Exploring the delayed and nonlinear impact of hydrometeorological extremes on dengue risk along an urban gradient in Brazil: a space-time modelling study

Rachel Lowe[1,2,3*] (PhD), Sophie Lee[1,2,3] (MSc), Kathleen M O'Reilly[1,3] (PhD), Oliver J Brady[1,3] (DPhil), Leonardo Bastos[1,2,3,4] (PhD), Gabriel Carrasco-Escobar[5,6] (MSc), Rafael de Castro Catão[7] (PhD), Felipe J. Colón-González[1,2,3] (PhD), Christovam Barcellos[8] (PhD), Marilia Sá Carvalho[4] (PhD), Prof Marta Blangiardo[9] (PhD), Prof Håvard Rue[10] (PhD), Prof Antonio Gasparrini[2,11,12] (PhD)

1. Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, UK
2. Centre on Climate Change and Planetary Health, London School of Hygiene & Tropical Medicine, London, UK
3. Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK
4. Scientific Computing Program, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil
5. Department of Medicine, University of California San Diego, USA
6. Health Innovation Lab, Institute of Tropical Medicine "Alexander von Humboldt", Universidad Peruana Cayetano Heredia, Lima, Peru
7. Department of Geography, Federal University of Espírito Santo, Brazil
8. Health Information and Communication Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil
9. MRC Centre for Environment and Health, Department of Epidemiology and Biostatistics, Imperial College London, London, UK
10. King Abdullah University of Science and Technology, Saudi Arabia
11. Department of Public Health Environments and Society, London School of Hygiene & Tropical Medicine, London, UK
12. Centre for Statistical Modelling, London School of Hygiene & Tropical Medicine, London, UK

*Correspondence to: Dr Rachel Lowe, Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK, Email: rachel.lowe@lshtm.ac.uk

Summary

Background: Temperature and rainfall patterns are known to influence dengue seasonality. However, the impact of extreme drought or extremely wet conditions on the timing and intensity of dengue epidemics is poorly understood. In this study, we quantify the non-linear and delayed effects of hydrometeorological extremes on dengue risk along an urban gradient in Brazil.

Methods: We coupled distributed lag non-linear models with a space-time Bayesian model framework to understand the exposure-lag-response association between dengue relative risk and a drought severity index. We fit the model to monthly dengue case data for the 558 microregions of Brazil between 2001-2019, accounting for unobserved confounding factors, spatial autocorrelation, seasonality, and interannual variability. We assessed the variation in relative risk along an urban gradient through an interaction between the drought severity index and urbanisation. We also examined the impact of hydrometeorological extremes on dengue risk in areas experiencing a high frequency of water supply shortages.

Findings: Extremely wet conditions increased dengue relative risk in the same month and up to three months later while drought conditions increased the risk three to five months later. Including a linear interaction between the drought severity index and level of urbanisation improved the model fit and showed the risk of dengue was greater in more rural areas during extremely wet conditions but greater in highly urbanised areas following extreme drought. We also found the dengue risk following extreme drought was greater in areas experiencing a higher frequency of water supply shortages.

Interpretation: Our study shows that both extremely wet conditions and extreme drought can increase dengue relative risk with different delays. The risk associated with extremely wet conditions was higher in more rural areas, while the risk associated with extreme drought is exacerbated in highly urbanized areas, which suffer from water shortages and intermittent water supply during droughts. This has implications for targeting mosquito control activities in poorly serviced urban areas, not only during the wet and warm season, but also during drought periods.

Funding: Royal Society, MRC, Wellcome Trust, NIH, FAPERJ, CNPq.

Research in context

Evidence before this study

Temperature and rainfall are known to influence the magnitude and seasonality of dengue transmission in regions where the disease is endemic. However, the timeframes in which extreme hydrometeorological events, such as droughts and extremely wet conditions, might alter the timing and intensity of dengue epidemics is poorly understood. Several drought severity indices have been developed by the meteorological community, assimilating data on rainfall and other water supply indicators. However, their potential use in dengue control and preparedness plans has been little explored. We searched PubMed on 15 Oct 2020, using the terms "dengue", "drought", "model". We found only one study that had used a drought indicator in a dengue prediction model and quantified the delayed impact of drought on dengue risk in an island setting.

Added value of this study

We found that extreme drought was associated with an increase in dengue risk in Brazil three to five months later, while extremely wet conditions increase the risk within a shorter timeframe of up to three months later. This study confirms that initial findings from Barbados related to the delayed and nonlinear impact of hydrometeorological extremes on dengue risk are robust across a large gradient of climate and urbanisation conditions across Brazil. Densely populated urban areas that suffer interrupted water supply during periods of water scarcity are more vulnerable to dengue outbreaks following drought conditions. The impact of extremely wet conditions on dengue risk is more immediate and exacerbated in rural areas, predominantly in the Amazon region.

Implications of all the available evidence

These findings raise awareness of the importance of targeting mosquito control activities in urban areas with intermittent water supply, not only during the warm, rainy season but also during intense drought periods. In the short term, a community effort is required to ensure improvised water storage containers do not serve as additional larval habitats in drought periods. During wet periods, outdoor water recipients, including discarded waste should be kept to a minimum. In the longer term, governments must invest in local infrastructure to ensure permanent water supply and promote environmental hygiene in areas prone to dengue and other mosquito-borne disease epidemics.

