Spatio-temporal dynamics of dengue-related deaths and associated factors

Lidia Maria Reis Santana[1,2] , **Oswaldo Santos Baquero**[3] , **Adriana Yurika Maeda**[4] , **Juliana Silva Nogueira**[4] , **Francisco Chiaravalloti-Neto**[5]

ABSTRACT

Since the reintroduction of dengue viruses in 1987, Sao Paulo State (SP), Brazil, has experienced recurrent epidemics in a growing number of municipalities, each time with more cases and deaths. In the present study, we investigated the spatio-temporal dynamics of dengue-related deaths and associated factors in SP. This was an ecological study with spatial and temporal components, based on notified dengue-related deaths in the municipalities of SP between 2007 and 2017. A latent Gaussian Bayesian model with Poisson probability distribution was used to estimate the standardized mortality ratios (SMR) for dengue and relative risks (RR) for the socioeconomic, demographic, healthcare-related, and epidemiological factors considered. Epidemiological factors included the annual information on the number of circulating serotypes. A total of 1,019 dengue-related deaths (0.22 per 100,000 inhabitant-years) between 2007 and 2017 were confirmed in SP by laboratory testing. Mortality increased with age, peaking at 70 years or older (1.41 deaths per 100,000 inhabitant-years). Mortality was highest in 2015, and the highest SMR values were found in the North, Northwest, West, and coastal regions of SP. An increase of one circulating serotype, one standard deviation in the number of years with cases, and one standard deviation in the degree of urbanization were associated with increases of 75, 35, and 45% in the risk of death from dengue, respectively. The risk of death from dengue increased with age, and the distribution of deaths was heterogeneous in space and time. The positive relationship found between the number of dengue serotypes circulating and years with cases at the municipality/ micro-region level indicates that this information can be used to identify risk areas, intensify surveillance and control measures, and organize healthcare to better respond to this disease.

KEYWORDS: Dengue mortality. Risk factor. Surveillance. Spatiotemporal.

[1]Secretaria de Estado de Saúde de São Paulo, Centro de Vigilância Epidemiológica "Professor Alexandre Vranjac", São Paulo, São Paulo, Brazil

[2]Universidade Federal de São Paulo, São Paulo, São Paulo, Brazil

[3]Universidade de São Paulo, Faculdade de Medicina Veterinária e Zootecnia, São Paulo, São Paulo, Brazil

[4]Instituto Adolfo Lutz, Núcleo de Doenças de Transmissão Vetorial, São Paulo, São Paulo, Brazil

[5]Universidade de São Paulo, Faculdade de Saúde Pública, São Paulo, São Paulo, Brazil

Correspondence to: Lidia Maria Reis Santana
Secretaria de Estado de Saúde de São Paulo, Centro de Vigilância Epidemiológica "Professor Alexandre Vranjac", Av. Dr Arnaldo, 351, CEP 01246-000, São Paulo, SP, Brazil

E-mail: lidia.santana@unifesp.br

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INTRODUCTION

The dengue virus (DENV; genus *Flavivirus*, family Flaviviridae) is transmitted by females of *Aedes aegypti* mosquitoes, and has at least four different serotypes (DENV1, DENV2, DENV3, and DENV4). The disease has a wide clinical spectrum, varying from asymptomatic forms to symptomatic ones, ranging from mild to severe, and even fatal. Dengue is primarily transmitted in urban areas, particularly in tropical and subtropical regions, with a strong seasonal influence and epidemic cycles occurring every 3-to-5 years[1].

Approximately 4 billion people are estimated to be at risk of infection with the dengue virus, and an average of 100-400 million new infections occur each year[2]. There were an estimated 57 million cases of dengue (uncertainty interval: 37,083,098.01-101,350,556.42) in 2019, and more than 36,000 deaths worldwide.

These numbers represent the highest global records of the disease since 1990[3].

