Spatio-Temporal Characteristics of Dengue Outbreaks

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Based on a data set of dengue cases in the Brazilian city of Fortaleza, collected from 2011 to 2016, we study the spatio-temporal characteristics of dengue outbreaks to characterize epidemic and non-epidemic years. First, we identify regions that show a high incidence of dengue cases and mosquito larvae in different years and analyze their corresponding correlations. We find that the characteristic correlation length of the epidemic is at least of the order of the system size, suggesting that factors such as citizen mobility may play a significant role in driving the spatial spread of the disease. We also find that in epidemic years, spatial correlations are substantially higher with a distribution skewed towards large values than non-epidemic years. Inspired by this observation, we perform a mean-field estimation of the basic reproduction number and find that the estimated values agree well with the values reported for other regions in Brazil and other countries, pointing towards similar underlying spreading mechanisms. These findings provide insights into the spreading characteristics of dengue in densely populated areas and may be relevant for improving disease containment strategies.

Keywords: dengue fever, Bayesian inference, disease spreading, mathematical modelling, data analysis

1 INTRODUCTION

According to a recent report of the world health organization (WHO), over 40% of the world's population are at the risk of a dengue infection [1, 2]. Alarmingly, in the last half-century, a 20 to 30-fold increase of dengue cases has been monitored world-wide [2]. As a vector-borne disease, the transmission of dengue fever occurs from infected to susceptible humans through female Aedes aegypti mosquitoes. Up to 12 days after symptom onset, infected individuals can transmit the virus to mosquitoes, which can further transmit the virus after an incubation period of 4–10 days [1–3]. Mosquitoes can remain alive and infectious for at least 2 weeks [1]. Symptoms include high fever, headache, vomiting, skin rash, and muscle and joint pains [1]. Aedes aegypti is also responsible for the transmission of other severe vector-borne diseases such as yellow fever, chikungunya and zika whose recent outbreaks are challenging health officials in different countries [4–6]. Vector-borne diseases are responsible for the death of more than one million humans each year, disrupt health systems, and obstruct the development of many countries [2]. As a consequence of the unavailability of vaccines
and/or drug resistance, as is the case for many vector-borne diseases, control measures such as personal protection, reduction of vector breeding habitats, and usage of insecticides are essential to contain outbreaks [2, 7].

Recent studies have demonstrated the poor correspondence between levels of infestation measured by entomological surveys at national and local level [8–10]. The correlation between high infestation, measured by larval entomological indicators, and risk of dengue epidemic has been shown to be weak in the most diverse scenarios [11–15]. Despite the evidence of the low usefulness and incipient positive predictive value of these larval surveys being extensively demonstrated, some countries still consider the thresholds of infestation indices as a main indicator of epidemic risk and trigger of spatially oriented vector control actions [8, 9, 15].

In fact, there is some skepticism about the suitability of larval indicators for the prediction of epidemics. Instead, several authors have suggested the systematic use of pupal indices and the direct measurement of the density of the adult mosquito, even if these imply a radical reformulation in the routines of vector control [25]. Theoretically, mapping cities in micro-areas with different levels of transmission risk could make vector control strategies more effective, especially in regions with limited human and financial resources [26–28]. However, human mobility patterns are still not subject to accurate monitoring and can be crucial for the definition of high-risk spatial units that should be prioritized by the national and local programs for the control of urban arboviruses transmitted by *Aedes aegypti* [8].

In this work, we study the spatio-temporal characteristics of dengue outbreaks in Fortaleza from 2011–2016 to characterize epidemic and non-epidemic years. Fortaleza, the capital of Ceará state, is one of the largest cities in Brazil and is located in the North-East of the country where dengue and other neglected tropical diseases show a high prevalence [16, 29]. We show in Figure 1 that up to 1,000 dengue cases have been reported per day in Fortaleza during 2011 and 2016. In our analysis, we identify regions that exhibit a large number of dengue infections and mosquito larvae in different years, and also analyze the corresponding correlations throughout all neighborhoods of Fortaleza. We show that the characteristic length scale of correlations between case numbers at different locations in the system (i.e., the correlation length) is at least of the order of the system size. This provides support to the hypothesis that factors such as citizen mobility drive the spatial spreading of the disease. Motivated by the observation that people interact across long distances, we also use a mean-field model to compare the outbreak dynamics of two characteristic epidemic years with corresponding analyses made for other regions [30]. In particular, we perform a Bayesian Markov chain Monte Carlo parameter estimation for a mean-field susceptible-infected-recovered (SIR) model which has been previously successfully applied to the modeling of dengue outbreaks [30]. Our results provide insights into the spatio-temporal characteristics of dengue outbreaks in densely populated areas and may be relevant for making dengue containment strategies more effective.

