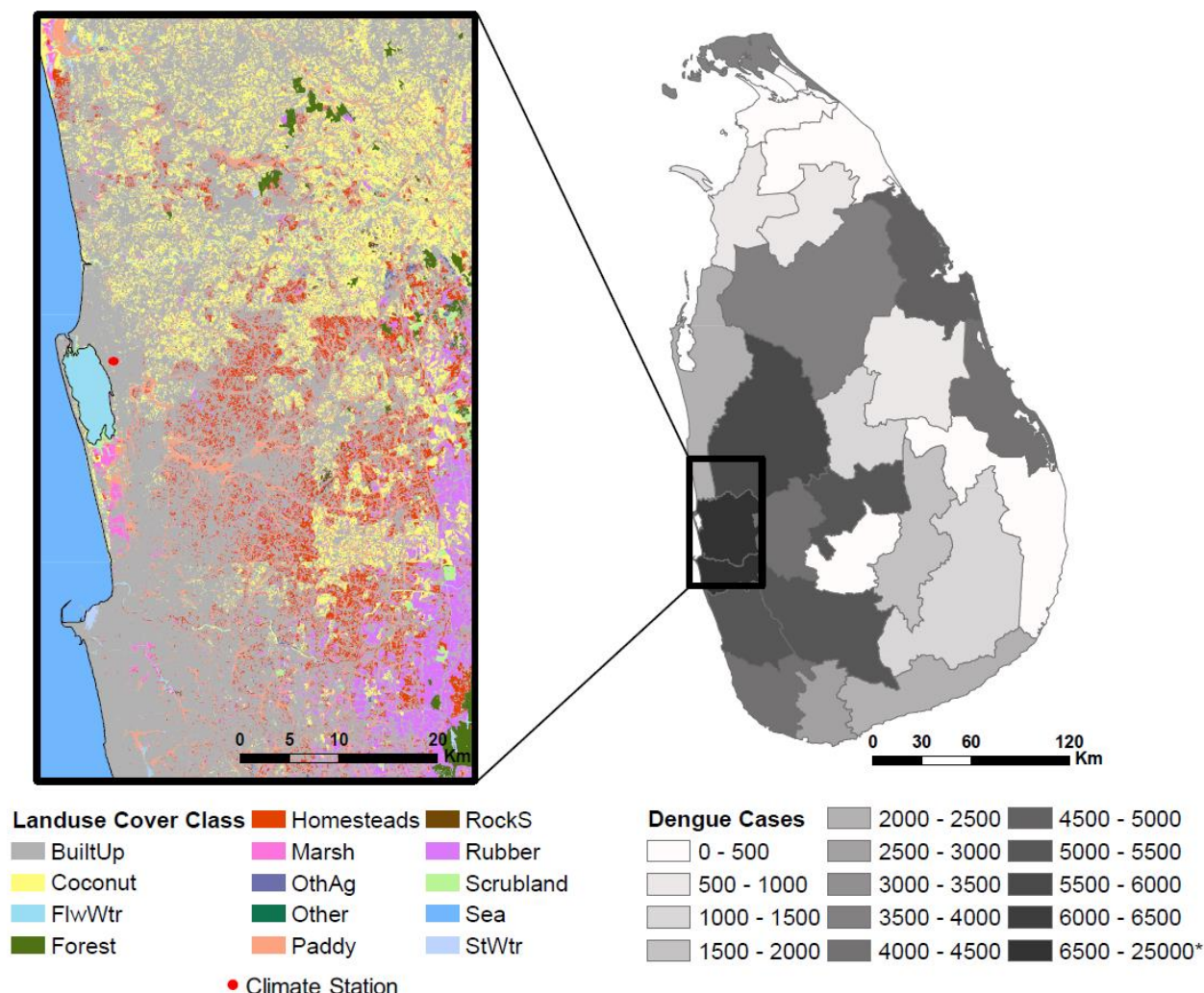- 6000 - 6500
- 6500 - 25000*

Fig. 1. Land-use groups and the climate station in the study region of Negombo, Sri Lanka (left), and the total number of dengue cases at the district level in Sri Lanka (40) during the months from October 2016 to June 2017 that cover our study period (right).

2. Data and Methods

A statistical model is applied to investigate the spatial-temporal dynamics of dengue outbreak with respect to a range of potential explanatory variables. The complete set of potential explanatory variables is listed in Table 1. Detailed descriptions of the data followed by a description of the methodology are provided below.

(a) Case and Mobility Data

A patient survey was conducted among dengue patients in the Negombo region of Sri Lanka over an approximately 8-month period during a major outbreak spanning from end of October 2016 to early July 2017. Data were collected from all patients admitted to the special High Dependency Unit (HDU) for critically ill dengue patients within the Clinical Centre for Managing Dengue and Dengue Haemorrhagic Fever (CCMDDHF) at the Negombo Hospital in Negombo, Sri Lanka. Specifically, the date of admission, home address, the complete set of locations visited, and corresponding trips made between all locations during the 10-days prior to hospital admission were collected from all HDU CCMDDHF admitted