Since its re-emergence in Brazil in the 1980s, the number of cases of dengue and the number of regions in Brazil affected by this disease have increased every year, with endemic and epidemic cycles. The four viral serotypes of dengue have been cocirculating in Brazil since at least 2010, and the scenario of the disease in the country is becoming increasingly complex with hyper endemicity and an increasing number of deaths[4-8].

Between 2008 and 2019, approximately 10.6 million dengue cases were reported in Brazil, with the years 2015 and 2019 ranking first and second in number of cases in the historical series, respectively. In the same period, 6,429 dengue-related deaths were confirmed in the country, 986 deaths in 2015, and 840 in 2019[9]. In subsequent years, there was a reduction in the number of dengue cases in Brazil, and between epidemiological weeks 1 and 51 of 2021, there were 526,032 cases (incidence of 246.6 cases per 100,000 inhabitants), of which 364 were severe and 235 were confirmed deaths[10].

The determinants of disease expansion and increased mortality are not entirely clear, and the intensity of dengue transmission varies significantly according to spatial and temporal parameters. Intrinsic (host-related) factors can contribute to these variations, since individuals develop homotypic immunity after subsequent infections with different serotypes[4,5]. They are also related to the clinical manifestation of the disease, as secondary infections by any of the four serotypes tend to be more severe, with a higher risk of death due to the presence of heterotypic antibodies[11].

When severe cases of dengue emerge, the organization of health services and the adequate provision of treatment may alter the mortality rate from this disease. Extrinsic factors, such as the biological characteristics of the vector and socio-environmental aspects (climate, demographic and economic factors, urbanization etc.) also influence the spatio-temporal distribution of dengue, as well as its heterogeneity[12-14].

Although there is an abundance of information available regarding dengue, few studies have addressed the spatial and spatio-temporal dynamics of dengue-related deaths and the role of socioeconomic, demographic, and epidemiological determinants in this process. The lack of such data can be considered a knowledge gap, since studies that consider geographical space are important in the identification of risk areas and contextual factors that determine the spatio-temporal heterogeneity of this disease. The results of such studies can also be extremely useful in developing surveillance, planning and control activities[15].

In a study developed in Latin America and the Caribbean (LAC), which considered as the unit of analysis the countries in that particular region, dengue mortality was evaluated by taking into account contextual factors and a partial approach on the circulation of viral serotypes by including data on DENV2 in the overall analysis[16]. Other studies have sought to relate mortality with contextual factors specific to geographic areas of Brazil as units of analysis, but without considering the history of circulating serotypes, which was pointed out as a limitation by the authors[17,18]. It is also noteworthy that the studies cited, even using data from specific geographic areas, did not take into account the possible presence of a spatial autocorrelation of the studied phenomenon, as established by the first law of geography[19].

For this reason, the aim of the present study was to investigate the spatio-temporal dynamics of dengue-related deaths, from 2007 to 2017, in Sao Paulo State (SP) municipalities, and to identify potentially associated factors, including socioeconomic, demographic, healthcare, and epidemiological aspects. It should also be noted that the epidemiologic factors evaluated included information about the annual circulation of the four DENV serotypes, which we considered from both, spatial and temporal points of view.

MATERIALS AND METHODS

Ethical aspects

The present study was approved by the University of Sao Paulo School of Public Health's institutional review board (N° 1.687.650), and was conducted in accordance with the Brazilian Guidelines and Standards for Research Involving Humans (CNS Resolution 466 of December 12, 2012).