### 2 METHODS

#### 2.1 Data Sets

In total, we use four data sets. The first one consists of spatio-temporal information on dengue infections in the city of

| Year | Number of Cases Reported |
|------|--------------------------|
|      | original | processed |
| 2011 | 33,953   | 33,836    |
| 2012 | 38,319   | 38,197    |
| 2013 | 8,761    | 8,706     |
| 2014 | 5,092    | 5,029     |
| 2015 | 26,425   | 26,176    |
| 2016 | 21,736   | 21,596    |
| Total| 134,286  | 133,540   |

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Fortaleza from 2011 to 2016. These data have been provided by the Epidemiological Surveillance Division of Fortaleza’s Health Secretariat, and contains both the date when an infected person reports a potential dengue infection to a physician and the corresponding geographic location with a granularity of approximately 200 m. Serology and clinical diagnosis were used to confirm dengue infections. This dataset was duly anonymized, epidemiological and clinical variables were removed as well as those cases of infected tourists and individuals who live outside the area of the city of Fortaleza. The total number of dengue cases between 2011 and 2016 in our data set after data processing is 133,540. Table 1 shows the number of cases reported for each year. The second data set contains information about *Aedes aegypti* larvae measurements in Fortaleza from 2011 to 2016. Measurement data is available in intervals of 2 weeks from 2,701 strategic points (SP) (e.g., junk yards, garages, buildings under construction, and warehouses) that are monitored by health authorities of Fortaleza. A SP is said to be positive if *Aedes aegypti* larvae have been found independent of the actual amount. Data on *Aedes aegypti* infestation according to each Strategic Point are available on the Fortaleza Daily Disease Monitoring System and were tabulated and consolidated by the epidemiological surveillance team. Due to the influence of precipitation on the mosquito population size, we also consider data from three different rain gauges in Fortaleza during 2011–2016. In addition to the temporal information on dengue cases, we collected data about the geographical locations of all infection cases. Additionally, in order to investigate the influence on human mobility, we use a origin-destination matrix generated from electronic bus pass data of Fortaleza’s transportation system for the year of 2015.

### 2.2 Correlations

The spreading dynamics of dengue in an urban environment can be better understood in terms of underlying spatio-temporal correlations, namely, the cross-correlations between the time series of dengue incidence calculated for different pairs of city neighborhoods. We therefore now focus on spatio-temporal correlations between dengue incidence time series of different districts. In total, there are 118 neighborhoods in Fortaleza, and for each neighborhood *i* we use NC* i* and POP* i*, to denote the number of reported dengue cases at time *t* and the corresponding population, respectively. The disease incidence in neighborhood *i* at time *t* is

\[
P^i_t = \frac{\text{NC}^i_t}{\text{POP}^i_t}.
\]

We characterize the spatio-temporal correlations of dengue outbreaks between sites *i* and *j* by

\[
c_{ij}(\tau) = \frac{1}{T} \sum_{t=1}^{T} \left( p^i_{t-\tau} - \langle p^i \rangle \right) \left( p^j_t - \langle p^j \rangle \right) \sigma_1 \sigma_2
\]

where \( \tau \) denotes a time lag, \( r_{ij} \) is the distance between neighborhood *i* and neighborhood *j*, \( \sigma_1^2 = T^{-1} \sum_{t=1}^{T} (p^i_t - \langle p^i \rangle)^2 \) represents the variance, and \( T \) is the length of the time series. In our analysis, we consider two time intervals: (i) 4 weeks (i.e., a series with \( T = 12 \) periods of 4 weeks) and (ii) 2 weeks (i.e., a series with \( T = 26 \) periods of 2 weeks). Here a time lag of \( \tau = 1 \) means that the two time series are shifted by 14 days. We also compute the cross-correlations in time between the number of dengue cases, the rainfall, and the number of positive SP. In this way, the correlation between any time series \( a_t \) and \( b_t \) is defined by

\[
c(t) = \frac{1}{T} \sum_{t=1}^{T} \frac{(a_t - \langle a \rangle)(b_{t+\tau} - \langle b \rangle)}{\sigma_a \sigma_b}
\]

where \( \sigma_a^2 \) and \( \sigma_b^2 \) are the variances of series \( a_t \) and \( b_t \). In what follows, series \( a_t \) and \( b_t \) will be a combination of the time series for dengue fever cases, the positive SPs, and rainfall in Fortaleza.