172 patients for the entire study period. The case data provide spatial-temporal information on the outbreak
173 patterns, while the mobility data collected captures daily travel activity of the admitted dengue patients.
174 The data were collected by trained students and supervised by a Senior House Officer on site. For
175 weekday admissions the patients were surveyed upon admittance, for night admissions data were
176 collected the following day, and for weekend admissions on the following Monday. The majority of
177 admissions were 48 to 72 hours following the onset of fever. Dengue infection was confirmed for the
178 patient set using either NS1 antigen or IgM antibody diagnostic test.
179
180 **(b) Climate Data**
181 We used the Global Surface Summary of the Day (GSOD) daily weather data (41) from a station in
182 Negombo (Figure 1) to explore the impact of climate factors on the dengue outbreak. The location of the
183 weather station (7.18ºN, 79.87ºE) is approximately in the center of the study region and it is the only
184 station that falls into our study region with a comprehensive set of climate data available during the study
185 period. There are several global reanalysis products that provide spatial-explicit climate data during the
186 study period; however, upon evaluation against the station observations, these globally gridded data sets
187 did not provide accurate representations of the local climate variables, particularly at a daily time-step
188 (Figure S1). Hence, the weather data are assumed to be representative for the region which has relatively
189 homogeneous weather patterns (42). We selected a range of potential climate variables based on previous
190 studies (8, 20-22, 25-31), including daily mean temperature (*T*avg), daily maximum temperature (*T*max),
191 daily minimum temperature (*T*min), diurnal temperature range (*DTR*), precipitation (*Pre*), the number of
192 raining days (*RD*), and relative humidity (*RH*) to analyze climatic influence for the weeks before and
193 during the same period of analysis that the mobility data was collected.
194
195 **(c) Population and Land-use Data**
196 We used a global population data layer based on Landscan 2016 (43), that is available at an
197 approximately 1 km × 1 km resolution to represent the population distribution spatially. We aggregated
198 the data to 5 km × 5 km grid for additional analysis with a coarser spatial resolution. Land-use data (44)
199 were obtained from the Sri Lanka Survey Department which performed an initial survey in 2000 and has
200 since continuously updated the maps. The map was extracted for our region of interest and reclassified
201 into several groups (Figure 1): *Sea, Standing Water (StWtr), Flowing Water (FlwWtr), Coconut, Marsh,*
202 *Paddy, Built-up (BuiltUp), Scrubland, Homesteads, Forest, Rubber, Rock/Sand (RockS), Other*
203 *Agriculture (OthAg), and Other.* Water bodies were categorized depending on the potential effect on
204 dengue transmission dynamics. Additional details on land-use classification groupings and processing is
205 available in the supplementary material.
206
207 **(d) Data Processing and Statistical Model**
208 We divided the study region (Figure 1) into a grid at a 1 km × 1 km resolution and aggregated daily data
209 into a 1-weekly resolution. The number of patients who were admitted to the hospital during each week of
210 the recorded time period was used to generate the weekly number of newly admitted dengue patients in
211 each cell based on their home locations.
212
213 To incorporate the role of mobility into the model we used the travel itineraries provided by the patients
214 to generate a time-dependent connectivity matrix, which represented the total number of trips made by
215 dengue infected patients between each pair of cells for each week of the study period. The travel data
216 included all destinations visited each day during the 10 days preceding hospital admittance (the time
217 interval that the patient is assumed to be able to spread the disease) for each patient. The number of daily
218 trips between each pair of cells was summed over all patients, to provide daily trip volumes between cells,
219 and then aggregated to the weekly level. For each cell the total incoming weekly trips was summed to
220 define our 'trip' variable, which is the total number of trips made by infected dengue patients entering a
221 given cell i in a given week t, V_t^i, and was used as a spatial-temporal explanatory variable in the model.
222 The same method was used for the 5 km × 5 km analysis.

223
224   Climate variables were averaged or aggregated temporally to a weekly resolution, including weekly
225   average Tavg, Tmin, Tmax, DTR, RH, weekly total Pre, and RD. Land-use data were aggregated spatially
226   to match the targeted spatial grid resolution. The population data were in an original resolution that
227   matched the 1 km × 1 km grid. For land-use, the percentage of occupied land of each type was determined
228   for each 1 km × 1km grid cell. Both were subsequently aggregated to a 5 km × 5 km grid.

229   A mixed-effects model combined with backward elimination of insignificant fixed effects was applied to
230   investigate the spatial-temporal dynamics of dengue outbreak with the potential explanatory variables at a
231   weekly time step and 1 km × 1 km spatial resolution. In building the model we first conducted sensitivity
232   analysis to identify the optimal set of climatic variables to include in the model, and corresponding time
233   lag for each of them. Among the climate variables, significant correlations were observed for weekly
234   averaged daily mean temperature (Tavg), daily minimum temperature (Tmin), and diurnal temperature
235   range (DTR) with a lead time ranging from 7 days to 17 days prior to the weekly admitted number of
236   patients (N_t), where the lead time (d_c) is the lag in days between the climate variable and N_t (Figure S2).
237   Regression models based on different combinations of the climate variables and lead time were developed
238   and compared; the best performance model was select based on F-test and adjusted-R^2. As a result, Tmin
239   with an optimal lead time of 10 days was included in the final set of mixed-effects models to account for
240   the partial influence of climate on the dengue outbreak ($R^2 = 0.248$; $adj.$ $R^2 = 0.226$). This is consistent
241   with previous findings (29) that daily minimum temperature were associated with increase in the larval
242   abundance. We assumed a relatively homogenous climate over the study region, thus $Tmin$ does not vary
243   spatially over the study region.
244
245   Along with the chosen climate variable, Tmin, the remaining set of potential explanatory variables (Table
246   1) was taken into the mixed-effects model initially, with population included in the spatial random effects.
247   Population density was incorporated using random effects in the model because population is likely to
248   have spatially heterogeneous effects on dengue outbreaks (39, 45). For example, high population areas
249   may imply access to tap water and better living conditions which could restrict dengue transmission (46),
250   while the higher density of population facilitates disease spread. Furthermore, there could be spatial
251   variance in the distribution of people living in a particular area. In addition to mobility, climate, and
252   land-use variables; the number of new cases in a given cell in the weeks prior were added as explanatory
253   variables to account for autocorrelations in the case data. Subsequently, the variable with the most
254   insignificant fixed-effects coefficient was eliminated each iteration, until only variables with significant
255   coefficients (at 95% significance level) remained in the model. A range of lead time for V_t^i prior to the
256   admitted week was also tested. A separate analogous process was conducted using a 5 km × 5 km
257   resolution, to test the sensitivity of model results across spatial resolutions, and the robustness of the
258   modeling framework and findings.
259
260   Thus, the mathematical representation of the model is given by:
261

262    $$N_t^i = \sum_{l \in \overline{L}} \alpha_l l^i + \sum_{c \in C} \beta_c c_{t,d_c} + \sum_u \gamma_u V_{t-u}^i + \sum_w \delta_w N_{t-w}^i + a^i + b^i P^i + \varepsilon_t^i$$

263
264   Where
265
266   i is the cell index; $i = 1, 2, \ldots$.
267   l is the land-use variable, which belongs to the land-use group set $\overline{L}$, where $\overline{L}$ includes *Sea, StWtr, FlwWtr,*
268   *Coconut, Marsh, Paddy, BuiltUp, Scrubland, Homesteads, Forest, Rubber, RockS, OthAg,* and *Other*.
269   l^i is the occupation percentage of land-use group l in cell i, time-invariant.
270 P^i is the population in cell i, time-invariant

271   t is the time index at weekly resolution; $t = 1, 2, \ldots$.