Study area, design, and study period

The present study focused on SP State, located in Southeastern Brazil (19–25° S, 44–53° W)[20]. Prior to 2017, when intermediate/immediate regions were implemented, SP was geographically divided into 63 micro-regions, which are spatial aggregates that express the organization at the micro or local level based on specific characteristics resulting from the presence of environmental elements or social and economic relationships[20]. Currently, SP has 645 municipalities (Figure 1), and according to the 2010 demographic census, 41,262,199 inhabitants live in 248,219,63 km² of territory , with a population density of 166.23 inhabitants/km², and approximately 95.96% of the population living in urban areas[20]. This was an ecological

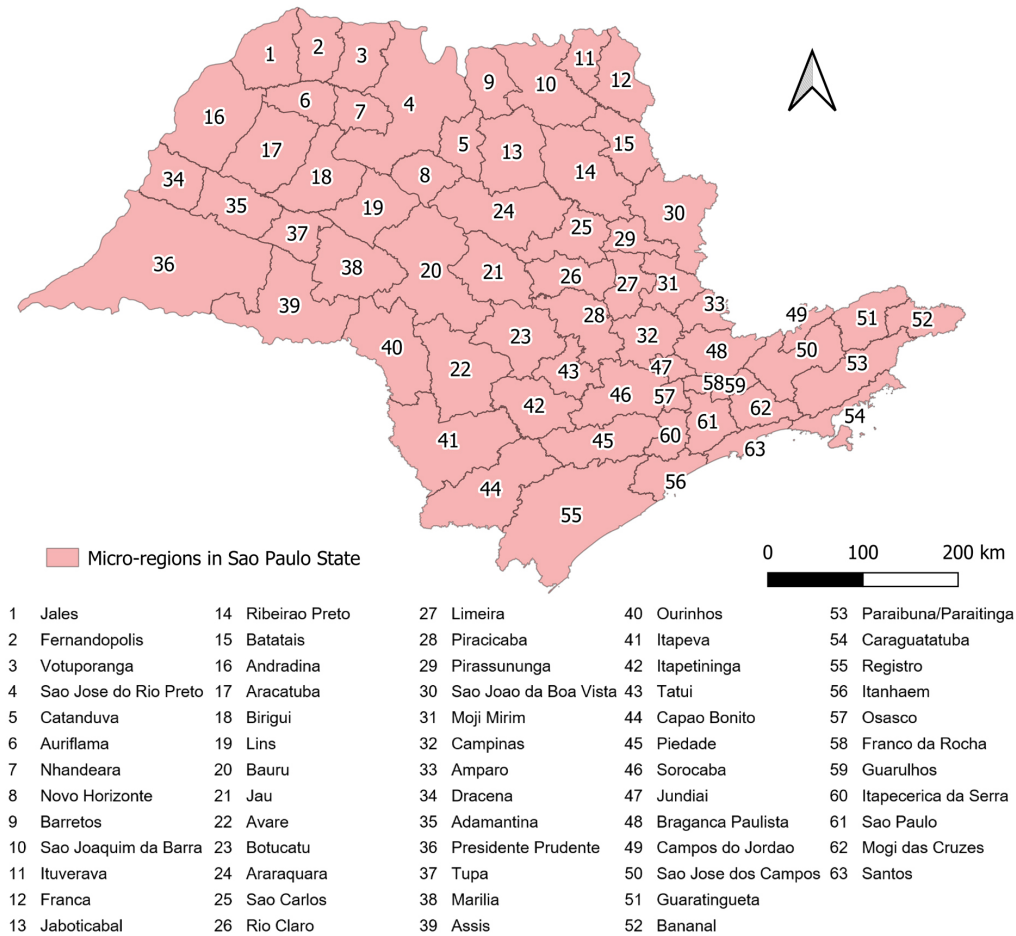|									
1	Jales	14	Ribeirao Preto	27	Limeira	40	Ourinhos	53	Paraibuna/Paraitinga
2	Fernandopolis	15	Batatais	28	Piracicaba	41	Itapeva	54	Caraguatatuba
3	Votuporanga	16	Andradina	29	Pirassununga	42	Itapetininga	55	Registro
4	Sao Jose do Rio Preto	17	Aracatuba	30	Sao Joao da Boa Vista	43	Tatui	56	Itanhaem
5	Catanduva	18	Birigui	31	Moji Mirim	44	Capao Bonito	57	Osasco
6	Auriflama	19	Lins	32	Campinas	45	Piedade	58	Franco da Rocha
7	Nhandeara	20	Bauru	33	Amparo	46	Sorocaba	59	Guarulhos
8	Novo Horizonte	21	Jau	34	Dracena	47	Jundiai	60	Itapecerica da Serra
9	Barretos	22	Avare	35	Adamantina	48	Braganca Paulista	61	Sao Paulo
10	Sao Joaquim da Barra	23	Botucatu	36	Presidente Prudente	49	Campos do Jordao	62	Mogi das Cruzes
11	Ituverava	24	Araraquara	37	Tupa	50	Sao Jose dos Campos	63	Santos
12	Franca	25	Sao Carlos	38	Marilia	51	Guaratingueta		
13	Jaboticabal	26	Rio Claro	39	Assis	52	Bananal		

