Socioeconomic and environmental conditions influence the risk of dengue infection in a subtropical city of Argentina

Dardo E. Costas[1]; Guillermo G. Barrenechea[2,6,✉]; Rocío Sánchez[3,4]; Javier Foguet[4]; María Peral[2]; Rossana F. Chahla[5]; Julieta Orosco[3] & Ezequiel Aráoz[3,4]

[1] *Laboratorio de Salud Pública. Ministerio de Salud Pública de Tucumán. San Miguel de Tucumán, Tucumán, Argentina.*
[2] *Dirección de Investigación en Salud. Ministerio de Salud Pública. San Miguel de Tucumán, Tucumán, Argentina.*
[3] *Facultad de Ciencias Naturales e Instituto Miguel Lillo. Universidad Nacional de Tucumán (UNT). San Miguel de Tucumán, Tucumán, Argentina.* [4] *Instituto de Ecología Regional (IER). Universidad Nacional de Tucumán (UNT) - Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET). Yerba Buena, Tucumán, Argentina.* [5] *Ministerio de Salud Pública. San Miguel de Tucumán, Tucumán, Argentina.* [6] *Programa de Pós-Graduação de Epidemiología em Saúde Pública - Programa Educacional VigiFronteiras-Brasil. Fundação Oswaldo Cruz. Rio de Janeiro, Brasil.*

Abstract. The increasing connectivity and urbanization of human population favor the reemergence and spread of dengue fever in subtropical and temperate regions, which poses onerous challenges to health systems. Analyzing the contribution of socioenvironmental conditions to the contagion risk is essential to design preventive strategies. In this retrospective analysis, we aim to assess the effects of social, demographic and environmental factors on the likelihood of becoming infected with dengue virus in Tucumán, the main subtropical city of Argentina. We implemented a case-control study to analyze the 2016 dengue outbreak. The control group included all persons reported with nonspecific febrile syndrome, and the cases were those confirmed with dengue virus after laboratory analyses. We recorded the age, sex and diagnostic date for every patient, and we georeferenced their house. This georeferentiation allowed us to estimate the distance to the nearest previous positive case (to control autocorrelation), population density, proportion of households with insufficient material constructive quality, overcrowding, educational level, NDVI, surface temperature and distance to nearest canal and cemetery. We constructed and compared logistic regression models to identify the combination of variables that best predicted dengue cases. Proximity to previous cases, cemeteries and canals, scarcity of surrounding vegetation, age and educational deficit were associated with an increased probability of being positive for dengue. In Argentina, socioeconomic differences are reflected in environmental inequalities, which reinforce the differential odds of suffering from dengue fever. Our results suggest that improving urban environmental quality may constitute an efficient way of preventing individual contagion of dengue and subsequent outbreaks.

[Keywords: neglected tropical diseases, epidemiology, public health, risk factors, socioecology, spatial distribution]

Resumen. Las condiciones socioeconómicas y ambientales influyen en el riesgo de infección por dengue en una ciudad subtropical de la Argentina. La creciente conectividad y urbanización de la población humana favorece que el dengue resurja y se expanda en las regiones subtropicales y templadas, lo que plantea desafíos a los sistemas de salud. Analizar la contribución de las condiciones socioambientales al riesgo de contagio es fundamental para diseñar estrategias preventivas. En este análisis retrospectivo pretendemos evaluar el efecto de factores sociales, demográficos y ambientales sobre la probabilidad de infectarse con el virus del dengue en Tucumán, la principal ciudad subtropical de Argentina. Realizamos un estudio de caso control durante el brote de dengue de 2016. El grupo control correspondió a todas las personas reportadas como síndrome febril inespecífico, y los casos fueron los confirmados por el virus del dengue a través de análisis de laboratorio. Registramos la edad, el sexo y la fecha de diagnóstico de cada paciente, y georreferenciamos su domicilio. Esta georreferenciación nos permitió estimar la distancia al caso positivo anterior más próximo (para controlar la autocorrelación), la densidad poblacional, la proporción de viviendas con calidad del material insuficiente, el hacinamiento, el nivel educativo, el NDVI, la temperatura superficial y la distancia a canales y cementerios. Construimos modelos de regresión logística para identificar la combinación de variables que mejor predecían los casos de dengue. La proximidad a casos anteriores, a cementerios y canales, la escasez de vegetación circundante, la edad y el déficit educativo se asociaron a un aumento en la probabilidad de ser positivos para dengue. En la Argentina, las diferencias socioeconómicas se reflejan en las desigualdades ambientales, que refuerzan las probabilidades diferenciales de padecer dengue. Nuestros resultados sugieren que mejorar la calidad ambiental urbana puede constituir una forma eficiente de prevenir el contagio individual de dengue y los consiguientes brotes.

[Palabras clave: enfermedades tropicales, epidemiología, salud pública, factores de riesgo, socioecología, distribución espacial]

Introduction

Dengue is a raising health problem at the global level that requires integrated socioecological consideration, since three components are involved: the pathogenic virus (DENV), the vector (mosquitoes: *Aedes aegypti* and *A. albopictus*) and human hosts. Each component responds to extrinsic factors (e.g., ecological, climatic) and intrinsic factors (e.g., physiological, behavioral) that constitute a complex matrix of combinations which varies in time and space, and differentially affects the occurrence of dengue and the risk of infection (Mordecai et al. 2017; Lippi et al. 2018; Ryan et al. 2019). Population growth, concentration in urban areas through unplanned expansion, a higher use of non-degradable products (e.g., bottles, plastic, cans, tires) and the unprecedented increase of the movement of people through trips and commerce are the main characteristics of our time (Spiegel et al. 2005). Since dengue is an eminently urban disease, it will likely be one of the main problems of the Anthropocene, and health systems should adequately handle socioecological conditions to prevent and reduce its impact (Barrera et al. 2000; Santos et al. 2019). dengue presence and control has been the focus of public health systems for decades in tropical developing countries, because their urban sprawl frequently takes place in scenarios of social inequity, fragile economies, social and political changes, and weakening of health systems (Stewart-Ibarra et al. 2014; Marcondes et al. 2017), but currently dengue is spreading around the world affecting subtropical and temperate regions, such as Argentina (Stanaway et al. 2016; López et al. 2018).

In Argentina, a progressive increase in cases has been reported since dengue reemergence in 1986 (Das et al. 1999). The spatial distribution and frequency of these cases is not homogeneous through the country and the northern region of the country (Jujuy, Salta, Misiones and Tucumán provinces) is the most affected area. Official reports identify three dengue outbreaks: 2009, 2016 and 2020 with 26923, 41207 and 56095 cases, respectively (argentina.gob.ar/salud/epidemiologia). Most studies of dengue in Argentina have addressed the activity of the vector, its occurrence (Vezzani et al. 2008; Mangudo et al. 2018), reproduction (Estallo et al. 2013) and the biophysical factors influencing its development (Batallán et al. 2015). The use of geospatial tools allowed the detection of areas with higher occurrence and increased spread likelihood of the vector (Carbajo et al. 2004; Estallo et al. 2013; Estallo et al. 2014). However, studies on the occurrence of the disease and its relationship with social and environmental factors inherent in urban population are scarce. Considering the rising incidence of dengue in Argentina, it is important to understand the influence of socioecological conditions on the occurrence and spread of dengue in the population to inform health policies and reduce its incidence on vulnerable population.