Keywords: dengue; climate; drought; hydrometeorological extremes; socio-economic; urban; rural; Bayesian model; distributed lag nonlinear model

Introduction

Dengue fever is an arboviral infection, considered one of the top 10 threats to global health.[1] Dengue is caused by four distinct dengue virus serotypes (DENV 1–4), which are transmitted to humans by *Aedes spp*. mosquitoes.[2] Most of Brazil is endemic to all four dengue serotypes and has experienced explosive epidemics in recent years with over 1.5 million notified cases in 2019, an increase of 645% compared to 2018.[3] Dengue transmission is expanding beyond previous boundaries to regions further south, higher altitude cities, such as Brasilia (the country capital), and into remote regions of the Amazon encouraged by environmental change, improved connectivity between regions, and increased urbanisation.[4,5]

Local living conditions, such as population density, human mobility, and sanitation are important collective risk factors. Poor sanitation conditions such as inadequate water supply and refuse collection services encourage mosquito breeding sites.[6] The distribution of the main vector species *Ae. aegypti* and *Ae. albopictus* are widespread across the country. *Ae. aegypti* is found predominantly in urban settings, breeding in artificial containers in and around the home, while *Ae. albopictus* is more commonly found in rural and peri-urban settings.[7] Recent studies have shown the geographical limits of *Ae. aegypti* are expanding into rural and peri-urban areas across Latin America.[8,9]

Variations in temperature and rainfall are thought to contribute to the magnitude and seasonality of dengue transmission.[10] In Brazil, large outbreaks are typically observed after wet and warm periods, particularly in densely populated urban areas. Ambient temperatures impact dengue transmission by affecting mosquito development rates, reproduction, survival, biting rates, and viral replication in the mosquito, with warmer temperatures increasing the risk of disease transmission up to an optimum mean temperature range of 26 - 29°C, depending on the vector species.[11]

The effect of rainfall on dengue risk is more complex. Extreme hydrometeorological events, such as droughts and heavy rainfall, interact with local living conditions, affecting mosquito infestation and the contact rate between humans and mosquitoes. Rainfall can increase mosquito density by creating additional larval habitat in rain-filled containers, particularly in areas with poor or irregular access to the water supply network. However, too much rain can lead to these larvae being washed away.[12] Periods of drought may lead to water supply shortage, encouraging household improvised water storage for basic washing and cooking, which can have the unintended consequence of creating additional breeding sites, in turn increasing contact between mosquitoes and humans.[13]

In recent years, Brazil has experienced an increased number of severe drought and flooding episodes throughout its Northeast, Amazon, and Southeast regions. The recent drought in the Northeast region (between 2010 and 2016) was the most intense experienced over the past 30 years. Studies have shown that the percentage of areas affected by these droughts is increasing with up to 20 million people affected per year.[14] The Brazilian Amazon has experienced several 'once in a century' hydrological events within the past decade, with record levels of flooding in 2009 and 2012, and record levels of drought in 2010.[15,16] Both the Northeast and Amazon regions are home to some of the most vulnerable populations in Brazil where much of the population lack access to water resources and rely on rainwater or wells.[17] Since the austral summer of 2014, Southeast Brazil has experienced one of the most severe droughts in decades. This rainfall deficiency generated water shortages and a water crisis that affected residents and local economies in the metropolitan region of São Paulo.[18] In more urbanized areas, access to the water network has increased in recent decades, but without guaranteeing the continuity, safety, and quality of water supply for all households connected to distribution networks.[19] The interruption of water supply services can occur due to structural failures in the system, meaning supply is insufficient to meet water demand, or the occurrence of prolonged droughts that compromise the water sources. These two factors combined force households to store water in improvised reservoirs or barrels, especially during droughts, creating conditions for the creation of *Aedes* mosquitoes.[20]

Although several studies have quantified associations between climatic factors and dengue risk, the relationship and lagged effects of extreme droughts and extremely wet conditions on mosquito-borne disease outbreaks is poorly understood. The impact of climate variability and climate change on dengue transmission is complex, nonlinear, and often delayed by several weeks to months, which limits inferences that can be made from traditional linear modelling methods. A recent study developed a model to quantify the impact of drought on dengue transmission in the small island developing state of Barbados for the period 1990-2016.[21] Drought conditions were found to positively influence dengue relative risk at long lead-times of three to five months while higher minimum temperatures and excess rainfall increased the risk at shorter lead times up to three months. Therefore, periods of drought followed by a combination of warm and wet weather several months later could provide optimum conditions for imminent dengue outbreaks. In this study, we extend this approach by designing a space-time model for Brazil to understand the nonlinear and delayed impacts of hydrometeorological extremes across a large and varied geographical domain. We build upon previous efforts to model the impact of climate and socio-economic factors in Brazil by coupling spatio-temporal Bayesian hierarchical models[6,22] with distributed lag nonlinear models (DLNM)[21,23] to simultaneously describe space-varying, non-linear, and delayed dependencies between dengue incidence rates and hydrometeorological factors. These exposure-lag-response associations can reveal how hydrometeorological extremes impact dengue risk in the months leading up to an outbreak. This has implications for designing early warning systems that consider the cumulative effect of hydrometeorological variations in the months leading up to the peak season and to be ready to detect out-of-season anomalous events. In this study we used the Palmer Drought Severity Index (PDSI), which is the most prominent standardised index for monitoring drought and long-term changes in aridity.[24] We fit the model to dengue case data across all 558 microregions in Brazil for the period 2001-2019, to identify exposure-lag-response associations between dengue, temperature variations, extremely wet and extreme drought conditions. We explore scenarios of hydrometeorological extremes along an urban gradient to understand how extremely wet conditions and extreme drought may differentially impact dengue risk depending on level of urbanisation and frequency of water supply shortages.