272   N_t^i is the number of patients who are admitted to the hospital during week t, whose home locations are in
273   cell i

274   N_{t-w}^i is the number of patients who are admitted to the hospital during week $t\text{-}w$, whose home locations
275   are in cell i, where w is measured in weeks; $w = 1, 2, \ldots$

276   V_{t-u}^i is the number of total number of trips made into cell i during the week $t\text{-}u$, where u is measured in
277   weeks; $u = 1, 2, \ldots$

278   c is the climate variable which belongs to the climate variable set $\bar{C}$. $\bar{C}$ includes Tavg, Tmax, Tmin, DTR,
279   Pre, RD, and RH.

280   c_{t,d_c} is the climate variable during the week that begins d_c days prior to the start of week t. d_c ranges
281   from 7 to 17 days and can be different for different climate variables. Multiple climate variables can be
282   included in the model.

283   ε_t^i is the model residuals associated with cell i and week t.

284   α_l is the estimated fixed-effects coefficient for l.

285   β_c is the estimated fixed-effects coefficient for c.

286   γ_u is the estimated fixed-effects coefficient for V_{t-u}^i.

287   δ_w is the estimated fixed-effects coefficient for N_{t-w}^i.

288   a^i is the intercept associated with cell i.

289   b^i is the estimated spatial random-effects coefficient for P^i.
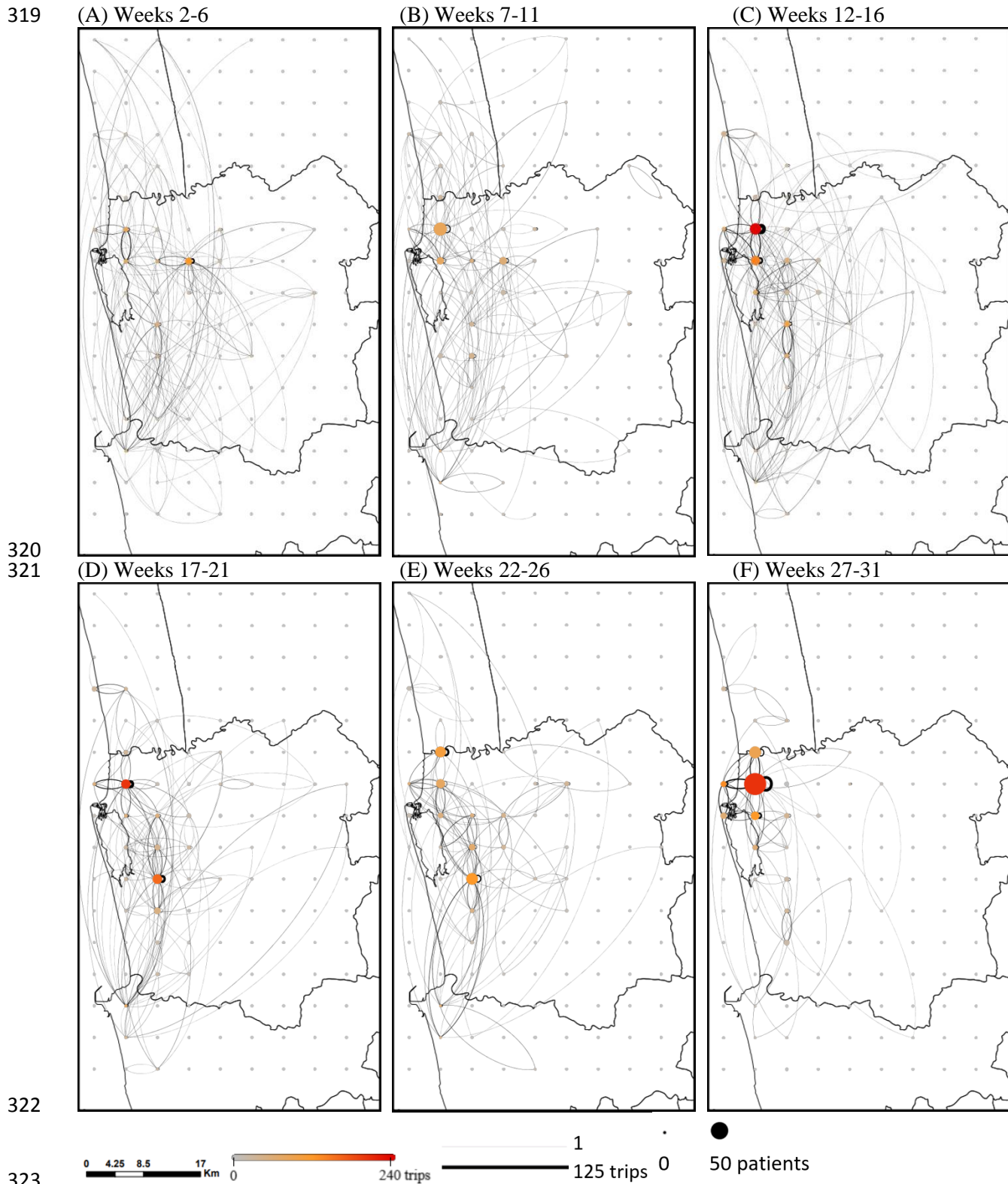
3. Results

(a) Data Analysis

292   The number of admitted dengue patients aggregated over the study region peaks during December and
293   June (Figure 2), aligned with the monsoon months (47). Figure 2A illustrates the relationship between the
294   total number of dengue patients, N_t, admitted during each week t and the total number of recorded patient
295   trips during the same week (V_t). Figure 2B illustrates N_t and the weekly averaged minimum daily
296   temperature in week t ($T\text{min}_t$). It shows a lagged relationship of N_t with $T\text{min}_t$, mostly in the same
297   direction. For the purposes of these graphics, the variables are aggregated over the entire study region.