Most studies on dengue risk focus on the density of dengue cases within specific areas, disregarding the inaccuracies that may arise from imperfect case recording. In underdeveloped areas of the world, many cases of dengue fever are poorly recorded and georeferenced (Das et al. 2017). For example, urbanized areas with poor socioeconomic conditions are frequently more difficult to georeference because they have no regular addresses, thus there can be an underestimation of the incidence of the epidemic in these areas. Additionally, certain groups may be underregistered due to the economic costs of medical care (Stewart-Ibarra et al. 2014). This situation is problematic because the biases of georeference are propagated to the results and their interpretation. To avoid biases associate to georeference issues we considered an alternative approach based on a case-control design, in which only correctly georeferenced events of nonspecific febrile syndrome were considered to assess the likelihood of presenting dengue in association with socioenvironmental conditions. This study uses an integrated, context-dependent approach to evaluate the association between sociodemographic and ecoepidemiological variables that characterize a community with the risk of dengue infection in an urban area in northern Argentina. For that, we 1) describe the spatial location of suspected and confirmed dengue cases during the 2016 outbreak; 2) quantify different socioeconomic, demographic and ecological indicators for every suspicious case, and 3) analyze the association between the output (confirmed or discarded) with the nearest previous case (to control spatial autocorrelation) and socioenvironmental conditions to assess the probability that a patient with nonspecific febrile syndrome is positive for dengue. We hypothesize that contagion risk depends on the presence of the virus, the availability of

reproducing sites for mosquitoes, inadequate handling of water services and spare urbanization. Thus, we predict negative associations of dengue risk with the distance to previous cases, which function as source of the virus; with socioeconomic variables, indicating poor infrastructure and inadequate handling of open environments, and positive associations with vegetation and water bodies, which favor the proliferation of mosquitoes.

Materials and Methods

Study area

The northern region of Argentina is the most tropical area of the country, with the highest rates of dengue incidence since its reintroduction, and thus higher risk of becoming endemic. Tucumán province has an area of 22524 km^2 inhabited by 1448188 people (INDEC 2010), the highest population density among all provinces (64.3 inhabitants/km^2), with a nonhomogeneous distribution (more than 90% concentrated in less than 25% of its area). Although dengue affects the overall province of Tucumán, we focus on Gran San Miguel de Tucumán (GSMT), the main urban agglomeration of northern Argentina, to understand the spatiotemporal dynamic with a high resolution and adequate spatial information for this study. GSMT is a subtropical city that extends in the foothills of Sierras del Aconquija, between 400 and 600 m a. s. l. It is located in the transition between two contrasting ecoregions: montane area, located to the west and dominated by rainforests (Yungas), and dry woodlands (Chaco) in lower elevations. The weather is sharply seasonal; summers are warm (mean: 25 °C) and winters are mild (mean 14° C). Eighty percent of the precipitations (1000 mm annually) are concentrated between October and April (warm months). GSMT is located in the center of Tucumán province and comprises San Miguel de Tucumán and other neighboring settlements, which constitute a functional unit. The population presents high inequalities in levels of education, age structure, household characteristics, and urban sprawl has occurred between two extremes: wealthy enclosed urbanizations and popular districts. Based on the information of the 1991, 2001 and 2010 population censuses, the spatial distribution reflects a process of increasing polarization and unsolved housing problems (Batista Zamora and Natera Rivas 2017).

Information sources

We used data from patients who reported a nonspecific febrile syndrome compatible with dengue fever. All our sample population presented febrile syndrome. From that population, we compared febrile patients who did not present the event (negative for dengue) with those who did present the event (positive for dengue). We used a case-control study, in which the cases were dengue positive patients confirmed by the laboratory and the controls were dengue negative patients, a similar criterion used in other spatial dengue studies (Parra et al. 2018). We evaluated whether exposure to any factor that is understood to be causal or strongly associated with the event is unequally present between dengue positive (cases) and negative (controls). Our research was very limited to the precise data we had. For most patients, we did not have information on people who resided in the same house and did not contract dengue. Neither do we have information on the population that lived in the same area and did not get dengue. These approach was useful to reduce biased representation of positive cases (e.g., underrepresentation due to inaccurate georeferentiation or due to the uneven accessibility to public health systems). We respected data confidentiality according to the National Law N° 25326 of personal data protection. In this ecological study, we used data from secondary sources of the pathologies, and public nonbinding knowledge. Thus, informed consent was not necessary. The project is approved by the ethical and methodological committee of the Tucumán Health Ministry. We worked with nonspecific febrile syndrome patients from Gran San Miguel de Tucumán, registered by the Health Ministry at División Virología, Departamento Bioquímico, Laboratorio de Salud Pública of Tucumán during the 2016 outbreak. It is the provincial reference diagnostic center and gathers all the information on suspected dengue patients. Relevant information of the patient was recorded, such as sex, age, date of symptom onset and address, and we used Python Client library for Google Geocoding API to convert the postal address of each record into a geographic coordinate. Of the total number of records (n=1531), it was possible to georeference 52.84% (n=809), and the rest were excluded from the analysis. This loss of information was not spatially homogeneous, but certain zones of the study area were underrepresented. This uneven

loss of information generates biased results on epidemiological assessments (Das et al. 2017; Stewart-Ibarra et al. 2014) that are overcome in our study by considering only correctly georeferenced patients in case and control groups. We used the location of the records to obtain the values of all the social-environmental variables.

We combined the location of every case with the date of symptom onset to calculate the minimum distance of each record to preexisting positive cases of dengue. Positive cases indicate the presence of the virus, and minimum distance to preexistent positive cases constitutes an indicator of distance to virus sources, which has been considered a predictor of dengue fever (Martínez-Vega et al. 2015). Furthermore, the inclusion of distances to previous cases allows controlling spatial autocorrelation in the response, which is characteristic of epidemiological patterns. To calculate such a distance, we built a distance matrix among all patients using Geosphere package in R. For every case, we identified the shortest distance to a positive case whose date of symptom onset occurred before the date of symptom onset of the focal case.