Methods

Study area and dengue data

Brazil is now the sixth most populated country in the world with more than 209 million inhabitants. Brazil can be divided into distinct climatic and ecological zones spanning 8.5 million km^2. There are five geo-political regions, 27 states and e 5 570 municipalities organized in 558 microregions, which consist of groups of municipalities surrounding a larger city. We obtained monthly notified dengue cases between January 2001 and December 2019 for each of the 558 microregions of Brazil from the Notifiable Diseases Information System (SINAN), freely available via the Ministry of Health Information Department (DATASUS).[25] The Brazilian Ministry of Health defines the dengue incidence rate (DIR) as the number of new dengue cases per 100 000 residents. To calculate the DIR for each microregion, we obtained yearly population estimates for microregions between 2001 and 2019 from the Brazilian Institute of Geography and Statistics (IBGE) via DATASUS[25]. Over the 19-year period, dengue incidence rates have increased, and the dengue transmission zone has expanded further South, into the Central-West region and into the Amazon. Seasonality varies across the country, with the peak transmission season occurring earlier in the year in the North (e.g., in Amazonas, Fig 1) and later in the year in the Northeast (e.g., in Ceará, Fig 1). Large nationwide epidemics occurred in 2010, 2013, 2015, 2016 and 2019 (Fig A2).

Meteorological data

The monthly average daily minimum temperature (Tmin), maximum temperature (Tmax) (°C) and the self-calibrated Palmer drought severity index (PDSI) were obtained from the Climatic Research Unit gridded Time Series (CRU TS) version 4·04, for the period January 2000 to December 2019 at a spatial resolution of 0.5° x 0·5° (data for 2000 was extracted to allow for a lag period before the first dengue observation in January 2001). The gridded datasets were aggregated to each microregion using the 'exactextractr' R package,[27] by taking the mean of grid boxes lying within each polygon. Grid boxes that were partially covered by the polygon were weighted by the percentage that lay within the polygon. The PDSI is one of the most widely used measures of meteorological drought, giving a measure of dryness in a region relative to 'normal' conditions. PDSI is calculated using moisture levels of the soil, expected evapotranspiration rate (the amount of evaporation from soil that would occur if sufficient water levels were available, based on average daily temperature and length of days in the month) and precipitation.[28,29] We used the self-calibrating PDSI, which provides a more spatially comparable index by calibrating a different 'normal' condition for each location.[30] The index ranges from -10 (very dry) to + 10 (very wet), with values below -4 or above +4 considered 'extreme'. Brazil has experienced extreme and prolonged drought in several states located in the north (Amazon) and northeast region, particularly since 2010 (Fig A3). Minimum temperature differs greatly across the country with the tropical North experiencing consistently high temperatures, able to support year-round virus transmission, whereas the temperate South experiences cold winters sometimes not able to sustain adult vector populations (Fig A4).

Urbanisation and access to water

To test if hydrometeorological-dengue associations vary according level of urbanisation and access to water supply services, we obtained data on the percentage of residents living in urban areas and with access to the piped water network from the 2010 census, from DATASUS[25]. Poor sanitation conditions, including limited access to water supply, can encourage mosquito breeding through use of improvised water storage containers. Accordingly, dengue risk is expected to increase as sanitation conditions deteriorate. However, at the microregion level, the proportion of residents living in urban areas (Fig 2a) is positively correlated with the proportion of residents with access to the piped water network (Fig 2b). Therefore, at this level of aggregation, the water access variable is not useful due to collinearity the level of urbanisation (Pearson correlation coefficient $r = \cdot 73$, $p = < \cdot 001$). While improved services that accompany increased levels of urbanisation may reduce dengue risk, the proportion of the population residing in urban areas is expected to increase dengue risk, as urban areas are ideal environments for mosquitoes and many people living in close proximity create a human virus reservoir. The quality and reliability of water supply services is difficult to measure. One way is to monitor supply system failures and interruptions, reported annually by service providers in the National Sanitation Information System.[31] For this study, the number of reported interruptions in water supply per municipality between 2000 and 2016 was divided by the number of years and municipalities for each microregion, to obtain the frequency of interruptions, ranging from 0 to 1. This variable has a weak positive correlation with urbanisation (r = ·13, p = ·002). Note, some microregions with the highest levels of access to the water network also experience the highest frequency of water supply shortages, for example, in urbanised areas in the South East (Fig 2c and Fig A5).

Modelling approach

We specified a spatio-temporal hierarchical model where the response consists of monthly counts of notified dengue cases for all 558 Brazilian microregions over 19 years, from January 2001 to December 2019.[6] A negative binomial distribution was assumed to account for potential overdispersion in dengue case counts. Spatio-temporal random effects were included to account for unobserved and unmeasured sources of variation and spatial and temporal dependency structures. We included DLNMs to account for exposure-lag response associations between dengue relative risk, temperature variations, and the drought severity index.[21,23] We tested a linear interaction between the drought severity index DLNM and level of urbanisation. The model parameters were estimated in a Bayesian framework using integrated nested Laplace approximations in R (R-INLA)[32,33] (see Appendix for model specification).

We constructed a baseline model comprising state-level monthly autocorrelated random effects, to account for seasonality, and year-specific microregion-level spatial random effects to allow for interannual variability in unknown and unmeasured factors (e.g., health care and vector control disparities) and dependency structures (i.e., human mobility) between microregions (see Appendix for details). DLNMs were then used to explore possible nonlinear and delayed associations between dengue incidence rates, temperature (minimum and maximum) and the Palmer drought severity index from zero to six months.

We assessed the impact of hydrometeorological extremes on underlying socio-economic conditions by including a linear interaction between the drought severity index DLNM, and a continuous variable of the percentage of residents living in urban areas.[34] To understand variations in dengue risk under different hydrometeorological extreme scenarios along an urban gradient, we centred the urbanisation variable at different points: high (upper quartile = 87%), intermediate (median = 73%) and low (lower quartile = 58%) levels of urbanisation. We also tested a linear interaction between the drought severity index DLNM and the frequency of water supply shortages variable. We centred this variable at high (upper quartile = 0·53), intermediate (median = 0·33) and low (lower quartile = 0·16) frequency levels (see Appendix for details).