Figure 1 - Geographical characteristics of the study area: Micro-regions in Sao Paulo State.

study with spatial and temporal components, based on notified dengue-related deaths from 2007 to 2017, which utilized the municipalities of SP as units for analysis.

Conceptual model

Hyper endemic areas, characterized as areas in which different viral serotypes cocirculate, and longer viral transmission times, are associated with an increased risk of epidemics and dengue mortality, likely due to effects of previous circulation of dengue virus serotypes and previous infections in the population. Furthermore, rapid and unplanned processes of urbanization in areas with high demographic densities often act favoring the occurrence of vector-transmitted diseases. The local ability to respond and prevent severe cases can also vary, based on the availability of hospital beds and budget resources. For this reason, we selected variables that could provide an approximation of this scenario, considering the spatio-temporal structure of data over a period that would allow the observation of the epidemic cycles, and reflect their variations in order to estimate the risk of death from dengue in SP.

Data sources, inclusion and exclusion criteria and study variables

Data on dengue-related deaths were obtained from the Brazilian Notifiable Disease Information System (SINAN). Notification data for dengue-related deaths, along with the city of residence in SP State were provided by the SP State Department of Health's Epidemiological Surveillance Center (CVE/SES-SP) as dBase files (SINAN database export format), one for each year in the period of 2007 to 2017. Confirmed cases of dengue in residents of SP, documented in SINAN, with symptoms that began during the study period and progressed to death were included. Deaths confirmed only by clinical-epidemiological criteria were excluded. The following variables were evaluated for deaths due to dengue: age, gender and municipality of residence.

The Brazilian Institute of Geography and Statistics (IBGE) databases were used to obtain census population data, population estimates and digital municipal networks related to the municipalities of SP. They also provided data on socioeconomic variables, demographic density, degree of

urbanization and per capita gross domestic product (GDP), which were used in the data modeling process[20].

Dengue in SP was characterized in epidemiological terms using the following variables for each year of study: number of years with confirmed cases that were based on the introduction of the virus to the calendar year, time interval between introduction of the virus and the calendar year for each municipality of residence, and number of serotypes identified by micro-region per year. The serotype data were obtained from the SP State Department of Health, provided by the Adolfo Lutz Institute (IAL). These analyzes were performed by micro-regions, as samples are sent to IAL for regional viral monitoring.

The hospital bed ratio (ratio between the number of beds per micro-region and its population, multiplied by 1,000) was used to estimate the health care capacity. Since not all municipalities in SP have inpatient beds in public or private hospitals, and the micro-region system groups neighboring municipalities according to their specific characteristics, we chose this unit of analysis for this variable instead of the municipal data[20]. Information on hospital beds was obtained from DATASUS, the Health Informatics Department of the Brazilian Ministry of Health[21].

Data analyzes

The number of observed dengue-related deaths from 2007 to 2017, according to the 645 municipalities of SP, was modeled using latent Gaussian Bayesian models, considering Poisson and zero-inflated Poisson probability distributions and a spatio-temporal structure. Initially, only models with intercept, spatial and temporal random effects relative to the interaction of space and time were considered. Next, covariates were included in the model. The best models were selected and those with the lowest deviance information criterion (DIC) values were chosen[22].