To characterize the socioeconomic condition of each record we used information of Argentinean census (Censo Nacional de Población, Hogares y Vivienda 2010) elaborated by Instituto Nacional de Estadísticas y Censos (INDEC) to extract relevant socioeconomic variables (Table 1). We worked at the censal radius level (the minimum spatial unit of censal information aggregation, which includes ~300 households); GSMT includes 760 censal radii. Every suspicious and confirmed case was assigned to a censal radius on the basis of its georeferentiation; from each censal radius we extracted five socioeconomic variables (see Table 1): a) population density; b) proportion of households with insufficient constructive quality; c) proportion of households with unsatisfied basic needs; d) overcrowding, and e) proportion of households in which the maximum level of education reached is basic school cycle.

To assign the values of the ecological variables to each record, we used different data sources (Table 1). To estimate the vegetation surrounding the household of each record, we used a map of the normalized difference vegetation index (NDVI), an indicator of photosynthetic activity and, in urban environments, of the proportion of vegetation cover. NDVI is estimated by remote sensing, thus it can be spatialized in natural and urban environments (Paolini et al. 2019). To estimate local temperature, we used soil surface temperature (SST), calculated from remote sensing (Li et al. 2013); although SST does not have a perfect correlation with air temperature, it is considered the best way to map spatial variations in temperature. To calculate these two variables, we used Landsat images (30 m resolution) from the summer season, and we calculated the median of each variable in a 250-m radius around each record. Additionally, from a map of canals and cemeteries of GSMT and its surroundings we calculated the distance of each record to these possible vector sources.

Data analyses

We performed a preliminary analysis to assess the difference in each explaining variable between patients who were positive (cases) and negative (control) for the dengue virus. To analyze the association between personal attributes of the patient (sex and age), social and environmental conditions, and distance to virus sources, we carried out logistic regressions with the result of the laboratory analysis (positive or negative). Univariate logistic regressions allow estimating the probability of a given response as a function of each explanatory variable individually (Gelman 2012). The response variable can only attain binomial values (0 and 1), which cannot be addressed through traditional statistics, so GLM were built using a binomial distribution of errors and a logit transformation to ensure the linear combination of predictors and estimates are restrained to the response range (Aiello Lammens 2008).

We also evaluated the joint effect of different variables on the probability of observing dengue cases through multivariate logistic regressions (Supplementary Material-Table S1).To evaluate the association between the group of explanatory variables and the likelihood that a patient with nonspecific febrile syndrome is diagnosed with dengue, we compared different multiple logistic regressions with the stepwise backward method, starting from a saturated model and eliminating the variables that less contributed, one at a time, which allowed us discarding redundant variables. Since most of the explaining variables (sex was the exception) were continuous, we did not include

Table 1. Descriptive metrics of the predictor variables of patients with nonspecific febrile syndrome. NDVI: normalized difference vegetation index.

Tabla 1. Medidas descriptivas de las variables predictoras de los pacientes con síndrome febril inespecífico. NDVI: índice de vegetación de diferencia normalizada.

Name	Indicator	Descriptive metrics					References
		mean	SD	min	max	n	
Socioeconomic variables (censal radius scale)							
Population density	N° individuals/m²	0.008	0.004	0	0.033	760	Sobral de Almeida et al. (2009); Díaz-Quijano and Waldman (2012);
Unsatisfied basic needs	Proportion of household with unsatisfied basic needs	0.107	0.097	0	0.55	760	Braga et al. (2010); Ryan et al. (2019)
Household quality	Proportion of households with insufficient constructive material quality	0.15	0.16	0	0.8	760	Toan et al. (2015); Lippi et al. (2018)
Overcrowding	Proportion of households with more than three people per room	0.044	0.044	0	0.214	760	Brunkard et al. (2007); Lippi et al. (2018)
Primary education	proportion of surveyed individuals who undertook primary studies	0.405	0.187	0.066	1	760	Siqueira-Junior et al. (2008); Moraes et al. (2013)
Demographic variables (individual scale)							
Age (years)	Age	31.83	16.84	0	92	779	Soghaier et al. (2014); Stewart-Ibarra et al. (2014);
Sex	Sex	0.5				391 392	Brunkard et al. (2007); Steward-Ibarra et al. (2014)
Ecological variables (household scale)							
NDVI	Mean NDVI in a 250-m buffer	0.16	0.06	0.042	0.415	781	Qi et al. (2015); Huang et al. (2018)
Soil surface temperature (SST)	Mean SST in a 250-m buffer	34.09	0.879	30.81	34.46	781	Vieira Araujo et al. (2015); Martínez-Bello et al. (2017)
Distance to canals (m)	Distance to the closest canal	1180.5	777.25	0	3472.2	781	Nakhapakorn and Tripathi (2005); Sánchez-Hernández et al. (2021)
Distance to cemeteries (m)	Distance to the closest cemetery	2337	1131	120	6069	781	Shafie (2011); Estallo et al. (2013)
Minimum distance (m)	Distance to the closest confirmed preexistent case	883.6	1096.37	0	7093	781	

interactions in the models. The analysis of statistical interactions requires huge amounts of records to avoid instability of the parameters and the interactions between two continuous variables are seldom informative. The models were ranked using the Akaike information criterion (Burnham et al. 2011). We calculated the AIC and the differences in AIC between models (AIC) and selected the one with the smallest values (Supplementary Material-Table S2). All analyses were performed using R, specifying a logistic modeling distribution in a generalized linear model (GLM).

Results

Spatial distribution of dengue

From the 1531 original records of patients with nonspecific febrile syndrome, we were able to correctly georeference 809 of them in Gran San Miguel de Tucumán (Figure 1). Of these, 20.89% (n=169) were positive for dengue. Half of the censal radii of GSMT (n=380) had patients with nonspecific febrile syndrome. Of this total, 56.27% of the censal raddi had one patient and the other censal radii had between two and 27 patients. There were 109 censal
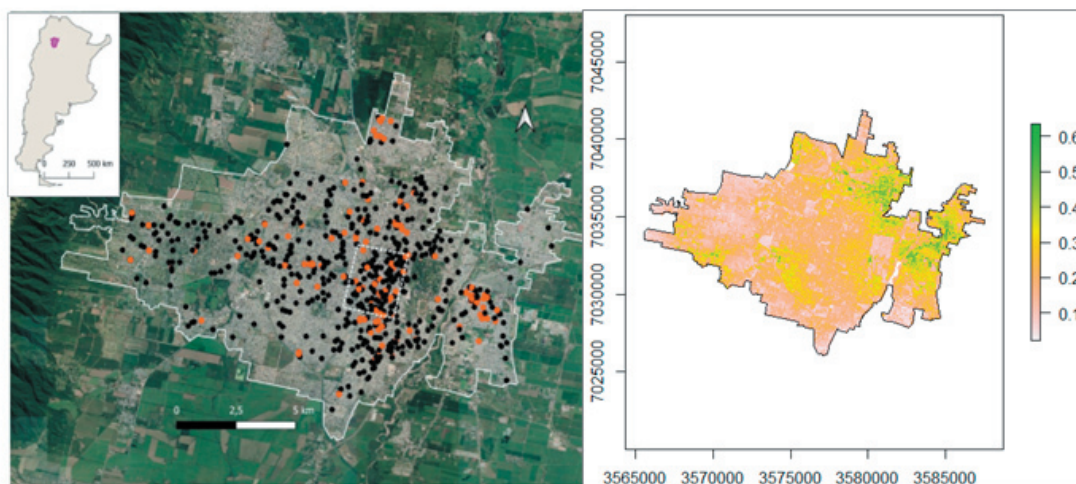
Figure 1. Left. Distribution of positive (orange) and negative (black) cases of dengue. The box shows the downtown area and macrocenter. Right: dengue infection probability map; higher values indicate higher chances of a suspected patient being positive for dengue. Gran San Miguel de Tucumán, Tucumán, Argentina, 2016.