The final model was selected by comparing models of increasing complexity, in terms of input variables and model structure, to the baseline model. We calculated goodness of fit measures, including the deviance information criterion (DIC),[35] which balances model accuracy against complexity, by penalising for the number of effective parameters in model, and the mean cross-validated (CV) log score,[36] which measures the predictive power of the model when leaving out one datapoint at a time. For both the DIC and log score, smaller values indicate better fitting models. We calculated the difference in mean absolute error (MAE) between the baseline model and the selected model,[37] to identify the proportion of microregion for which a more complex, data-driven model improved model fit. We also performed cross-validation, by refitting the selected model 19 x 12 times, excluding a month per year from the fitting process each time and compared observations to out-of-sample posterior predictive distributions for each state between Jan 2001 – Dec 2019.

Role of the funding sources

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Model selection

The dataset included 12 895 293 reported dengue cases between 2001-2019 in 558 microregions in Brazil (Fig. 1). To select the best fitting models, we included state-level monthly random effects, to account for varying seasonality between area (e.g., Amazonas and Pernambuco, Fig A6), and year-specific microregion-level spatial random effects to account for unexplained interannual spatial variability per year (Fig A7). We then included exposure-lag-response functions (DLNMs) for Tmin, Tmax and PDSI, lagged zero to six months. The inclusion of both Tmin and PDSI as DLNMs (drought severity model) resulted in the greatest reduction in DIC and mean logarithmic score compared to the baseline model (see Table A1). We then tested a linear interaction between the drought severity index DLNM and the continuous 'urbanisation' variable (drought severity - urban model). This model resulted in an improvement of the model fit compared to the drought severity model, with a reduction in DIC despite the inclusion of 13 additional terms, comprising the additional cross-basis variables and the urbanisation variable as a fixed effect (Table A1, see Appendix for details). We fitted the drought severity - urban model three times, centring the urbanisation variable at three points along an urban gradient ranging from highly urbanised (upper quartile) to more rural (lower quartile, see Appendix for details). We also tested a linear interaction between the drought severity index DLNM and the continuous 'water supply shortage frequency' variable (drought severity - water model), centred at three points ranging from high frequency (upper quartile) to low frequency (lower quartile). The inclusion of the water supply shortage interaction resulted in an improvement in model fit, similar to the drought severity – urban model (Table A1).

The MAE of the drought severity - urban model was smaller than the MAE using the baseline model for 409 of the 558 (73%) microregions (see Fig A8), suggesting the selected model improved the model fit above the baseline in these areas. When stratifying the added value by geo-political region, the drought severity – urban model performed best in the Southeast (84% of microregions with improved model fit) and South (80% of microregions with improved model fit) regions (Table A2). In the microregions for which the baseline model fits better than the drought severity models, other unexplained factors likely dominate space-time dynamics in those areas.

Yearly summaries of 'out-of-sample' posterior predictive median estimates of the dengue incidence rate, simulated from the drought severity - urban model fitted in 'leave one month out' cross validation mode, are shown in Figure A9. The model correctly identified widespread outbreaks in 2010, 2013, 2015-2016 and 2019 as well as years of low incidence, for example in 2014 and 2017 (see observed values in Fig A2). Overall, the model successfully distinguished interannual variability in the dengue incidence rate between states (Fig A10). One notable exception was the estimate of an unobserved dengue peak in Acre in 2014.

Hydrometeorological extremes and dengue risk

Temperature-dengue associations

Figure 3a shows a contour plot of the exposure–lag–response association between Tmin and dengue, relative to the overall mean Tmin of 19 °C for lags zero to six months. Figure 3b shows dengue lag–response association for different temperature scenarios relative to the baseline of 19°C. The greater the value of Tmin, the greater the relative risk of dengue, with maximum values found with a lag of two - four months. The relative risk of dengue gradually increases with rising Tmin above the mean and is greatest at the maximum Tmin value of 25·5 °C (Fig A11). Note, the inclusion of Tmin and PDSI resulted in improved model adequacy statistics compared to using Tmax (see Table A1) and was used for further model exploration with drought severity and socio-economic interactions.

Drought severity-dengue associations

Variations in dengue relative risk for different drought severity index exposures and time lags, relative to normal conditions (PDSI = 0), are shown in Figure 4. Figure 4a shows the relationship averaged across all Brazilian microregions (using the drought severity model, with no interactions). Figure 4b shows the relationship for a high level of urbanisation (upper quartile = 87% of the population reside in urban areas) and Figure 4c shows the relationship for a low level of urbanisation (using the drought severity - urban model). Output from the drought severity model (with no interactions) can be interpreted as the average effect across the whole of Brazil whilst the drought severity - urban model distinguishes the average effect along an urban gradient, depending on the value at which the urbanisation value is centred. Figure 5 shows lag-response associations for two extreme hydrometeorological scenarios: extreme drought (PDSI = -7) and exceptionally wet (PDSI = 7) conditions relative to the baseline (PDSI = 0) at lags between zero and six months for a high level of urbanisation (Fig 5a) and a low level of urbanisation (Fig 5b). The maximum relative risk and associated time lags for both dry and wet conditions are reported in Table 1. Overall, the relative risk of dengue is enhanced in the same month and up to three months after extremely wet conditions, but a secondary peak in relative risk was also found between three and five months after extreme drought conditions (Fig 4a). The drought-dengue association estimated from both the drought severity model and the drought severity - urban model was greatest at a lag of four months (Table 1). The greater the level of urbanisation, the higher the relative risk of dengue following extreme drought, with a relative risk of 1·6 (95% CI: 1·33, 1·92; Table 1, Fig 4b, Fig. 5a). The relative risk of extremely wet conditions was greater and more immediate at lower levels of urbanisation with a relative risk of 1·77 (95% CI: 1·32, 2·37; Table 1, Fig 4c, Fig 5b). We also found an increased relative risk of dengue following drought given a high frequency of water supply shortages compared to a lower frequency of water supply shortages (Fig A12, Fig A13 and Table A3).