299   (A)   (B)
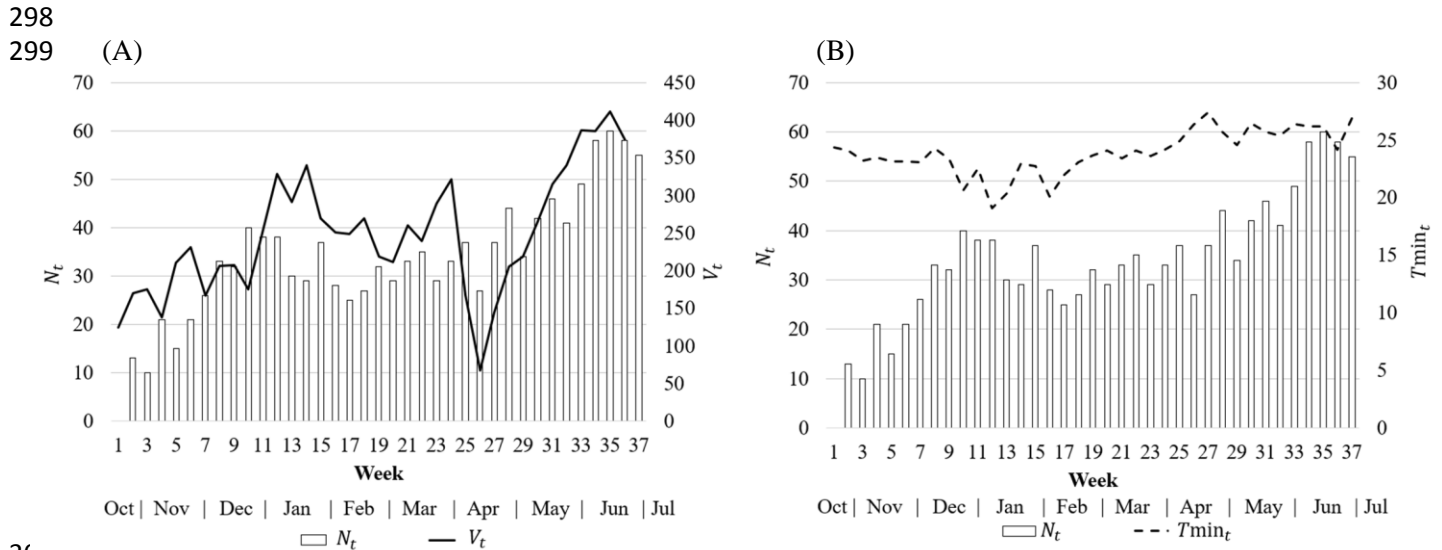
Fig. 2. The number of admitted dengue patients in week t (N_t) and (A) the number of recorded trips in week t (V_t) summed over the entire study region, and (B) the weekly averaged minimum daily temperature ($T\text{min}_t$).

305   The travel destinations recorded in our study include medical facilities, homes, workplaces, schools, and
306   others (Figure S3). Additional analysis performed reveals that a vast majority of trips were longer than the
307   distance a mosquito can travel. Specifically, 96.6% of the trips were longer than 0.4 km (Table S1; Figure
308   S4), outside the range of a mosquito's maximum travel distance (16-19), further supporting the role
309   human mobility is likely to play in the outbreak.

310

311   Figure 3 illustrates both the spatial-temporal distribution of dengue patients' home locations over the
312   course of the outbreak, and the corresponding travel patterns of the patients during 5-week periods. The
313   patient home locations were well distributed over the area of the study region for the first few months of
314   the outbreak, with correspondingly scattered travel patterns. However, as the outbreak progressed, the
315   recorded case locations and the trip ends of newly infected dengue patients became more concentrated
316   near the town center and just above the lake. There were also a large amount of trips (>100) within the
317   cell near the town center.

318

319 (A) Weeks 2-6 (B) Weeks 7-11 (C) Weeks 12-16

320
321 (D) Weeks 17-21 (E) Weeks 22-26 (F) Weeks 27-31

322

323

Fig. 3. Weekly number of patients and the number of trips summed over 5-week intervals for a 5 km × 5 km resolution. Patient home locations are plotted as the case location. The size of the circle indicates the number of patients admitted during the time period. The color of the circle indicates the number of trips

327 that end in the grid cell during the time period. The thickness of the line is proportional to the number of
328 trips made between two locations. Week 2 begins on October 27, 2016 and week 31 begins on May 18,
329 2017. For visual clarity, the 5 km × 5 km resolution was used for the figure, instead of 1 km × 1 km.

330

331 **(b) Model Results**
332 A mixed-effects model was developed to estimate the number of new dengue cases in a given cell in a
333 given week as a function of the mobility patterns of individuals infected with dengue in the preceding
334 week(s), as well as land-use and climate data from days prior.

335 **Table 1: Summary of potential explanatory variables**

336

Variables	Description	Properties
l^i	occupation percentage of land-use group l in cell i (%)	
BuiltUp	urban area	
Coconut	coconut cultivation land	
Homesteads	homesteads and garden	spatially-explicit, time-invariant
Paddy	rice cultivation land	
Sea	ocean	
StWtr	standing water	
FlwWtr	flowing water	
c_{t,d_c}	weekly value of climate variable in week t with a lag of d_c	
*T*avg	weekly averaged daily mean temperature	
*T*max	weekly averaged maximum daily temperature	
*T*min	weekly averaged minimum daily temperature	
DTR	weekly averaged diurnal temperature range	time-varying, spatially-invariant
Pre	weekly total precipitation	
RD	weekly number of raining days	
RH	weekly averaged daily relative humidity	
P^i	population in cell i	spatially-explicit, time-invariant
V^i_{t-u}	number of trips made to cell i in week t-u	spatially-explicit, time-varying
N^i_{t-w}	number of patients admitted to hospital who live in cell i in week t-w	spatially-explicit, time-varying

337
338 *Note: t, u,* and *w* in weeks, d_c in days. For notation, variable superscripts in Table 1 denote spatial indices
339 and subscripts denote time indices.

340

341 Multiple models with explanatory variables representing land-use, climate, and mobility were created,
342 and the three representative models are presented here. The three models vary based on the type of
343 mobility variable included, specifically how far back in time travel is accounted for. The first model
344 includes the mobility patterns one-week prior ($u = 1$), the second model includes the mobility patterns
345 two-weeks prior ($u = 2$), and the third model excludes mobility altogether ("Exclude *V*"). The final set of
346 climate and land-use variables found to be significant varies between models. All explanatory variables
347 were standardized to a mean of zero and a standard deviation of one in the mixed-effects model. The
348 fixed-effects coefficients (Table 2) therefore reflect the relative influence of each explanatory variable on
349 the dengue outbreak dynamics.