Figura 1. Izquierda. Distribución de casos positivos (naranja) y negativos (negros) para dengue. El recuadro muestra la zona céntrica y el macrocentro. Derecha. Mapa de probabilidad de infección por dengue; los valores más altos indican mayores probabilidades de que un paciente sospechoso sea positivo para dengue. Gran San Miguel de Tucumán, Tucumán, Argentina, 2016.

radii with positive cases, ranging from 1 (n=81) to 15 cases per censal radius (n=1).

Risk factors for the presence of positive cases of dengue

The distance between a patient with nonspecific febrile syndrome (NFS) and a pre-existing positive case was the variable that best explained the probability of being positive for dengue. In Table 1, we summarized the descriptive measures of the selected predictor variables (demographic, socioeconomic and ecological) of patients with nonspecific febrile syndrome. Mean values of the socioeconomic variables were very similar between cases and control patients (Figure 2). On the contrary, the mean value of the ecological variables (particularly the distance to the canals and cemeteries) was lower for positive cases, while the mean age was slightly higher for dengue cases (Figure 2). Individually, socioeconomic variables were less strongly associated with the probability that a febrile patient is positive for dengue than ecological variables (Table 2). The variables that best explained the probability that a patient with NFS was positive for dengue were distance to the closest preexistent case, age of the patient, vegetation index (NDVI), distance to cemeteries, and

Table 2. Summary of the association between the explaining variables (Factor) and the probability of a nonspecific febrile syndrome patient being positive for dengue. NDVI: normalized difference vegetation index.

Tabla 2. Resumen de la asociación entre las variables explicativas (Factor) y la probabilidad de que un paciente con síndrome febril inespecífico sea positivo para dengue. NDVI: índice de vegetación de diferencia normalizada.

| Factor	Estimate	SE	z-value	P-value
Sex	0.12	0.17	0.7150	0.47
Population density	0.09	0.08	1.0750	0.28
Unsatisfied basic needs	-0.05	0.09	-0.5190	0.60
Insufficient household quality	0.20	0.09	2.2760	0.0228*
Overcrowding	-0.03	0.09	-0.3820	0.70
Primary education	0.12	0.09	1.3500	0.18
NDVI	-0.29	0.10	-2.2867	0.00283**
Soil surface temperature	0.14	0.09	1.6160	0.11
Distance to canals	-0.09	0.09	-1.0570	0.29
Distance to cemeteries	-0.22	0.09	-2.4680	0.0136*
Minimum distance	-0.32	0.12	-2.7570	0.00583**
Signif. codes: ***0.001, **0.01, *0.05				
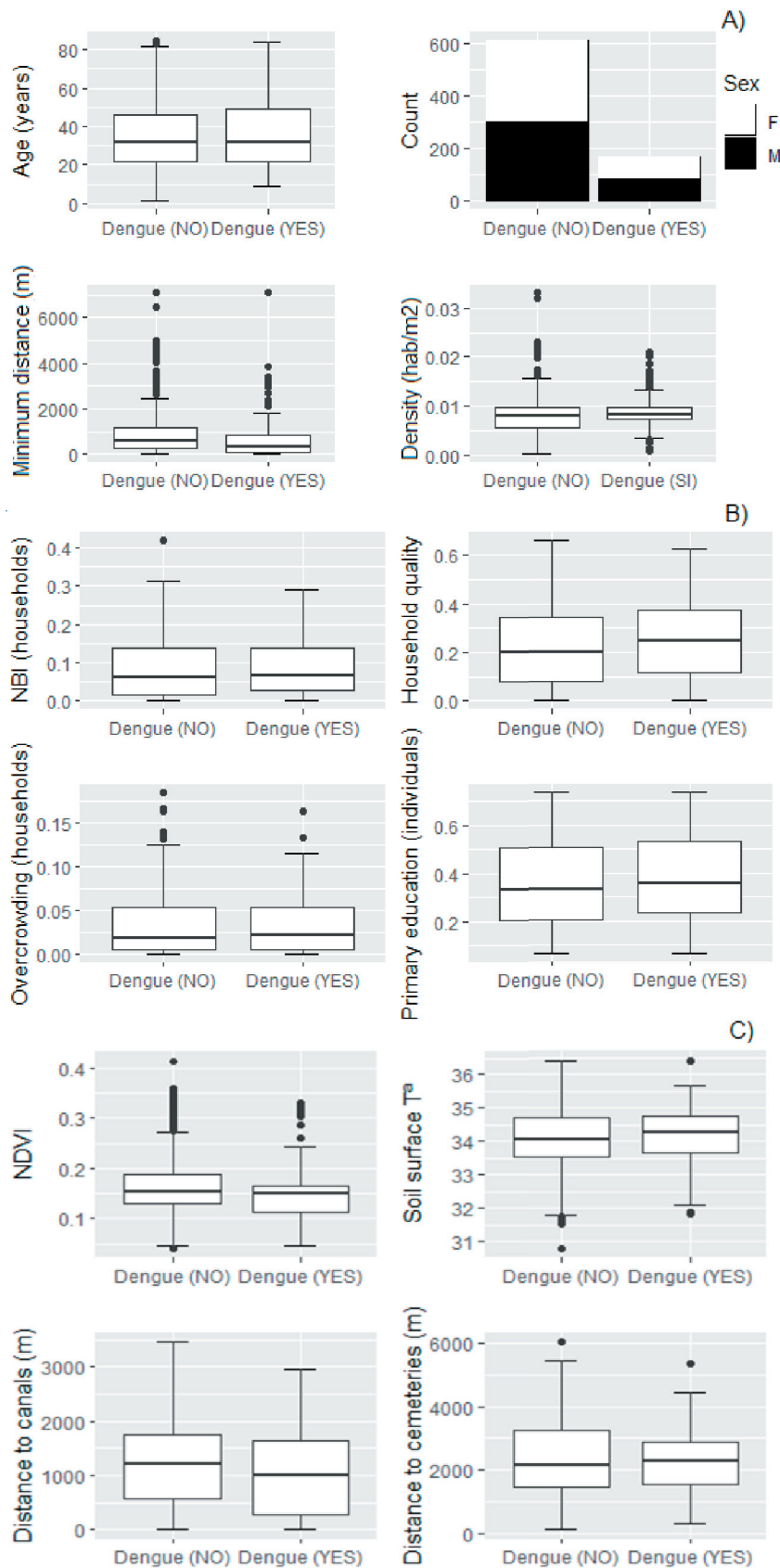
Figure 2. Description of A) demographic, B) socioeconomic, and C) ecological variables of the positive (n=168) and negative (n=6139) patients of dengue in GSMT, Tucumán, during 2016. NDVI: normalized difference vegetation index.