Discussion

By combining state-of-the-art statistical modelling approaches, we performed a space-time modelling analysis to describe the delayed and nonlinear effects of extremely wet and extreme drought conditions on dengue risk across Brazil, an area of 8·5 million km^2, spanning six different biomes. To our knowledge, this is one of the most comprehensive assessments of the impacts of drought on dengue risk across a large gradient of climate and urbanisation conditions. We explored how hydrometeorological events may interact with underlying socio-economic characteristics and human behaviour to determine the risk of dengue outbreaks. Extreme drought conditions were found to positively influence dengue relative risk at lead-times between three to five months while extremely wet conditions increased the risk at shorter lead times up to three months. While the relative risk of dengue was greatest during extremely wet conditions in more rural areas, the effect of extreme drought was exacerbated in highly urbanised areas, as well as areas experiencing a higher frequency of water supply shortages.

The effects of hydrometeorological events on dengue transmission depend on the local social-ecological conditions that determine the types of larval habitat available in the environment, as well as household water supply and storage practices. Some studies have shown that rainfall shortages can increase dengue risk in regions where people store water.[12,13,38] The 3-5 month delay between drought events and increased dengue risk observed here may arise from the gradual change in human behaviour in response to drought, which can lead to households taking measures to store water in improvised containers around the home as they become aware of water scarcity. Changes in water storage practices can increase the availability of larval habitat for *Ae. aegypti*, whose eggs have been found to survive a 120 day dry period.[39] The presence of additional mosquito breeding sites may also affect surrounding households regardless of water storage practices, reinforcing the importance of considering contextual socio-economic factors when modelling climate-dengue associations.

Following a rainfall event, the availability of larval habitat increases (e.g., rain-filled abandoned containers, plastic waste, etc), and within a relatively short period of time eggs hatch and adult mosquito populations grow (depending on ambient temperatures). The risk of dengue transmission then increases several weeks later, a lag associated with the intrinsic and extrinsic viral incubation periods.[40] In more rural areas, we observed an immediate increase in the relative risk of dengue during extremely wet conditions, compared to normal conditions, which persists for 2-3 months. At short time frames (i.e. within a month), heavy rainfall could temporarily decrease the risk of dengue due to flushing of water container out in the open.[41] However, the relative availability of indoor vs outdoor breeding containers is likely to strongly affect the potential impact of flushing. We do see a slight dip in the increased dengue relative risk for recent extremely wet conditions in highly urbanised areas (Figure 5a), which may be subjected to more outdoor breeding sites, such as discarded waste. However, we were unable to characterise this in more detail due to unavailability of data on vector habitat at this scale and over the time period.

This study supports findings from a previous study in Barbados that showed an increase in dengue risk following drought at longer lead times (3-5 months) and following extremely wet conditions at shorter lead times (up to 3 months).[21] This work builds upon the time series approach developed by Lowe et al.[21] by imbedding DLNM methodology in a Bayesian space-time model framework, while simultaneously accounting for spatial heterogeneity and autocorrelation. The models used here were developed using an extensive open-access database of over 12 million reported dengue cases, applied over a vast and varied geographical domain. This study provides additional and robust evidence on the potential delayed impacts of drought on dengue risk over a large gradient of climate conditions and urbanisation. This work also advances previous efforts to model space-time dynamics of dengue in Brazil and provide dengue early warnings by allowing the model to consider delayed and nonlinear climatic exposures, interacted with underlying socio-economic conditions. This study provides additional evidence to motivate the incorporation of drought monitoring and seasonal climate forecasts in vector surveillance and dengue early warning systems, to effectively intervene and engage at the community level not only during the wet and rainy seasons but also during anomalous drought conditions. The use of pre-defined climatic indicators, such as the sc-PDSI, can enhance our capacity to predict the timing and intensity of dengue outbreaks.

Despite these scientific advances, several limitations exist. Working at the national scale has advantages for exploring the hydrometeorological impacts of dengue risk across a wide range of climatic and socio-economic conditions but this comes at the cost of an imperfect outcome variable. Dengue case data is based on Brazil's passive surveillance system, which means that patients with mild or asymptomatic infections, thought to be the majority of dengue cases,[42] may be missed. In addition to this, only a small proportion of notified cases are laboratory confirmed (ranging from 10% in the Northeast to 30% in the South), although this may be even lower during epidemics.[43] One study estimated that only around 1 in 40 dengue cases were identified in Brazil during a period of low transmission.[44] Lack of laboratory confirmation also increases risk of misclassification, particularly since 2016 with the widespread circulation of Zika and chikungunya, which are spread by the same vector and often have similar symptoms to dengue. Further, cross-protection may have suppressed incidence of dengue in 2017 following the 2015-2016 Zika epidemic.[45] The dengue case data or population offset are not stratified by age group or serotype. Unequal population growth rates across the country, due to increased birth rate and internal migration, as well as previous dengue or Zika infection, may impact the overall susceptibility, either as a protective factor or increasing disease severity.[46] A lack of access to data on serotype and seroprevalence studies limits our ability to account for immunity other than via the year-specific spatial random effects, which account for unmeasured interannual spatial heterogeneity and dependencies between microregions. The formulation of the spatial component of the model assumes connectivity exists between neighbouring regions in Brazil. Microregions located along the inland border have neighbours in bordering countries, which are not accounted for in the neighborhood matrix. In reality, the movement of people, goods and services between large metropolises in Brazil creates an urban network connecting distant regions.[47] Human mobility has been shown to influence the spread of dengue.[48] We plan to improve the representation of spatial connectivity in future iterations of the model using the hierarchical urban network, combined with transport and mobility data.