### 3 RESULTS AND DISCUSSION

#### 3.1 Dengue Outbreaks in Fortaleza

According to the Brazilian ministry of health and the health administration of the City Hall of Fortaleza, the population of Fortaleza had been at a high risk of a dengue infection during the years 2011, 2012, 2015, and 2016, being therefore classified as epidemic years. The corresponding number of reported dengue cases are given in Table 1 and shown in Figure 1(right). Due to the equatorial location of Fortaleza, the mean temperature over 1 year is 26.3 ± 0.6 °C and can be regarded as constant with only limited impact on the local dengue spreading dynamics. Considering the population size of 2.6 million, an alarmingly high number of several hundred up to almost 1,000 new infections per day have been reported from 2011 to 2016.

We illustrate the geographical distribution of dengue cases in Figure 2 from 2011 until 2016. If the total number of dengue infections in a certain area is large over the course of 1 year, this area appears in red. Areas with small numbers of dengue infections are colored blue. In 2011 and 2012 the main outbreaks occur in similar regions and cover almost the whole city except some parts in the Eastern outskirts. In the non-epidemic years 2013 and 2014, the overall dengue incidence is clearly reduced. However, some parts in the city center in the North-West that also exhibit large numbers of dengue cases in the epidemic years are still at a high risk of dengue outbreaks. Also in the epidemic years 2015 and 2016, some neighborhoods in the south show a high dengue incidence.

In addition to the geographical location of dengue cases, we also show a heatmap of the spatial distribution of positive SPs in Figure 3. Interestingly, and in contrast to the spatial distribution of dengue cases, the majority of positive SPs are located at the same places in Fortaleza regardless of the year. In particular, the
city center and some parts in the North and South-West of the town exhibit a large number of positive SPs. While according to Figure 3, the regions of major outbreaks change substantially between 2011, 2013, and 2015, the number of positive SPs does not at all. Concerning the outbreak year of 2015, the recurrent dengue outbreak and number of positive SPs seem to be even anti-correlated, since the number of dengue cases are concentrated at the southeast region of the city, a region with low incidence of positive SPs. These observations confirm the low usefulness of these larval surveys, as has been extensively demonstrated before and suggest that an effective disease intervention measure should target the neighborhoods which exhibit recurrent dengue outbreaks instead of numbers of positive SPs. In particular, the density of SPs is not homogeneous, and in fact Figure 3 is mostly reproducing the distribution of SPs, because it is common to find at least one larvae during the year and thus it is likely that most SPs will be identified as positive.

As shown in Figure 4, the number of reported dengue cases starts to increase in January and February just shortly after the beginning of the rain season and typically reaches its peak before July. This shows that the corresponding climate conditions facilitate the growth of mosquito populations. In addition, we also show the time evolution of the number of positive SPs. The data in Figure 4 indicates that the way the number of positive SPs changes in time is similar to the rainfall, although their relative amplitudes vary substantially from year to year.

In Table 2, we show the time lags $\tau_{max}$ that correspond to the maximum correlation, as defined by Eq. 3. In the case of dengue occurrences and rainfall, we find a mean value of $\tau_{max}(D, R) = 2.3(2)$ fortnights. This result agrees well with findings of other studies [31] reporting that a maximum of dengue cases will be observed a few weeks up to a few months after the rainfall maximum. The largest correlation between dengue cases and SPs indicates that the dengue incidence reaches a maximum after $\tau_{max}(D, SP) = 2.2(8)$ fortnights after a maximum of positive SPs has been found. This result implies that the number of positive SPs may be an appropriate early warning sign to estimate when the number of dengue cases reaches its maximum.