Figura 2. Descripción de variables A) demográficas, B) socioeconómicas, y C) ecológicas de los pacientes positivos (n=168) y negativos (n=6139) para dengue en GSMT, Tucumán, durante 2016. NDVI: índice de vegetación de diferencia normalizada.

Table 3. Summary of the best-fit model (AIC=790.71; df=7; weight=0.4937) for the probability of being positive for dengue in a multivariate logistic model within Gran San Miguel de Tucumán, 2016.

Tabla 3. Resumen del modelo de mejor ajuste (AIC=790.71; df=7; peso=0.4937) para la probabilidad de ser positivo a dengue dentro del Gran San Miguel de Tucumán, 2016.

Factor	Estimate	SE	z-value	P-value
Intercept	-1.36715	0.09289	-14.718	<2e-16***
Minimum distance	-0.23695	0.11802	-2.008	0.04467*
Age (years)	0.19389	0.08868	2.186	0.02880*
Primary education	0.18430	0.10414	1.770	0.07679
NDVI	-0.27981	0.10411	-2.688	0.00720**
Distance to canals	-0.28206	0.10553	-2.673	0.00752**
Distance to cemeteries	-0.24951	0.10120	-2.465	0.01368*
Signif. codes: ***0.001; **0.01; *0.05				

insufficient household quality. The model that best explained the probability of having dengue included distance to virus sources, three ecological variables (NDVI and distance to canals and cemeteries), one socioeconomic variable (educational precariousness of head of household) and patient age. The proximity to pre-existing cases, cemeteries and canals, scarcity of surrounding vegetation, age, and educational precariousness in a censal radius increased the probability of being positive for dengue (Table 3). Figure 1 shows the map of the probability in having dengue of a 30-year-old person in GSMT without considering the distance to the nearest infected neighbor (because it depends on the case). More information on the complete set of models we considered to explain the probability of being positive for dengue can be found in the Supplementary Material-Table S2.

Discussion

Our results highlight the importance of using a multidisciplinary approach to understand the functioning of dengue outbreaks. This study evaluates the association between sociodemographic and eco-epidemiological variables with the risk of dengue infection in an urban area of northwestern Argentina. The model with the highest predictive capacity included social and ecological indicators, demographic characteristics of the patient and proximity to virus sources. During the 2016 outbreak, in Gran San Miguel de Tucumán, the social-ecological variables that were associated with a higher probability of having dengue were the distance to a positive case, the age of the patient, educational precariousness and proximity to canals and cemeteries. These findings show the importance of controlling spatial autocorrelation of epidemiological output and addressing both human and ecological components, and their interactions. Other studies have evaluated some of these variables or a group of them simultaneously (Brunkard et al. 2007), but few studies have considered them as a whole and very few have controlled potential biases due to poorly georeferenced patients.

This study presents a novel approach that contrast a group, that had nonspecific febrile syndrome (NSF) was negative for dengue and NSF cases diagnosed with dengue fever. Most studies evaluating the prevalence of dengue fever in relation to population density disregard the difficulties in georeferencing some cases (e.g., those occurring in poorly urbanized). The bias that we may have and that always occurs with the notifications of these pathologies is to have precise data on the residence in some areas and lack of analyzable information in other areas of the province. In this context, the methodology proposed here attempts to analyze the entire analyzable population (in terms of precise georeferencing data available) as the set of patients who arrived at the public health system with the same syndrome. Among all this exposed population, only some were positive for dengue (cases) while others did not have the disease (control). In this way, we evaluated the probability of each patient having dengue according to their environmental (residence), social (census radius) and epidemiological (individual and residence) context. Thus, we understand that our inferences are an unbiased interpretation of the dengue contagion. Furthermore, the Tucumán patient who arrived at the Public Health Laboratory with non-specific febrile syndrome could be positive for another pathology. In this study we only considered the pathology of dengue that shares the same syndrome with other infections. However, our approach was specific to dengue and

therefore we did not consider the subsequent diagnosis of the rest of the patients who were diagnosed negative for dengue. The drawback highlighted does not constitute bias: it is just a mistake, but there is no reason to think that this occurs disproportionately under some social or ecological conditions.

Different studies highlight the problems that incorrectly georeferenced cases pose to adequately addressing the infection process of dengue fever (Oliveira et al. 2013; Stewart-Ibarra et al. 2014). By contrast, a study carried out in Mexico also used a case-control approach, but it did not consider the distance to previous cases as an indicator of the virus presence (Sánchez-Hernández et al. 2021). We acknowledge that our approach could present some drawbacks. For example, an outbreak of other pathologies generating nonspecific febrile syndrome could present an aggregated pattern that increases the uncertainty of the predictions, but it does not constitute bias. However, no pattern of spatial aggregation was detected in a visual inspection of our dataset (Figure 1). Besides, the inclusion of the distance to previously infected persons is essential to understand the epidemiology, especially if the disease is not endemic to a region; the inclusion of this variable controls for spatial autocorrelation of positive cases and the statistical significance of the contribution of each variable is less likely to be overstated.

Our study shows a large dispersion of positive cases of dengue within the urban area. Since dengue is predominantly an urban pathology (Harapan et al. 2020) we focused in the area of GSMT, mirroring many other studies evidencing transmission hotspots in urban centers (Barrera et al. 2000; Stewart-Ibarra et al. 2014). The NSF population with was concentrated in the downtown area (highest population density) while positive cases were more homogeneously distributed within GSMT. Some areas of recent or precarious urbanization are underrepresented due to the impossibility of correctly georeferencing addresses (e.g., north and south areas), a problem that has been described in other studies (Das et al. 2017).

The growing urban concentration of the population suggests that future outbreaks may be more detrimental. Since the decade of the 1970s Tucumán underwent a significant urbanization process, with 81% of population living in urban areas (INDEC, 2010) and GSMT

hosts almost 70% of the total population of the province and presents an aggregated and asymmetric growth (Gutiérrez Angonese 2015; del Castillo 2015). Since 1986, when dengue was reintroduced into Argentina to the present, Tucumán underwent four periods of dengue outbreaks: 2009, 2016, 2020 and 2023, during the COVID-19 pandemic. These outbreaks seem to increase their frequency over time probably associated with increasing urban temperatures and regional rainfall (Rodríguez et al. 2015) but mainly with international movement (De Haas et al. 2019).