350

351   The results (Table 2) for each of the three models are presented for both a 1 km × 1 km and 5 km × 5 km
352   resolution, and reveal that the mobility patterns of dengue patients, specifically the number of trips made
353   into a cell in a given week, to be the most reliable predictor of new dengue cases in that cell the following
354   week. Under the spatial resolution of 1 km × 1 km, the fixed-effects coefficient for the trips one week
355   prior ($u = 1$) is 0.483, which is considerably greater than the fixed-effects coefficients for other
356   explanatory variables, suggesting human mobility plays a critical role in dengue outbreak dynamics.
357   Results also illustrate a decrease in explanatory power of mobility patterns further than a week in advance,
358   with the magnitude of the trips variable coefficient drastically decreased with a lead time of two weeks (u
359     $= 2$) to 0.078. This result highlights the importance of collecting and utilizing mobility data within an
360   appropriate lead time for the purposes of outbreak prediction modeling. When mobility data is excluded
361   from the model altogether, the adjusted R^2 decreases from 0.419 to 0.262. In general, the power of the
362   number of trips in predicting dengue cases deteriorates with longer lead time, with the number of trips
363   two-weeks prior showing little advantage over other explanatory variables. The same conclusion is
364   applicable for the results under the 5 km × 5 km resolution, as shown in Table 2.
365

366   Among the seven land-use groups (see variable descriptions in Table 1) under the 1 km × 1 km resolution,
367   only *BuiltUp* shows significant positive fixed effects on dengue cases, but only when the mobility
368   variable one week prior was excluded (Table 2). Under the coarser spatial rasterization of 5 km × 5 km,
369   *StWtr* and *Sea* also show significant positive fixed effects, in addition to *BuiltUp*. Whereas *BuiltUp* shows
370   significant fixed effects in all three models with the coefficients ranging from 0.032 to 0.050, *StWtr*
371   shows significant coefficients of 0.031 and 0.032 in two of the models, and *Sea* shows the significant
372   coefficient of 0.029 only in the model with the trip variable excluded. It indicates that urban areas, areas
373   with standing water, and areas near the coastline are associated with a higher risk of dengue infections;
374   the effect is stronger under the 5 km × 5 km spatial resolution. In contrast, human mobility is shown to be
375   a significant and robust predictor of dengue dynamics for both spatial resolutions.
376

377 **Table 2: Fixed-effects coefficients and standard error of the mixed-effects model outputs based on**
378 **the 1 km × 1 km and 5 km × 5 km resolution, respectively. The presented results are post-completion**
379 **of the backward elimination of nonsignificant fixed effects. Variables without coefficients listed in**
380 **the table were eliminated during the backwards elimination procedure for each model (each**
381 **column). Variable descriptions are listed in Table 1.**

	1 km × 1 km			5 km × 5 km		
	$u = 1$	$u = 2$	Exclude V	$u = 1$	$u = 2$	Exclude V
BuiltUp		0.050***	0.053***	0.032*	0.034*	0.050**
		(0.013)	(0.014)	(0.014)	(0.014)	(0.016)
Sea						0.029*
						(0.013)
StWtr					0.031**	0.032**
					(0.011)	(0.011)
$Tmin_{t,\,d_{Tmin}}$	0.030***	0.028***	0.026***	0.032***	0.024*	0.021*
	(0.0066)	(0.0074)	(0.0074)	(0.0088)	(0.010)	(0.0098)
V^i_{t-1}	0.483***			0.417***		
	(0.0080)			(0.015)		
V^i_{t-2}		0.078***			0.059**	
		(0.010)			(0.018)	
N^i_{t-1}	0.085***	0.162***	0.195***	0.204***	0.330***	0.0359***
	(0.0076)	(0.0095)	(0.0083)	(0.016)	(0.020)	(0.016)
N^i_{t-2}	0.156***	0.206***	0.217***	0.258***	0.394***	0.403***
	(0.0074)	(0.0085)	(0.0082)	(0.015)	(0.017)	(0.016)
R^2	0.419	0.268	0.262	0.783	0.728	0.727
Adj. R^2	0.419	0.267	0.262	0.782	0.728	0.727
No. obs	13532	13134	13532	2856	2772	2856

Standard errors are reported in parentheses.

t is in weeks, $d_{Tmin} = 10$ days, and all variables are normalized.

*, **, *** indicates significance at the 95%, 99%, and 99.9% level, respectively.

382 **4. Discussion**

383 The results from this study illustrate the dominant contribution of human mobility on the location and
384 timing of new dengue cases, relative to land-use and climate variables. The results are sensitive to the
385 temporal patterns of travel during the week immediately preceding the appearance of new case reports.
386 This was the variable with the greatest predictive power. Travel patterns two weeks prior still showed a
387 significant effect on dengue outbreaks, but this effect was weaker and comparable to the effects of
388 land-use and climate patterns. Our results are consistent with Stoddard, Forshey (11), who concluded that
389 visits to households by dengue infected individuals determines the infection risk, further validating our

390 use of patient home locations in the model. Furthermore, the significance of mobility in outbreak
391 prediction was found to be robust under both spatial resolutions of 1 km × 1 km and 5 km × 5 km.
392
393 In contrast to the role of mobility, which we found to be a consistently significant indicator of new
394 dengue cases, the effect of land-use patterns on the number of new cases is sensitive to the spatial
395 resolution of the models. Land-use variables played a larger explanatory role at the coarser spatial
396 resolution of 5 km × 5 km (compared to the finer 1 km × 1 km resolution), particularly for smaller
397 spatially-dominant land-use patterns such as *Sea* and *StWtr*. *BuiltUp* showed the strongest positive effect
398 overall, indicating urbanization is associated with an increased risk of dengue outbreak (which is
399 consistent with multiple previous findings (48, 49)). *StWtr* also showed significant positive effect, which
400 is to be expected because standing water provides suitable mosquito breeding habitat (19). The positive
401 effect of *Sea* only appeared significant when human mobility was excluded from the model. Given the
402 significant positive correlation between *Sea* and the number of trips (Table S2), it is likely that the large
403 travel volume towards the area near the coastline makes the study region prone to dengue outbreaks. If
404 this pattern holds in other regions, as seems likely, that fact can be used for the spatial prioritization of
405 resource allocation for disease case and vector surveillance and control.
406
407 Among the climate factors, temperature-related variables including *T*avg, *T*min, and *DTR*, were more
408 strongly associated with the outbreak emergence than precipitation-related variables including *Pre* and
409 *RD,* or *RH,* which is related to both. This finding is in accordance with (22), which concluded that
410 "rainfall strongly modulates the timing of dengue (*e.g.*, epidemics occurred earlier during rainy years)
411 while temperature modulates the annual number of dengue fever cases." Based on regression analysis, we
412 found *T*min with a 10-day lead time to be the best climate-based predictor of new weekly dengue cases.
413 Given the likely robustness of this result in other regions, this fact can be used for the temporal
414 prioritization of resources.
415
416 In addition to human mobility, climate, and land-use variables, which were included as fixed effects,
417 population density was incorporated using random effects in the model because population is likely to
418 have spatially heterogeneous effects on dengue outbreaks, as noted in the *Data and Methods*. Based on
419 the model results, the random-effects coefficients for population are mostly positive, as expected,
420 indicating that higher population density is associated with a higher number of dengue cases (Figure S5).
421 The most significant positive effect is seen north of the lagoon along the coastline, highlighting
422 potentially high risk areas, where higher populations are likely to facilitate the emergence of dengue
423 outbreaks. A few cells resulted in negative random-effects coefficients, which may be due to confounding
424 interactions between different variables included in the model, or alternative factors not captured in the
425 model; these cells were few in number, and only occurred in the model when the dominant mobility
426 variable was included. It is possible the dominant role of mobility could over compensate for the impact
427 of population, *e.g.,* because people are likely to travel to crowded downtown areas, along the lagoon, or
428 near the ocean where the large number of trips made to those regions has the ability to offset the impact of
429 population. That the random-effects coefficients for population density are positive and negative lends
430 support to the modeling decision to treat it as having enough stochasticity to qualify as a random-effects
431 variable.
432
433 The results of this analysis have implications that are relevant to the design of measures to control dengue
434 cases, such as allocation of resources for mosquito vector control. Previous global modeling of ecological
435 suitability for dengue vector mosquito species (both *Aedes aegypti* and *Aedes albopictus*) have shown that
436 the entire study area is a prime habitat for these species (50, 51). This conclusion drawn from the global
437 models finds validation in our analysis, which shows that climate and land-use variables are not the most
438 strongly associated with dengue case outbreaks. Consequently, epidemiological risk based on vector
439 ecology may be insufficient for the purposes of optimizing vector control resource allocation, as it is
440 unable to distinguish between potential sites to target within the study area. Because travel into the sites is