Despite the very similar curve shapes, the results are less conclusive in the case of correlations between rainfall and positive SPs. In some years, the maximum number of positive SPs is found after the rainfall maximum, whereas the opposite situation occurs in other years. In any case, the time lag is zero when averaged over the 5-years reporting period, suggesting that both phenomena occur almost simultaneously, but are subject to strong fluctuations. This can be also observed by comparing the
time evolutions of rainfall and the number of positive SPs in Figure 4.

A possible explanation for this result may be that a SP measure, as provided by the health authorities of Fortaleza, do not provide a quantitative measure for the amount of larvae, but only provides a binary indicator which is considered positive even if only a small amount of larvae was found at the location. Due to this qualitative nature of the SP, its positiveness indicates the spatial extent of mosquitoes and not its concentration. Therefore, correlations between rainfall and positive SPs have to be interpreted with caution. Still, the similar shapes of the positive SP and rainfall curves indicate that the spatial spread of mosquitoes is correlated with the precipitation level. The influence of climate conditions on dengue outbreaks in Brazil has also been analyzed in Ref. [31].

3.2 Spatio-Temporal Correlations

Dengue outbreaks that occur in a certain region of the city may lead to outbreaks in another more distant region due to human mobility [21, 36, 37]. To analyze this effect and identify characteristic correlation length-scales, we study the correlation between the dengue incidence in neighborhood $i$ and in another neighborhood $j$ located within a distance of $r_{ij}$, which is measured in kilometers. Here, $r_{ij}$ is the distance between the barycenters of neighborhoods $i$ and $j$ extracted from their geographical contours. Specifically, we study the correlations between neighborhoods $i$ and $j$, i.e. $c_{ij}(\tau, r_{ij})$ as defined by Eq. 2, for different time lags $\tau$ and radii $r_{ij}$. According to the definition of $c_{ij}(\tau, r_{ij})$ in Eq. 2, a correlation length $\xi$ smaller than our considered system size would lead to an observable decay of $c_{ij}(\tau, r_{ij})$ for $r_{ij} > \xi$. In all considered years, the correlations $c_{ij}(\tau)$ only vary slightly with the distance $r_{ij}$ as shown in Figure 5. Within the error bars of our data, we do not observe a substantial decay of $c_{ij}(\tau)$ for values of $r_{ij}$ smaller than the system size of about 15 km. We thus conclude that the characteristic correlation length $\xi$ is at least of the order of the system size.

It is unlikely that disease vectors are responsible for such correlation effects over distances of multiple kilometers due to their limited movement capabilities. In particular, it is known that the maximum flight distance reached by the Aedes aegypti from its breeding location is of the order of approximately 100 m. Humans, however, travel through densely populated urban regions on a daily basis, and may transfer the virus to Aedes aegypti mosquitoes at different locations. This virus transfer mechanism is therefore compatible with the large correlation lengths revealed in this study and also agrees well with recent studies that suggest that human mobility is a key component of dengue spreading [21, 36, 37].

We choose three time lags, namely, $\tau_0 = 0$ weeks, $\tau_1 = 2$ weeks and $\tau_2 = 4$ weeks which are of the order of the transmission time scale of 12 days [2]. The dependence of the correlations on different time lags, distances, and years is shown in Figure 5.
For no time lag, $\tau_0 = 0$ weeks, or a time lag of $\tau_1 = 2$ weeks, we find that the correlations are substantially larger in the epidemic years 2011, 2012, 2015, and 2016 as compared to the non-epidemic years 2013 and 2014. However, in 2016 the correlations are less pronounced compared to other epidemic years since the outbreaks are widely distributed and their densities rather small, as shown in Figure 2. For the larger time lag, $\tau_2 = 4$ weeks, the average correlation $\langle c_{ij}(\tau_2) \rangle$ is smaller than that obtained for time lag $\tau_1$. This behavior is compatible with the fact that a time lag of 4 weeks exceeds the dengue transmission period, and we expect to find smaller correlations. In Figure 5 (right), we show the corresponding distributions of $P(c_{ij})$ and find that they allow to clearly distinguish between epidemic and non-epidemic years for no time lag and a time lag of $\tau_1 = 2$ weeks. In the particular case of no time lag, the distributions are strongly skewed towards larger correlations in epidemic years compared to the non-epidemic ones.