Risk factors for the presence of positive cases of dengue

Proximity to a viraemic individual increase the probability of contagion by providing the virus that is the limiting factor in non-endemic regions. Some studies found an aggregated pattern of dengue cases (e.g., Stewart-Ibarra et al. 2014), highlighting their role as sources of virus. A study that considered the distribution of cases over time found that the distance between cases increases with time since first case, probably due to under-reporting of positive cases (Vazquez-Prokopec et al. 2010). However, although it is essential to inform public health strategies, the distance from infected people is rarely assessed in contagion risk analyses. The early detection of dengue cases and the quantification of the influence area is essential to determining the area that should be targeted for preventive and fumigation actions. However, one limitation of our analysis is that it assigns a fixed location to patients and does not consider patient movement or action radius. Although it would be demanding and methodologically complex, it might be valuable to include in the model the areas visited by each patient to consider alternative contagion sites.

Our analysis shows that the probability of having dengue increases with age. The results of other studies were not always consistent with our results, partly because certain studies treated age as a categorical variable (Braga et al. 2010; Soghaier et al. 2014). In Sudán, the presence of antibodies was found to be more frequent in people under 35 years (Soghaier et al. 2014), and in Ecuador, the mean age of patients infected with dengue was 20 years (Stewart-Ibarra et al. 2014). In contrast with these results, a study in Brazil found that seroprevalence was sharply higher in people older than 15 years (Braga et al. 2010). In this study, we included

age as a continuous variable, and we evaluated people with dengue on a particular date (i.e., the probability of having antibodies from previous infections increases with age). The age of the patients in our study ranged from 0 and 92 years with an average age of 32 years. It is expected that economically active people have higher exposition to contagion due to greater movility.

Our results suggest that educational precariousness, rather than household precariousness, is a better indicator of the probability of having dengue. Unlike many studies that found a higher incidence of dengue in areas with household and infrastructure precariousness (Braga et al 2009; Brunkard et al. 2007; Ryan et al. 2019), our study suggests that housing conditions do not sharply influence the contagion probability. It is likely that spatial aggregation (censal radii) is not good enough to capture this effect and that some environmental variables, such as distance to canals (measured for each individual patient) partly reflecting socioeconomic precariouness.

Environmental variables seem to strongly influence the probability of having dengue. The median NDVI within a 250 m radius around each NSF case was negatively related with the probability of having dengue, while Proximity to cemeteries and canals increased that probability. Other studies that analyzed the association between NDVI and dengue found overall similar results (Qi et al. 2015; Huang et al. 2018), but other studies also found the opposite association (Martínez-Bello et al. 2017). Our result can be counterintuitive, considering that greener areas have a higher abundance of insects. We would expect that areas with more vegetation cover would increase the probability of infection due to the presence of the vector. However, *Aedes aegypti* has urban habits, for which it is expected that more urbanized areas (with lower availability of green areas) are associated with greater vector presence. Besides, a study carried out in San Pablo found that higher incidence of dengue in areas with lower vegetation was due to the effect of urban heat islands (Araujo et al. 2015). Urbanization involves alterations in land use and replacement of vegetation cover by impervious infrastructure (houses, buildings, roads, highways, etc.), generating an increase in temperature, known as urban heat islands (UHI). Tucumán has increased its population, generating important changes in the patterns of inland use: on the one hand, it

has increased built in the downtown area; and, on the other hand, it has expanded its urban area to the outskirts of the city, occasionally to areas with low infrastructure (Gioia et al. 2014). More humans, more food resources for the vector, but also places with water (i.e., flower containers, containers in general) increase the establishment of the vector in earlier stages. Therefore, the combination of the habits of the mosquito and the presence of sites for its reproduction provides an adequate scenario for the proliferation of *A. aegypti*. Some of these indicators represent underlying processes, such as the proliferation of landfills and situations of fragility, such as the proliferation of open-air dumps that are not adequately captured by socioeconomic indicators, and which cannot be mapped with remote sensing (Malizia et al. 2020).

The attributes of the social and ecological variables are not homogeneously distributed within the Gran San Miguel de Tucumán. This work shows that the probability of being positive for dengue can increase as some social and ecological variables increase or decrease. Specifically, areas with lower NDVI values, closer to canals and cemeteries, and lower level of primary education would be more likely to present positive cases of dengue. In this context, it can be seen that the peripheral areas and, in particular, those in the northeastern sector, are the most likely to present positive cases for dengue. These are the areas where we were unable to obtain accurate spatial references. This situation highlights the need to incorporate new tools at the time of patient data that help to improve the quality of spatial data. With this information, we can design more precise studies that visualize the problem of dengue in the province, in a spatial-temporal context where the entire exposed population is equally representative.

The global increase in the incidence of dengue is likely to continue in the coming years. Intensification of urban life, internal and international migration and the global increase of temperatures will not revert in the short-term. The increase gives place to a complete vector cycle of the vector throughout the year in subtropical areas, exacerbated by urban heat islands. Urban vegetation decreases both in urban expansion areas and in downtown areas were construction intensifies (Paolini et al. 2016). As property costs increase, precisely vulnerable people have access to a lower proportion of urban vegetation (Spescha et

al. 2020), which suggest that different forms of urbanization may affect habitat quality, environmental health and human well-being. If considering that an increasing number of people will use the same area, it is urgent to address which 'models' of urban expansion are more efficient and compatible with the quality of life of its inhabitants.

References

Aiello Lammens, M. 2008. Ecology Ecological Models and Data in R. By Benjamin M. Bolker. Index of R arguments, functions, and packages and general index. Princeton University Press. Q Rev Biol 84(3):288-288. https://doi.org/10.1086/644667.

Araujo, R. V., M. R. Albertini, A. L. Costa-da-Silva, et al. 2015. São Paulo urban heat islands have a higher incidence of dengue than other urban areas. Brazilian J Infect Dis 19(2):146-155. https://doi.org/10.1016/j.bjid.2014.10.004.

Barrera, R., N. Delgado, M. Jiménez, I. Romero, and I. Villalobos. 2000. Estratificación de una ciudad hiperendémica en dengue hemorrágico. Rev Panam Salud Pública/Pan Am J Public Heal 8(4):225-233. https://doi.org/10.1590/S1020-49892000000900001.

Batista Zamora, A. E., and J. J. Natera Rivas. 2017. La evolución del mapa social del Gran San Miguel de Tucumán. Un estudio del periodo 1991 a 2010 a través del análisis factorial. Geograficando 13(2):027. https://doi.org/10.24215/2346898xe027.