441　the most important predictor of new case clusters, it may well be time to optimize vector control resources
442　based on mobility data, with the aim to prevent exposure to the day-biting mosquitoes, *i.e., Aedes aegypti,*
443　at the highest risk locations. To the best of our knowledge, such a design for dengue control measures has
444　not yet been tried in the field.

446　Finally, various limitations of this study should be noted. First, only dengue patients admitted to the
447　CCMDDHF at the Negombo Hospital were included and surveyed in this study. Thus mild or
448　asymptomatic cases, which account for the majority of dengue cases (1), were not accounted for in the
449　study. Second, some patients infected in the study region may have gone to hospitals in other districts,
450　and would therefore not be included. Third, the mobility data was based on patients' recollections over a
451　10-day period prior to hospital admission, and therefore may have inaccuracies due to human error in
452　recalling the information. However, detailed analysis of the travel data revealed the vast majority of trips
453　recorded represent daily commuting routines. Thus, while some trips may be excluded due to human error,
454　we believe the relative connectivity between cells is accurately captured by the survey responses. Fourth,
455　the distance traveled and the time spent in a certain location were not considered due to the unavailability
456　of relevant data; however these factors have been shown to have little influence on dengue transmission
457　(11), and thus their exclusion does not invalidate the methodology used in this analysis. Fifth, by utilizing
458　all the mobility data collected, we made an implicit assumption that the patients were infectious during
459　the entire 10-day period prior to hospital admittance. This period does fall within the combined intrinsic
460　incubation period (4-10 days) (52) and the early symptomatic period before admitted to the hospital. A
461　sixth assumption was that the patients were infected at or around their home locations. This assumption is
462　consistent with a wide variety of previous studies that revealed homes as the primary point of contact for
463　dengue transmission (11, 53, 54). Vazquez-Prokopec, Montgomery (12) tried to identify the most
464　plausible transmission locations based on reported contact locations from a dengue outbreak in Cairns,
465　Australia and found that only 10.2% of the identified transmission sites were at out-of-home locations,
466　and a notable portion of them were actually within 1 km of the home locations. Given that our objective
467　was not to model the transmission chains of dengue as in (12), assuming home locations as the site of
468　infection provides reasonable support for predicting where infected individuals reside, and therefore the
469　risk posed around homes of infected individuals. Lastly, the climate data were obtained from a single
470　station, thus a homogenous climatic region was assumed for our study region. Therefore, the role of
471　climate factors on the dengue outbreak may be underestimated.

473　While the modeling framework used here is readily applicable to other contexts, future work should
474　investigate how widely transferable the model results are. More specifically using general mobility data
475　(tracking movements for all residents); such as using mobile phone data as in (13), or transport planning
476　data, which may be more readily available and cost effective; should be compared to the use of patient
477　mobility surveys as in this study.

480　**Ethics.** The research protocol was approved by the Director of the Negombo Hospital. Patient consent
481　was obtained in writing from all participants for the purposes of this study.

483　**Data Accessibility.** Patient case reports and travel diaries can not be shared due to privacy restrictions.
484　The remaining data used in this study is provided as a supplementary file, along with the code used to
485　generate the results.

487　**Competing Interests.** We have no competing interests.

489　**Authors' Contributions.** L.G. conceived the study. Y.Z., S.Siddique and L.G. designed the experiments.
490　Y.Z., H.S., L.F. and J.R. collected the data. Y.Z. developed the model and performed the computational

491 analysis. All authors analyzed the data and model results. Y.Z., S.Siddiqui., S.Sarkar, J.R., K.O., and L.G.,
492 contributed to the writing of the manuscript.