In order to better understand this result, we used an origin-destination matrix between pairs of neighborhoods of Fortaleza, made available in the mentioned Refs. [33, 34]. Precisely, this matrix was built from an extensive dataset of human mobility in the city collected during 2015, consisting of public bus validations records with smart cards of passengers. As reported in Ref. [33], the average flux of passengers $f_{ij}$ between neighborhoods $i$ and $j$ is defined as,
where the brackets represent an average over 52 weeks. As shown in Figure 6A, apart from small random fluctuations, the fluxes $f_{ij}$ show practically no dependency on the neighborhood distance $r_{ij}$. Similarly, the Figure 6B shows that the average spatio-temporal correlations $c_{ij}$ remains practically invariant with $f_{ij}$. This result is consistent with our finding that the correlation length of the contagion process of dengue fever in Fortaleza between pairs of distinct neighborhoods should be at least larger than the system size. Furthermore, it also indicates that the human mobility at the city scale has a more profound impact on the transmission of the disease than expected since it connects the neighborhoods in such an efficient way that even the largest distances between them are too small to make a difference in the contagion process. It is interesting to compare our findings with the results obtained by Brockmann and Helbing presented in the Ref. [38], where the network-driven contagion is investigated at larger scales, such as the global viral epidemics of SARS in 2003, and MERS in 2009. In these cases, the variability in the fluxes between different regions play an important role on the disease spreading.

3.3 Estimating Disease Transmission Parameters

As described in the previous section, the studied dengue outbreaks in Fortaleza exhibit a correlation length $\xi$ which is at least of the order of the underlying system size. Based on this observation, we can apply a mean-field epidemic model, as an approximation, to further characterize the observed spreading dynamics. In particular, we aim at comparing the disease
transmission parameters of dengue outbreaks in Fortaleza with the results of previous studies [30]. To do so, we consider the two epidemic years 2012 and 2015 and perform a Bayesian Markov chain Monte Carlo parameter estimation for an SIR model that has been previously applied in the context of dengue outbreaks in Thailand [30]. More details about the methodology are presented in Supplementary Material.

We determine the basic reproduction number $R_0$ of dengue outbreaks in Fortaleza and compare it with the values of other disease outbreaks. The basic reproduction number is an important epidemiological measure and is defined as the average number of secondary cases originating from one infectious individual during the initial outbreak period (i.e., in a fully susceptible population) [39]. Different models exist to characterize and predict epidemic outbreaks [39–43]. In the case of dengue, some models explicitly incorporate a mosquito population, whereas others take into account such effects by using an effective spreading rate [30, 44]. According to Ref. [30], an explicit treatment of vector populations just increases agreement between model and data. We therefore do not explicitly model a vector population and consider an SIR model with an effective spreading rate which has been found to capture the essential features of dengue outbreaks in Thailand [30]. The governing equations are.

\[
\begin{align*}
\frac{dS}{dt} &= -\beta S - \mu S, \\
\frac{dI}{dt} &= \beta S - \gamma I - \mu I, \\
\frac{dR}{dt} &= \gamma I - \mu R,
\end{align*}
\]

where $N = S + I + R$ is the human population size and $S = S(t), I = I(t), R = R(t)$ denote the numbers of susceptible, infected, and recovered individuals at time $t$, respectively. The human mortality and recovery rates are denoted by $\mu_H$ and $\gamma_H$, respectively. The term $\mu_H N$ in Eq. 5 corresponds to the birth rate and is chosen such that the population size is kept constant. Furthermore, the composite human-to-human transmission rate $\beta$ accounts for transitions from susceptible to infected. The relation connects $\beta$ with the mosquito-to-human transmission rate per bite $\beta_{Hh}$, human-to-mosquito transmission rate $\beta_{Vh}$, number of mosquitoes per person $m$, mean rate of bites per mosquito $c$, and mosquito mortality rate $\mu_V$ [30]. The basic reproduction number of the described SIR model variant is [39].

\[
R_0 = \frac{\beta}{\mu_H + \gamma_H}.
\]

For $R_0 > 1$ there exists a stable endemic state, whereas the disease-free equilibrium is stable for $R_0 < 1$. In addition to Eqs. 5–7, 10, the cumulative number of reported dengue cases $C = C(t)$ evolves according to

\[
\frac{dC}{dt} = p\beta \frac{I}{N} S,
\]

where $p$ is the fraction of infected individuals that were diagnosed with dengue and reported to the health officials. As mentioned above, Fortaleza has a population of $N = 2.6$ million. We use a mortality rate of $\mu_H = 1/76$ year$^{-1}$ in accordance with the latest World Bank life expectancy estimates 4.