Batallán, G. P., E. L. Estallo, F. S. Flores, P. Sartor, M. S. Contigiani, and W. R. Almirón. 2015. St. Louis Encephalitis virus mosquito vectors dynamics in three different environments in relation to remotely sensed environmental conditions. Acta Trop 146:53-59. https://doi.org/10.1016/j.actatropica.2015.03.009.

Braga, C., C. F. Luna, C. M. T. Martelli, W. V. de Souza, M. T. Cordeiro, N. Alexander, et al. 2010. Seroprevalence and risk factors for dengue infection in socio-economically distinct areas of Recife, Brazil. Acta Trop 113(3):234-240. https://doi.org/10.1016/j.actatropica.2009.10.021.

Brunkard, J. M., J. L. Robles López, J. Ramírez, and E. Cifuentes. 2007. Dengue Fever Seroprevalence and Risk Factors, Texas-Mexico Border, 2004. Emerg Infect Dis 13:1477-1483. https://doi.org/10.3201/eid1310.061586.

Burnham, K. P., D. R. Anderson, and K. P. Huyvaert. 2011. AIC model selection and multimodel inference in behavioral ecology: some background, observations, and comparisons. Behav Ecol Sociobiol 65:23-35. https://doi.org/10.1007/s00265-010-1029-6.

Carbajo, A. E., S. M. Gómez, S. I. Curto, and N. J. Schweigmann. 2004. Variación espacio-temporal del riesgo de transmisión de dengue en la Ciudad de Buenos Aires. Medicina (B Aires) 64(3):231-234.

Das, S., A. Sarfraz, N. Jaiswal, et al. 1999. Dengue History in Argentina. Emerg Infect Dis 5(5):575-578. https://doi.org/10.3201/eid0504.990424.

Das, S., A. Sarfraz, N. Jaiswal, and P. Das. 2017. Impediments of reporting dengue cases in India. J Infect Public Health 10(5):494-498. https://doi.org/10.1016/j.jiph.2017.02.004.

De Haas, H., M. Czaika, M. L. Flahaux, E. Mahendra, K. Natter, S. Vezzoli, and M. Villares-Varela. 2019. International migration: Trends, determinants, and policy effects. Population and Development Review 45(4):885-922. https://doi.org/10.1111/padr.12291.

del Castillo, A. C. 2015. De pobrezas y persistencias… Un estudio de caso sobre la pobreza urbana en Gran San Miguel de Tucumán (Argentina) en los inicios del siglo XXI. Trab y Soc 25:493-516.

Díaz-Quijano, F. A., and E. A. Waldman. 2012. Factors associated with dengue mortality in Latin America and the Caribbean, 1995-2009: An ecological study. Am J Trop Med Hyg 86(2):328-334. https://doi.org/10.4269/ajtmh.2012.11-0074.

Estallo, E. L., A. E. Carbajo, M. G. Grech, et al. 2014. Spatio-temporal dynamics of dengue 2009 outbreak in Córdoba City, Argentina. Acta Trop 136(1):129-136. https://doi.org/10.1016/j.actatropica.2014.04.024.

Estallo, E. L., G. Más, C. Vergara-Cid, et al. 2013. Spatial Patterns of High Aedes aegypti Oviposition Activity in Northwestern Argentina. PLoS ONE 8(1):1-8. https://doi.org/10.1371/journal.pone.0054167.

Gelman, A., and J. Hill. 2006. Data Analysis Using Regression and Multilevel/Hierarchical Models (Analytical Methods for Social Research). Cambridge: Cambridge University Press. https://doi.org/10.1017/CBO9780511790942.

Gioia, A., L. Paolini, A. Malizia, R. Oltra-Carrió, and J. A. Sobrino. 2014. Size matters: vegetation patch size and surface temperature relationship in foothills cities of northwestern Argentina. Urban Ecosyst 17:1161-1174. https://doi.org/10.1007/s11252-014-0372-1.

Gutiérrez Angonese, J. 2015. Historia de uso del territorio en el área peri-urbana de la Sierra de San Javier y el Gran San Miguel de Tucumán, Argentina (1972-2010). Tesis de Doctorado en Ciencias Biológicas. Facultad de Ciencias Exactas, Físicas y Biológicas. Universidad Nacional de Córdoba. http://hdl.handle.net/11086/13236.

Harapan, H., A. Michie, R. T. Sasmono, and A. Imrie. 2020. Dengue: A minireview. Viruses 12(8):1-35. https://doi.org/10.3390/v12080829.

Huang, C. C., T. Y. T. Tam, Y. R. Chern, S. C. C. Lung, N. T. Chen, C. Da Wu. 2018. Spatial clustering of dengue fever incidence and its association with surrounding greenness. Int J Environ Res Public Health 15(9):1-12. https://doi.org/10.3390/ijerph15091869.

Li, X., W. Zhou, and Z. Ouyang Z. 2013. Relationship between land surface temperature and spatial pattern of greenspace: What are the effects of spatial resolution? Landsc Urban Plan 114(June):1-8. https://doi.org/10.1016/j.landurbplan.2013.02.005.

Lippi, C. A., A. M. Stewart-Ibarra, Á. G. Muñoz, M. J. Borbor-Cordova, R. Mejía, K. Rivero, et al. 2018. The social and spatial ecology of dengue presence and burden during an outbreak in Guayaquil, Ecuador, 2012. International Journal of Environmental Research and Public Health 15(4):827. https://doi.org/10.3390/ijerph15040827.

López, M. S., M. V. Müller, and W. Sione. 2018. Analysis of the spatial distribution of scientific publications regarding vector-borne diseases related to climate variability in South America. Spat Spatiotemporal Epidemiol 26:35-93. https://doi.org/10.1016/j.sste.2018.04.003.

Malizia, A., P. Boldrini, M. Malizia, and C. Monmany. 2020. ¿Qué pasa con el dengue? Una opinión socio-ambiental para el aglomerado Gran San Miguel de Tucumán. Investig en Salud 3:15-19.

Mangudo, C., J. P. Aparicio, G. C. Rossi, and R. M. Gleiser. 2018. Tree hole mosquito species composition and relative abundances differ between urban and adjacent forest habitats in northwestern Argentina. Bull Entomol Res 108(2): 203-212. https://doi.org/10.1017/S0007485317000700.

Marcondes, C. B., M. Contigiani, R. M. Gleiser, and W. Reisen. 2017. Emergent and reemergent arboviruses in South America and the Caribbean: Why so many and why now? J Med Entomol 54(3):509-532. https://doi.org/10.1093/jme/tjw209.

Martínez-Bello, D. A., A. López-Quílez, and A. Torres Prieto. 2017. Relative risk estimation of dengue disease at small spatial scale. Int J Health Geogr 16(1):1-15. https://doi.org/10.1186/s12942-017-0104-x.