Whilst we tested the hypothesis of an association between dengue relative risk and hydrometeorological extremes along an urban gradient and in relation to water supply shortages, we acknowledge these indicators are crude and and may oversimplify the many other factors that engender specific landscape characteristics that determine dengue transmission potential. The proportion of the population residing in urban areas is a static variable, obtained from the 2010 census and is likely to have changed in the last decade. The water supply shortage variable depends on water service providers declaring water system failures to the National Sanitation Information System and is subject to reporting error. However, this variable gives an indication of where piped water is not reliable and alternative sources must be used. For example, the southeast region was affected by a severe drought between 2014 and 2016. Although this region has good access to the water supply system, lowering of waterbody level led to water supply shortages in many urban areas, including São Paulo. This resulted in households storing water in improvised indoor reservoirs leading to an unprecedented dengue outbreak in the city in 2015.[49] There could be bias towards increased reporting of dengue cases in urban areas (i.e. better access to healthcare facilities). Further, we did not have access to data on vector density or vector surveillance at the scale of this study to formally assess the exposure-lag-response associations between hydrometeorological extremes and the vectors themselves. This limits the conclusions we draw related to the role of vectors as mediators between hydrometeorological extremes and dengue risk. To make this work useful for developing prevention strategies, alternative finer scale studies are needed to detect basic hygiene disparities within urban areas and to assess interventions at a community level, which may include improved water storage care where piped water is unavailable or the supply is irregular.[20]

Despite these limitations, this research provides an indicative lead-time to carry out mosquito control activities and prepare health facilities for an increase in dengue cases following extreme hydrometeorological events. This work also highlights that extreme climatic events can impact regions differently depending on the socioeconomic conditions. This work highlights the importance of supporting local communities to prevent dengue outbreaks, by providing alternative water storage options and increasing the reliability of water supply, particularly in areas in which the frequency of water supply failures in unacceptably high. Monitoring and forecasting the occurrence, intensity, and evolution of hydrometeorological extreme events will be critical for public health agencies in their efforts to prepare, mitigate, and manage responses to epidemics of dengue and other climate-sensitive diseases. The advantage of our approach is the ability to capture cumulative and combined effects of anomalous climate conditions in the months leading up to a dengue epidemic. Our study shows that both extremely dry and wet conditions can increase dengue relative risk at different lead times. This provides stakeholders with usable timelines for planning and targeting mosquito control activities in poorly serviced areas, not only during the wet and warm season but also during and following periods of drought.

Contributors

RL was responsible for the study design, model development, data analysis and wrote the manuscript. SL collated and managed the database and helped with visualisation and drafting the manuscript. CB, RCC, and MSC collected data and performed a literature search. AG and HR contributed to code development. SL, LB, and FJCG reviewed the code. All authors contributed to the study design, discussed the results, and reviewed and approved the final manuscript.

Declaration of interests

The authors declare no conflicts of interest.

Acknowledgements

RL was supported by a Royal Society Dorothy Hodgkin Fellowship. SL was supported by a Royal Society Research Grant for Research Fellows. AG was supported by the Medical Research Council UK (Grant ID: MR/R013349/1) and the Natural Environment Research Council (Grant ID: NE/R009384/1). OJB was funded by a Sir Henry Wellcome Fellowship funded by the Wellcome Trust (206471/Z/17/Z). GCE was supported by NIH/Fogarty International Center Global Infectious Diseases Training Program (D43 TW007120). MSC received grants from Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ, http://www.faperj.br/, E_26/201.356/2014) and support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, http://www.cnpq.br/, 304101/2017-6). CB was supported by the Brazilian Climate and Health Observatory, financed by Rede Clima, National Council for Scientific and Technological Development (CNPq) and Brazilian Ministry of Health. We are grateful to Ian Harris from NCAS-Climate at the Climatic Research Unit, School of Environmental Sciences, University of East Anglia for providing the sc-PDSI data for version 4·04 ahead of public release for the purpose of this study. We also acknowledge useful discussions of this work with members of the Planetary Health Infectious Disease Lab at the London School of Hygiene & Tropical Medicine.

References

1 World Health Organization. Ten threats to global health in 2019. 2019 https://www.who.int/emergencies/ten-threats-to-global-health-in-2019 (accessed Oct 6, 2019).

2 Guzman MG, Harris E. Dengue. *The Lancet* 2015; **385**: 453–465.

3 PAHO/WHO. PLISA Health Information Platform in the Americas. 2019. http://www.paho.org/data/ (accessed Feb 4, 2020).

4 Barcellos C, Lowe R. Expansion of the dengue transmission area in Brazil: the role of climate and cities. *Trop Med Int Health* 2014; **19**: 159–168.

5 Gubler DJ. Dengue, Urbanization and Globalization: The Unholy Trinity of the 21st Century. *Trop Med Health* 2011; **39**: S3–S11.

6 Lowe R, Barcellos C, Coelho CA, *et al.* Dengue outlook for the World Cup in Brazil: an early warning model framework driven by real-time seasonal climate forecasts. *Lancet Infect Dis* 2014; **14**: 619–626.

7 Kraemer MU, Reiner RC, Brady OJ, *et al.* Past and future spread of the arbovirus vectors Aedes aegypti and Aedes albopictus. *Nat Microbiol* 2019; **4**: 854.

8 Guagliardo SA, Barboza JL, Morrison AC, Astete H, Vazquez-Prokopec G, Kitron U. Patterns of geographic expansion of Aedes aegypti in the Peruvian Amazon. *PLoS Negl Trop Dis* 2014; **8**.

9 Pérez-Castro R, Castellanos JE, Olano VA, *et al.* Detection of all four dengue serotypes in Aedes aegypti female mosquitoes collected in a rural area in Colombia. *Mem Inst Oswaldo Cruz* 2016; **111**: 233–240.