A parameter estimation based on Eqs. 5–7, 10 means that we have to determine the parameters $\beta$, $\gamma_H$, $p$ and the initial fraction of recovered individuals $r_0 = R(0)/N$ that best describe the observed dengue outbreaks. To do so, we use Bayes’ theorem to determine the posterior parameter distribution

\[
P(\theta|D) \propto P(D|\theta)P(\theta)
\]

based on the likelihood function $P(D|\theta)$ (i.e., the conditional probability of obtaining the data $D$ for given model parameters $\theta$) and the prior parameter distribution $P(\theta)$. For more details on the Bayesian Markov chain Monte Carlo algorithm, see Supplementary Material.



\*Dataset\*  https://data.worldbank.org/indicator/SP.DYN.LE00.IN, Retrieved 5 December 2020.
To model one complete outbreak period, we use November as the starting month in our simulations since the precipitation level and case numbers then typically reach a minimum. In this way, we can compare our results with those of Ref. [30]. In Table 3, we summarize the inferred model parameters, median values, and 95% confidence intervals of the posterior distributions. In addition, we also present the maximum likelihood (ML) estimates which we use to compare the SIR model with the actual dengue case data in Figure 7. We find good agreement between the model predictions and the reported numbers of dengue cases. Only the dengue outbreak peak between April and June 2012 is difficult to capture due to an overwhelming number of up to 1,000 new infections per day.

We now compare the obtained estimates with those of Ref. [30] which focuses on dengue outbreaks in Thailand. In Ref. [30], the number of reported dengue hemorrhagic fever (DHF) cases, a more severe form of dengue fever, has been used, while we considered the number of all reported dengue cases. The total number of mentioned DHF cases in Thailand is roughly 75,000 with a total population size of 46.8 million in 1984 [30]. In contrast to these results, the number of reported dengue cases in Fortaleza in 2012 is almost 40,000 with a total population size of 2.5 million. The attack rate in Fortaleza is thus about one order of magnitude larger than that in Thailand. This alarming difference may be partially a result of the different definitions of reported cases (“DHF” versus “dengue fever”) as well as due to under-notification, but it also points out to the need of better control measures to contain the outbreaks in Fortaleza. Overall, the parameter estimation for the epidemic years 2012 and 2015 leads to values in a similar range compared to the results of Ref. [30]. The ML estimates of the probability of reporting a dengue case, $p$, and the initial fraction of recovered individuals, $r_0$, are by a factor 2–3 larger in our parameter estimation. On the other hand, the ML estimates of $\beta$ and $\gamma$ are slightly smaller in Fortaleza. According to our statistical analysis, the basic reproduction number as defined in Eq. 9 (basically the fraction of $\beta$ and $\gamma_H$) is 1.44 (2012) and 1.50 (2015). These ML estimates are about 30–40% larger than the corresponding ML estimate reported for the aforementioned dengue outbreak in Thailand [30].

### 4 CONCLUSION

The re-emergence of dengue and other neglected tropical diseases is a major threat to public health in different countries. Various factors such as environmental conditions and human mobility affect the spread of dengue [21, 31, 36, 37], making it difficult to contain an outbreak [45, 46].
We analyzed recent dengue outbreaks in Fortaleza, one of the largest Brazilian cities, and identified regions which exhibit a large number of dengue infections and Aedes aegypti larvae over different years. Our results show that the characteristic length scale of correlations between the number of cases at different locations is at least of the order of the system size. Using data from bus transportation between pairs of neighborhoods in the city, we propose that a plausible explanation for this observation is that the human mobility can affect the dissemination of the virus. Indeed, human movement seems to be a factor in the transmission dynamics, particularly in large tropical cities where successive dengue epidemics have been recorded. Interestingly, there is an extensive literature on the investigation of spatial correlations of events in urban areas in terms of clustering and percolation transition (see, for example, Refs. [47, 48]). In these studies, the correlations between pairs of sites usually decay with their geographical distance. In the present case, due to urban mobility, the correlation length of the contagion process is at least of the order of the system size, leading to the observed flat behavior of the correlations with distance.