499 **References**
500 1.   Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global
501 distribution and burden of dengue. Nature. 2013 04/07/online;496:504.
502 2.   Simmons CP, Farrar JJ, van Vinh Chau N, Wills B. Dengue. New England Journal of
503 Medicine. 2012;366(15):1423-32. PubMed PMID: 22494122.
504 3.   Vannice KS, Roehrig JT, Hombach J. Next generation dengue vaccines: A review of the
505 preclinical development pipeline. Vaccine. 2015 2015/12/10/;33(50):7091-9.
506 4.   Aldstadt J, Yoon I-K, Tannitisupawong D, Jarman RG, Thomas SJ, Gibbons RV, et al.
507 Space-time analysis of hospitalised dengue patients in rural Thailand reveals important temporal intervals
508 in the pattern of dengue virus transmission. Tropical Medicine & International Health.
509 2012;17(9):1076-85.
510 5.   Chadee DD. Landing periodicity of the mosquito Aedes aegypti in Trinidad in relation to the
511 timing of insecticidal space-spraying. Medical and Veterinary Entomology. 1988;2(2):189-92.
512 6.   Yasuno M, Tonn RJ. A study of biting habits of Aedes aegypti in Bangkok, Thailand. Bulletin of
513 the World Health Organization. 1970;43(2):319-25. PubMed PMID: PMC2427649.
514 7.   Wong J, Astete H, Morrison AC, Scott TW. Sampling Considerations for Designing Aedes
515 aegypti (Diptera: Culicidae) Oviposition Studies in Iquitos, Peru: Substrate Preference, Diurnal
516 Periodicity, and Gonotrophic Cycle Length. Journal of Medical Entomology. 2011;48(1):45-52.
517 8.   Pathirana S, Kawabata M, Goonatilake R. Study of potential risk of dengue disease outbreak in
518 Sri Lanka using GIS and statistical modelling. Journal of Rural and Tropical Public Health. 2009;8:8-17.
519 9.   Lana RM, Gomes MFdC, Lima TFMd, Honório NA, Codeço CT. The introduction of dengue
520 follows transportation infrastructure changes in the state of Acre, Brazil: A network-based analysis. PLOS
521 Neglected Tropical Diseases. 2017;11(11):e0006070.
522 10.   Reiner RC, Stoddard ST, Scott TW. Socially structured human movement shapes dengue
523 transmission despite the diffusive effect of mosquito dispersal. Epidemics. 2014 2014/03/01/;6:30-6.
524 11.   Stoddard ST, Forshey BM, Morrison AC, Paz-Soldan VA, Vazquez-Prokopec GM, Astete H, et
525 al. House-to-house human movement drives dengue virus transmission. Proceedings of the National
526 Academy of Sciences. 2013;110(3):994-9.
527 12.   Vazquez-Prokopec GM, Montgomery BL, Horne P, Clennon JA, Ritchie SA. Combining contact
528 tracing with targeted indoor residual spraying significantly reduces dengue transmission. Science
529 Advances. 2017;3(2).
530 13.   Wesolowski A, Qureshi T, Boni MF, Sundsøy PR, Johansson MA, Rasheed SB, et al. Impact of
531 human mobility on the emergence of dengue epidemics in Pakistan. Proceedings of the National
532 Academy of Sciences. 2015;112(38):11887-92.
533 14.   Adams B, Kapan DD. Man Bites Mosquito: Understanding the Contribution of Human
534 Movement to Vector-Borne Disease Dynamics. PLOS ONE. 2009;4(8):e6763.
535 15.   Stoddard ST, Morrison AC, Vazquez-Prokopec GM, Paz Soldan V, Kochel TJ, Kitron U, et al.
536 The Role of Human Movement in the Transmission of Vector-Borne Pathogens. PLOS Neglected
537 Tropical Diseases. 2009;3(7):e481.

538   16.   Harrington LC, Scott TW, Lerdthusnee K, Coleman RC, Costero A, Clark GG, et al. Dispersal of
539   the dengue vector Aedes aegypti within and between rural communities. American Journal of Tropical
540   Medicine and Hygiene. 2005;72(2):209-20.

541   17.   Hemme RR, Thomas CL, Chadee DD, Severson DW. Influence of Urban Landscapes on
542   Population Dynamics in a Short-Distance Migrant Mosquito: Evidence for the Dengue Vector Aedes
543   aegypti. PLOS Neglected Tropical Diseases. 2010;4(3):e634.

544   18.   Getis A, Morrison AC, Gray K, Scott TW. Characteristics of the spatial pattern of the dengue
545   vector, Aedes aegypti, in Iquitos, Peru. American Journal of Tropical Medicine and Hygiene.
546   2003;69(5):494-505.

547   19.   World Health Organization, Special Programme for Research, Training in Tropical Diseases,
548   World Health Organization. Department of Control of Neglected Tropical Diseases, World Health
549   Organization. Epidemic & Pandemic Alert. Dengue: guidelines for diagnosis, treatment, prevention and
550   control: World Health Organization; 2009.

551   20.   Xu L, Stige LC, Chan K-S, Zhou J, Yang J, Sang S, et al. Climate variation drives dengue
552   dynamics. Proceedings of the National Academy of Sciences. 2017;114(1):113-8.

553   21.   Sirisena P, Noordeen F, Kurukulasuriya H, Romesh TA, Fernando L. Effect of Climatic Factors
554   and Population Density on the Distribution of Dengue in Sri Lanka: A GIS Based Evaluation for
555   Prediction of Outbreaks. PLOS ONE. 2017;12(1):e0166806.

556   22.   Morin CW, Monaghan AJ, Hayden MH, Barrera R, Ernst K. Meteorologically Driven
557   Simulations of Dengue Epidemics in San Juan, PR. PLOS Neglected Tropical Diseases.
558   2015;9(8):e0004002.

559   23.   Metcalf CJE, Walter KS, Wesolowski A, Buckee CO, Shevliakova E, Tatem AJ, et al. Identifying
560   climate drivers of infectious disease dynamics: recent advances and challenges ahead. Proceedings of the
561   Royal Society B: Biological Sciences. 2017;284(1860).

562   24.   Gloria-Soria A, Armstrong PM, Powell JR, Turner PE. Infection rate of Aedes aegypti
563   mosquitoes with dengue virus depends on the interaction between temperature and mosquito genotype.
564   Proceedings of the Royal Society B: Biological Sciences. 2017;284(1864).

565   25.   Lambrechts L, Paaijmans KP, Fansiri T, Carrington LB, Kramer LD, Thomas MB, et al. Impact
566   of daily temperature fluctuations on dengue virus transmission by Aedes aegypti.
567   Proceedings of the National Academy of Sciences. 2011;108(18):7460-5.

568   26.   Bar-Zeev M. The Effect of Temperature on the Growth Rate and Survival of the Immature Stages
569   of Aëdes aegypti (L.). Bulletin of Entomological Research. 2009;49(1):157-63. Epub 07/01.

570   27.   Rueda LM, Patel KJ, Axtell RC, Stinner RE. Temperature-Dependent Development and Survival
571   Rates of Culex quinquefasciatus and Aedes aegypti (Diptera: Culicidae). Journal of Medical Entomology.
572   1990;27(5):892-8.

573   28.   Tun-Lin W, Burkot TR, Kay BH. Effects of temperature and larval diet on development rates and
574   survival of the dengue vector Aedes aegypti in north Queensland, Australia. Medical and Veterinary
575   Entomology. 2000;14(1):31-7.