Martínez-Vega, R. A., R. Danis-Lozano, F. A. Díaz-Quijano, et al. 2015. Peridomestic Infection as a Determining Factor of dengue Transmission. PLoS Negl Trop Dis 9(12). https://doi.org/10.1371/journal.pntd.0004296.

Moraes, G. H., E. D. F. Duarte, and E. C. Duarte. 2013. Determinants of mortality from severe dengue in Brazil: A population-based case-control study. Am J Trop Med Hyg 88(4):670-676. https://doi.org/10.4269/ajtmh.11-0774.

Mordecai, E. A., J. M. Cohen, M. V. Evans, et al. 2017. Detecting the impact of temperature on transmission of Zika, dengue, and chikungunya using mechanistic models. PLoS Negl Trop Dis 11(4):1-18. https://doi.org/10.1371/journal.pntd.0005568.

Nakhapakorn, K., and N. K. Tripathi. 2005. An information value based analysis of physical and climatic factors affecting dengue fever and dengue haemorrhagic fever incidence. Int J Health Geogr 4:1-13. https://doi.org/10.1186/1476-072X-4-13.

Oliveira, M. A. de, H. Ribeiro, and C. Castillo-Salgado. 2013. Geospatial analysis applied to epidemiological studies of dengue: a systematic review Análise geoespacial aplicada em. Rev Bras Epidemiol 16(4):907-917. https://doi.org/10.1590/S1415-790X2013000400011.

Paolini, L., L. Schwendenmann, E. Aráoz, and P. A. Powell. 2019. Decoupling of the urban vegetation productivity from climate. Urban For Urban Green 44:126428. https://doi.org/10.1016/j.ufug.2019.126428.

Paolini, L., E. Aráoz, A. Gioia, and P. A. Powell. Vegetation productivity trends in response to urban dynamics. Urban For Urban Green 17:211-216 https://doi.org/10.1016/j.ufug.2016.04.005.

Parra, M. C. P., E. A. Fávaro, M. R. Dibo, et al. 2018. Using adult Aedes aegypti females to predict areas at risk for dengue transmission: A spatial case-control study. Acta Trop 182(January):43-53. https://doi.org/10.1016/j.actatropica.2018.02.018.

Qi, X., Y. Wang, Y. Li, et al. 2015. The Effects of Socioeconomic and Environmental Factors on the Incidence of dengue Fever in the Pearl River Delta, China, 2013. PLoS Negl Trop Dis 9(10):1-13. https://doi.org/10.1371/journal.pntd.0004159.

Rodríguez, G. A., C. A. Veggiani Aybar, G. L. Claps, and M. S. Lizarralde de Grosso. 2015. Seasonal Oviposition Activity of Aedes aegypti (Diptera: Culicidae) in San Miguel de Tucumán, Northwestern Argentina. Florida Entomol 98(4): 1241-1243. https://doi.org/10.1653/024.098.0435.

Ryan, S. J., C. A. Lippi, R. Nightingale, et al. 2019. Socio-ecological factors associated with dengue risk and Aedes aegypti presence in the Galápagos Islands, Ecuador. Int J Environ Res Public Health 16(5):1-16. https://doi.org/10.3390/ijerph16050682.

Sánchez-Hernández, D., C. A. Aguirre-Salado, G. Sánchez-Díaz, Alejandro I. Aguirre-Salado, C. Soubervielle-Montalvo, et al. 2021. Modeling spatial pattern of dengue in North Central Mexico using survey data and logistic regression. Int J Environ Health Res 31(7):872-888. https://doi.org/10.1080/09603123.2019.1700938.

Santos, J. P. C. dos, N. A. Honório, and A. A. Nobre. 2019. Definition of persistent areas with increased dengue risk by detecting clusters in populations with differing mobility and immunity in Rio de Janeiro, Brazil. Cad Saude Publica 35(12):e00248118. https://doi.org/10.1590/0102-311X00248118.

Shafie, A. 2011. Evaluation of the spatial risk factors for high incidence of dengue Fever and dengue Hemorrhagic Fever using GIS application. Sains Malaysiana 40(8):937-943.

Siqueira-Junior, J. B., I. J. Maciel, C. Barcellos, et al. 2008. Spatial point analysis based on dengue surveys at household level in central Brazil. BMC Public Health 8:1-9. https://doi.org/10.1186/1471-2458-8-361.

Soghaier, M. A., S. F. Mahmood, O. Pasha, et al. 2014. Factors associated with dengue fever IgG sero-prevalence in South Kordofan State, Sudan, in 2012: Reporting prevalence ratios. J Infect Public Health 7(1):54-61. https://doi.org/10.1016/j.jiph.2013.07.008.

Spescha, V., L. Paolini, P. Powell, and B. Covaro. 2020. Unequal Appropriation of Urban Vegetation in Argentine Cities. Ecosystems 23:1395-1407. https://doi.org/10.1007/s10021-019-00476-5.

Spiegel, J., S. Bennett, L. Hattersley, M. H. Hayden, P. Kittayapong, and D. Gubler. 2005. Barriers and Bridges to Prevention and Control of dengue: The Need for a Social-Ecological Approach. EcoHealth 2:273-290. https://doi.org/10.1007/s10393-005-8388-x.

Stanaway, J. D., D. S. Shepard, E. A. Undurraga, et al. 2016. The global burden of dengue: an analysis from the Global

Burden of Disease Study 2013. Lancet Infect Dis 16(6):712-723. https://doi.org/10.1016/S1473-3099(16)00026-8.

Stewart-Ibarra, M. A., G. A. Muñoz, J. S. Ryan, et al. 2014. Spatiotemporal clustering, climate periodicity, and social-ecological risk factors for dengue during an outbreak in Machala, Ecuador, in 2010. BMC Infect Dis 14(1):1-16. https://doi.org/10.1186/s12879-014-0610-4.

Team R core. 2017. R: A language and environment for Statistical Computing. URL: r-project.org.

Toan, D. T. T., L. N. Hoat, W. Hu, P. Wright, and P. Martens. 2015. Risk factors associated with an outbreak of dengue fever/dengue haemorrhagic fever in Hanoi, Vietnam. Epidemiol Infect 143(8):1594-1598. https://doi.org/10.1017/S0950268814002647.

Vázquez-Prokopec, G. M., U. Kitron, B. Montgomery, P. Horne, and S. A. Ritchie. 2010. Quantifying the spatial dimension of dengue virus epidemic spread within a tropical urban environment. PLoS Negl Trop Dis 4(12):1-14. https://doi.org/10.1371/journal.pntd.0000920.

Vezzani, D., and A. E. Carbajo. 2008. *Aedes aegypti*, *Aedes albopictus* and dengue in Argentina: Current knowledge and future directions. Mem Inst Oswaldo Cruz 103(1):66-74. https://doi.org/10.1590/S0074-02762008005000003.