We also compared the disease transmission characteristics of dengue outbreaks in Fortaleza with those reported for Thailand [30]. The inferred basic reproduction number of dengue outbreaks in Fortaleza is about 30–40% larger than the ML estimate reported in Ref. [30]. Moreover, we classified epidemic and non-epidemic years based on an analysis of spatio-temporal correlations and their corresponding distributions. We found that for non-epidemic years the distribution of spatial correlations is strongly skewed towards strong correlations in epidemic years. This means that in an epidemic year, spatial correlations are typically of the same size, pointing towards recurrent connections between neighborhoods. By comparing spatial correlations between epidemic and non-epidemic years, we found that in epidemic years spatial correlations are higher by a factor of about three as compared to non-epidemic years. This shows that during an epidemic the outbreaks do not occur independently in different neighborhoods but affect each other. Using spatial-correlation analyses may also allow to predict at an early stage if a year tends to be epidemic or not.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://github.com/rafaellpontes/dengue_mobility_paper.

AUTHOR CONTRIBUTIONS

All authors designed research. GS and AL collected and prepared the Dengue data sets. SS, LB, and JN processed the Dengue data. All authors analyzed and interpreted the Dengue data. SS, LB, AL, HH, and JA wrote the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphy.2022.923099/full#supplementary-material

REFERENCES

1. World Health Organization. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization (2009).
2. World Health Organization. Sustaining the Drive to Overcome the Global Impact of Neglected Tropical Diseases. Geneva: World Health Organization (2013).
3. World Health Organization. A Global Brief on Vector-Borne Diseases. Geneva: World Health Organization (2014).
4. Barrett ADT, Higgs S. Yellow Fever: a Disease that Has yet to Be Conquered. Annu Rev Entomol (2007) 52:209–29. doi:10.1146/annurev.ento.52.110405.091454
5. Charrel RN, de Lallemand X, Raoult D. Chikungunya Outbreaks - the Globalization of Vectorborne Diseases. N Engl J Med (2007) 356:769–71. doi:10.1056/nejm078013
6. Brasil P, Pereira JP, Jr, Moreira ME, Ribeiro Nogueira RM, Damasceno L, Wakimoto M. Zika virus infection in pregnant women in rio de janeiro. N Engl J Med (2016) 375:2321–34. doi:10.1056/nejmoa1602412
7. Hotze PJ, Bottazzi ME, Franco-Paredes C, Ault SK, Perigao MR. The Neglected Tropical Diseases of Latin america and the Caribbean: a Review of Disease burden and Distribution and a Roadmap for Control and Elimination. Plos Negl Trop Dis (2008) 2:e300. doi:10.1371/journal.pntd.0000300
8. Ensenl AW, Lima Neto AS, Castro MC. Infestation Measured by aedes Aegypti Larval Surveys as an Indication of Future Dengue Epidemics: an Evaluation for Brazil. Trans Roy Soc Trop Med Hyg (2020) 114:506–12. doi:10.1093/trstmh/traa021
9. MacCormack-Gelles B, Neto ASL, Sousa GS, do Nascimento OJ, Castro MC. Evaluation of the Usefulness of aedes Aegypti Rapid Larval Surveys to Anticipate Seasonal Dengue Transmission between 2012–2015 in Fortaleza, Brazil. Acta Trop (2020) 205:105391. doi:10.1016/j.actatropica.2020.105391
10. Sanchez I, Vanlerberghde V, Alfonso L, del Carmen Marquetti M, Guzman MG, Bisset J, et al. Aedes aegypti Larval Indices and Risk for Dengue Epidemics. Emerg Infect Dis (2006) 12:800. doi:10.3201/eid1205.050866
11. Cromwell EA, Stoddard ST, Barker CM, Van Rie A, Messer WB, Moshnik SR, et al. The Relationship between Entomological Indicators of aedes Aegypti Abundance and Dengue Virus Infection. PLoS Negl Trop Dis (2017) 11: e0005429. doi:10.1371/journal.pntd.0005429
12. Focks DA, Chadee DD. Pupal Survey: an Epidemiologically Significant Surveillance Method for aedes Aegypti: an Example Using Data from trinidad. Am J Trop Med Hyg (1997) 56:159–67. doi:10.4269/ajtmh.1997.56.159