10 Campbell KM, Haldeman K, Lehnig C, *et al.* Weather Regulates Location, Timing, and Intensity of Dengue Virus Transmission between Humans and Mosquitoes. *PLoS Negl Trop Dis* 2015; **9**.

11 Mordecai EA, Cohen JM, Evans MV, *et al.* Detecting the impact of temperature on transmission of Zika, dengue, and chikungunya using mechanistic models. *PLoS Negl Trop Dis* 2017; **11**: e0005568.

12 Stewart Ibarra AM, Ryan SJ, Beltrán E, Mejía R, Silva M, Muñoz Á. Dengue Vector Dynamics (Aedes aegypti) Influenced by Climate and Social Factors in Ecuador: Implications for Targeted Control. *PLOS ONE* 2013; **8**: e78263.

13 Pontes RJ, Freeman J, Oliveira-Lima JW, Hodgson JC, Spielman A. Vector densities that potentiate dengue outbreaks in a Brazilian city. *Am J Trop Med Hyg* 2000; **62**: 378–83.

14 Brito SSB, Cunha APMA, Cunningham CC, Alvalá RC, Marengo JA, Carvalho MA. Frequency, duration and severity of drought in the Semiarid Northeast Brazil region. *Int J Climatol* 2018; **38**: 517–529.

15 Jiménez-Muñoz JC, Mattar C, Barichivich J, *et al.* Record-breaking warming and extreme drought in the Amazon rainforest during the course of El Niño 2015–2016. *Sci Rep* 2016; **6**: 33130.

16 Marengo JA, Espinoza JC. Extreme seasonal droughts and floods in Amazonia: causes, trends and impacts. *Int J Climatol* 2016; **36**: 1033–1050.

17 Cunha APM do A, Marchezini V, Lindoso DP, Saito SM, Alvalá RCDS. The challenges of Consolidation of a Drought-Related Disaster Risk Warning System to Brazil. *Sustentabilidade Em Debate* 2019; **10**: 43–76.

18 Nobre CA, Marengo JA, Seluchi ME, Cuartas LA, Alves LM. Some characteristics and impacts of the drought and water crisis in Southeastern Brazil during 2014 and 2015. *J Water Resour Prot* 2016; **8**: 252–262.

19 Andreazzi MAR, Barcellos C, Hacon S. Velhos indicadores para novos problemas: a relação entre saneamento e saúde. *Rev Panam Salud Publica* 2007; **22**: 211–217.

20 Caprara A, Lima JWO, Marinho ACP, Calvasina PG, Landim LP, Sommerfeld J. Irregular water supply, household usage and dengue: a bio-social study in the Brazilian Northeast. *Cad Saúde Publica* 2009; **25**: S125–S136.

21 Lowe R, Gasparrini A, Van Meerbeeck CJ, *et al.* Nonlinear and delayed impacts of climate on dengue risk in Barbados: A modelling study. *PLoS Med* 2018; **15**: 1–24.

22 Lowe R, Bailey TC, Stephenson DB, *et al.* The development of an early warning system for climate-sensitive disease risk with a focus on dengue epidemics in Southeast Brazil. *Stat Med* 2013; **32**: 864–883.

23 Gasparrini A. Modeling exposure–lag–response associations with distributed lag non-linear models. *Stat Med* 2014; **33**: 881–899.

24 NCAR. The Climate Data Guide: Palmer Drought Severity Index (PDSI). 2019. https://climatedataguide.ucar.edu/climate-data/palmer-drought-severity-index-pdsi (accessed June 14, 2020).

25 Ministério da Saúde. DATASUS - Departamento de Informática do SUS. Informações de Saúde (TABNET). http://www2.datasus.gov.br/DATASUS/index.php?area=02 (accessed June 7, 2020).

26 Harris I, Osborn TJ, Jones P, Lister D. Version 4 of the CRU TS monthly high-resolution gridded multivariate climate dataset. *Sci Data* 2020; **7**: 1–18.

27 Daniel Baston. exactextractr: Fast Extraction from Raster Datasets using Polygons. 2020 https://CRAN.R-project.org/package=exactextractr.

28 Palmer WayneC. Meteorological drought. *US Dep Commer* 1965; **45**: 58.

29 Alley WM. The Palmer Drought Severity Index: Limitations and Assumptions. *J Clim Appl Meteorol* 1984; **23**: 1100–1109.

30 Wells N, Goddard S, Hayes MJ. A Self-Calibrating Palmer Drought Severity Index. *J Clim* 2004; **17**: 2335–51.

31 SNIS. Sistema Nacional de Informações sobre Saneamento. 2020. http://www.snis.gov.br (accessed Oct 12, 2020).

32 Rue H, Martino S, Chopin N. Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. *J R Stat Soc Ser B Stat Methodol* 2009; **71**: 319–392.

33 Lindgren F, Rue H, others. Bayesian spatial modelling with R-INLA. *J Stat Softw* 2015; **63**: 1–25.

34 Gasparrini A, Guo Y, Hashizume M, *et al.* Temporal variation in heat–mortality associations: a multicountry study. *Environ Health Perspect* 2015; **123**: 1200–1207.

35 Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc Ser B Stat Methodol* 2002; **64**: 583–639.

36 Gneiting T, Raftery AE. Strictly proper scoring rules, prediction, and estimation. *J Am Stat Assoc* 2007; **102**: 359–378.

37 Lowe R, Cazelles B, Paul R, Rodó X. Quantifying the added value of climate information in a spatio-temporal dengue model. *Stoch Environ Res Risk Assess* 2016; **30**: 2067–2078.