576   29.   Nagao Y, Thavara U, Chitnumsup P, Tawatsin A, Chansang C, Campbell-Lendrum D. Climatic
577   and social risk factors for Aedes infestation in rural Thailand. Tropical Medicine & International Health.
578   2003;8(7):650-9.

579   30.   Naish S, Dale P, Mackenzie JS, McBride J, Mengersen K, Tong S. Climate change and dengue: a
580   critical and systematic review of quantitative modelling approaches. BMC Infectious Diseases. 2014
581   March 26;14(1):167.

582   31.   Chakravarti A, Kumaria R. Eco-epidemiological analysis of dengue infection during an outbreak
583   of dengue fever, India. Virology Journal. 2005 April 14;2(1):32.

584   32.   Vanwambeke SO, Lambin EF, Eichhorn MP, Flasse SP, Harbach RE, Oskam L, et al. Impact of
585   Land-use Change on Dengue and Malaria in Northern Thailand. EcoHealth. 2007 March 01;4(1):37-51.

586   33.   Patz JA, Daszak P, Tabor GM, Aguirre AA, Pearl M, Epstein J, et al. Unhealthy Landscapes:
587   Policy Recommendations on Land Use Change and Infectious Disease Emergence. Environmental Health
588   Perspectives. 2004 04/22 11/25/received 04/22/accepted;112(10):1092-8. PubMed PMID: PMC1247383.

589   34.   Norris DE. Mosquito-borne Diseases as a Consequence of Land Use Change. EcoHealth. 2004
590   March 01;1(1):19-24.
591   35.   Cheong YL, Leitão PJ, Lakes T. Assessment of land use factors associated with dengue cases in
592   Malaysia using Boosted Regression Trees. Spatial and Spatio-temporal Epidemiology. 2014
593   2014/07/01/;10:75-84.
594   36.   Sarfraz MS, Tripathi NK, Tipdecho T, Thongbu T, Kerdthong P, Souris M. Analyzing the
595   spatio-temporal relationship between dengue vector larval density and land-use using factor analysis and
596   spatial ring mapping. BMC Public Health. 2012 October 09;12(1):853.
597   37.   Vanwambeke SO, van Benthem BHB, Khantikul N, Burghoorn-Maas C, Panart K, Oskam L, et al.
598   Multi-level analyses of spatial and temporal determinants for dengue infection. International Journal of
599   Health Geographics. 2006 2006/01/18;5(1):5.
600   38.   World Health Organization. Dengue fever - Sri Lanka: World Health Organization; 2017 [cited
601   2018 Feb. 11]. Available from: http://www.who.int/csr/don/19-july-2017-dengue-sri-lanka/en/.
602   39.   Favier C, Schmit D, Müller-Graf CDM, Cazelles B, Degallier N, Mondet B, et al. Influence of
603   spatial heterogeneity on an emerging infectious disease: the case of dengue epidemics. Proceedings of the
604   Royal Society B: Biological Sciences. 2005;272(1568):1171-7.
605   40.   Epidemiology Unit in Ministry of Health of Sri Lanka. Distribution of Notification(H399)
606   Dengue Cases by Month 2017 [cited 2018 July 13]. Available from:
607   http://www.epid.gov.lk/web/index.php?option=com_casesanddeaths&Itemid=448&lang=en.
608   41.   National Centers for Environmental Information (NCEI). Global Surface Summary of the Day
609   (GSOD) U.S.: NOAA/NESDIS/NCEI; 2015 [updated February 8, 2018; cited 2017 September 19].
610   Available from: https://catalog.data.gov/dataset/global-surface-summary-of-the-day-gsod.
611   42.   Wickramagamage P. Seasonality and spatial pattern of rainfall of Sri Lanka: Exploratory factor
612   analysis. International Journal of Climatology. 2010;30(8):1235-45.
613   43.   Bright EA, Rose AN, Urban ML, McKee JJ. LandScan 2016. 2016 ed. Oak Ridge, TN: Oak
614   Ridge National Laboratory; 2017.
615   44.   Survey Department of Sri Lanka. Spatial Data Infrastructure 2018 [cited 2018 June 29]. Available
616   from: https://www.survey.gov.lk/nsdi/lis/index_cad.php.
617   45.   Romeo-Aznar V, Paul R, Telle O, Pascual M. Mosquito-borne transmission in urban landscapes:
618   the missing link between vector abundance and human density. Proceedings of the Royal Society B:
619   Biological Sciences. 2018;285(1884).
620   46.   Schmidt W-P, Suzuki M, Dinh Thiem V, White RG, Tsuzuki A, Yoshida L-M, et al. Population
621   Density, Water Supply, and the Risk of Dengue Fever in Vietnam: Cohort Study and Spatial Analysis.
622   PLOS Medicine. 2011;8(8):e1001082.
623   47.   Sirisena PDNN, Noordeen F. Evolution of dengue in Sri Lanka—changes in the virus, vector, and
624   climate. International Journal of Infectious Diseases. 2014 2014/02/01/;19:6-12.
625   48.   Gubler DJ. Dengue and Dengue Hemorrhagic Fever. Clinical Microbiology Reviews.
626   1998;11(3):480-96. PubMed PMID: PMC88892.
627   49.   Gubler DJ. Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic
628   problem in the 21st century. Trends in Microbiology. 2002 2002/02/01/;10(2):100-3.
629   50.   Gardner L, Sarkar S. A Global Airport-Based Risk Model for the Spread of Dengue Infection via
630   the Air Transport Network. PLOS ONE. 2013;8(8):e72129.
631   51.   Gardner LM, Fajardo D, Waller ST, Wang O, Sarkar S. A Predictive Spatial Model to Quantify
632   the Risk of Air-Travel-Associated Dengue Importation into the United States and Europe. Journal of
633   Tropical Medicine. 2012;2012.
634   52.   World Health Organization. Dengue and severe dengue 2018 [cited 2018 July 29]. Available
635   from: http://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue.
636   53.   Mammen MP, Jr., Pimgate C, Koenraadt CJM, Rothman AL, Aldstadt J, Nisalak A, et al. Spatial
637   and Temporal Clustering of Dengue Virus Transmission in Thai Villages. PLOS Medicine.
638   2008;5(11):e205.

639   54.   Yoon I-K, Getis A, Aldstadt J, Rothman AL, Tannitisupawong D, Koenraadt CJM, et al. Fine
640   Scale Spatiotemporal Clustering of Dengue Virus Transmission in Children and Aedes aegypti in Rural
641   Thai Villages. PLOS Neglected Tropical Diseases. 2012;6(7):e1730.

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