38 Hayden MH, Uejio CK, Walker K, *et al.* Microclimate and Human Factors in the Divergent Ecology of Aedes aegypti along the Arizona, US/Sonora, MX Border. *EcoHealth* 2010; **7**: 64–77.

39 Trpiš M. Dry season survival of Aedes aegypti eggs in various breeding sites in the Dar es Salaam area, Tanzania. *Bull World Health Organ* 1972; **47**: 433.

40 Rohani A, Wong Y, Zamre I, Lee H, Zurainee M, others. The effect of extrinsic incubation temperature on development of dengue serotype 2 and 4 viruses in Aedes aegypti (L.). *Southeast Asian J Trop Med Public Health* 2009; **40**: 942.

41 Seidahmed OM, Eltahir EA. A sequence of flushing and drying of breeding habitats of Aedes aegypti (L.) prior to the low dengue season in Singapore. *PLoS Negl Trop Dis* 2016; **10**: e0004842.

42 Bhatt S, Gething PW, Brady OJ, *et al.* The global distribution and burden of dengue. *Nature* 2013; **496**: 504–7.

43 Siqueira JB, Martelli CMT, Coelho GE, Simplício AC da R, Hatch DL. Dengue and Dengue Hemorrhagic Fever, Brazil, 1981–2002. *Emerg Infect Dis* 2005; **11**: 48–53.

44 Silva GDM da, Bartholomay P, Cruz OG, Garcia LP. Evaluation of data quality, timeliness and acceptability of the tuberculosis surveillance system in Brazil’s micro-regions. *Cienc Saude Coletiva* 2017; **22**: 3307–19.

45 Borchering RK, Huang AT, Mier-y-Teran-Romero L, *et al.* Impacts of Zika emergence in Latin America on endemic dengue transmission. *Nat Commun* 2019; **10**: 1–9.

46 Carvalho MS, Freitas LP, Cruz OG, Brasil P, Bastos LS. Association of past dengue fever epidemics with the risk of Zika microcephaly at the population level in Brazil. *Sci Rep* 2020; **10**: 1–9.

47 IBGE. Regiões de influência das cidades 2007. *Rio Jan* 2008.

48 Stoddard ST, Forshey BM, Morrison AC, *et al.* House-to-house human movement drives dengue virus transmission. *Proc Natl Acad Sci U S A* 2013; **110**: 994–9.

49 Cohen DA. The rationed city: The politics of water, housing, and land use in drought-parched São Paulo. *Public Cult* 2016; **28**: 261–289.

Table 1. Relative risk of dengue for hydrometeorological extremes along an urban gradient

Relative risk (RR) of dengue compared to normal conditions (PDSI = 0) (i) overall (i.e. from the drought severity model without interactions) and for (ii) high levels of urbanisation (upper quartile % of residents living in urban areas = 87%), (iii) intermediate levels of urbanisation (median of % of residents living in urban areas = 73%) and (iv) low levels of urbanisation (lower quartile of % of residents living in urban areas = 58%) , from the drought severity - urban interaction model. The PDSI, lag (in months) and RR (and 95% confidence interval, CI) at the maximum are reported for both wet (PDSI > 0) and dry conditions (PDSI <= 0).

Figure 1: Spatial and temporal variation in dengue incidence rates for Brazilian states

Annual cycle of dengue incidence rate (DIR) per 100,000 inhabitants from Jan 2001 – Dec 2019 aggregated at the state level in Brazil (note log10 scale). Note, states are ordered by their geographical location.

Figure 2: Distribution of urban areas and relationship with access to the water network and frequency of water shortages

(a) Percentage (%) of residents per microregion living in urban areas, (b) % of residents per microregion with access to the piped water network against % of residents living in urban areas, and (c) frequency of water shortages per microregion against % of residents living in urban areas, stratified by geo-political region.

Fig 3. Dengue lag-response for different temperature scenarios

(a) Contour plot of the exposure–lag–response association between Minimum temperature and dengue, relative to the overall mean minimum temperature (Tmin = 19 °C). The deeper the shade of purple, the greater the increase in relative risk of dengue compared to the average minimum temperature (Tmin = 19 °C). The deeper the shade of green, the greater the decrease in relative risk of dengue compared to the average minimum temperature. (b) Dengue lag–response association for cool (Tmin = 15 °C) warmer (Tmin = 21 °C) and warmest (Tmin = 25 °C) minimum temperatures relative to the overall mean minimum temperature (Tmin = 19 °C). Results are for the drought-severity model (with no interactions).

Fig 4. Relative risk of dengue given the drought severity index at different time lags overall, and for high and low levels of urbanisation

Contour plots of the exposure–lag–response association between the Palmer drought severity index (PDSI) and dengue, relative to neutral conditions (PDSI = 0) (a) overall using the drought severity model (with no interactions), and for (b) high levels of urbanisation (upper quartile % of residents living in urban areas = 87%) and (c) low levels of urbanisation (lower quartile of % of residents living in urban areas = 58%) using the drought severity - urban interaction model. The index ranges from -10 (very dry) to + 10 (very wet), with values below -4 or above +4 considered ‘extreme’. The deeper the shade of purple the greater the increase in relative risk of dengue compared to normal conditions (PDSI = 0). The deeper the shade of green the greater the decrease in relative risk of dengue compared to normal conditions.

Fig 5. Dengue lag-response association for extreme hydrometeorological scenarios, given high and low levels of urbanisation

Lag–response association for extreme values of the Palmer drought severity index: exceptionally wet (PDSI = 7, green curve) and extreme drought (PDSI = -7, brown curve) conditions relative to the baseline (PDSI = 0) at lags between zero and six months for (a) high levels of urbanisation (upper quartile of % of residents living in urban areas = 87%) and (b) low levels of urbanisation (lower quartile of % of residents living in urban areas = 58%). Shaded areas represent 95% confidence intervals.