The temporal autocorrelation of data was represented by a structured random effect obtained from an autoregressive model of the random walk-1 (RW1) type, and by an unstructured random effect[22]. A Besag-York-Mollié (BYM) type model, composed of spatially structured and unstructured random effects, was considered to represent the spatial dependence of data[23]. The BYM model was used with the parameterization proposed by Riebler *et al.*[24]. The interaction between space and time was represented by unstructured random effects in both, space and time[22].

The expected dengue-related deaths, according to municipality and year, were estimated by indirect standardization, taking into account the respective age and gender structures of each municipality and year. To do so, the deaths that occurred during the study period

(2007-2017) and the mortality rates for the entire SP State were calculated by age group and gender, based on the population in 2012 (midpoint). To consider the expected deaths in the models allowed us to interpret the coefficients generated after exponentiation as relative risks (RR), and to obtain the standardized mortality ratios (SMR) for dengue in the units of analysis and years evaluated.

Before including the covariates in the modeling, an exploratory analysis was performed to identify outliers and collinearity. Covariates with 2-to-2 correlation coefficients ≥ 0.60 were considered collinear. Since the covariates "number of serotypes present" and "hospital bed ratio" were expressed by micro-regions, an unstructured independent and identified distributed (iid) random effect was considered to represent the grouping of deaths according to micro-region. All covariates included in the modeling, except for the number of serotypes present in the micro-regions, were standardized by subtracting the respective means and dividing by the respective standard deviations. In this way, the RR obtained from this modeling, for each of the standardized covariates, could be interpreted as an increase or decrease in risk, corresponding to its variation of one standard deviation.

The modeling was performed in a Bayesian context, using the integrated nested Laplace approximation (INLA), which is a more efficient computational option than the Markov chain Monte Carlo (MCMC) model[25]. The INLA approach is especially advantageous over MCMC for spatially- and temporally-structured data[22]. Minimally informative priors were considered for the fixed effects. For the random effects related to grouping the data by micro-regions, temporal random effects and spatial random effects, penalized complexity priors were considered, as proposed by Simpson *et al.*[26].

Software used

The R software environment v. 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) with the Tidyverse v.1.2.1, Epitools v. 0.5-10, R-INLA v. INLA_18.05.28, and INLA Outputs v. 1.4.0 packages were used for database construction and statistical analyses, and QGis v. 2.18.9 (QGIS Development Team) was used to build the maps for each topic.

RESULTS

From 2007 to 2017, 1,019 (505 males and 514 females) deaths due to dengue were confirmed by laboratory testing in SP State. The overall mortality rate for this period was 0.22 deaths per 100,000 inhabitant-years, with the same rates for both genders. The ≥ 70 age group was the most

Table 1 - Dengue mortality rates (per 100,000 inhabitant-years) by gender and age in Sao Paulo State, 2007-2017.

Age group (years)	0-14	15-29	30-49	50-69	70+	Total
Female						
Deaths	27	54	140	140	153	514
Population	4,264,364	5,293,253	6,600,292	4,042,128	1,330,837	21,530,874
Rate	0.06	0.09	0.19	0.31	1.05	0.22
Male						
Deaths	31	38	86	157	193	505
Population	4,423,307	5,365,067	6,225,351	3,496,412	898,986	20,409,123
Rate	0.06	0.06	0.13	0.41	1.95	0.22
Total						
Deaths	58	92	226	297	346	1019
Population	8,687,671	10,658,320	12,825,643	7,538,540	2,229,823	41,939,997
Rate	0.06	0.08	0.16	0.36	1.41	0.22

affected, with 1.41 deaths per 100,000 inhabitant-years, and the rate in this group was higher in males than in females (1.95 vs. 1.05, respectively). These data can be seen in Table 1.

The models considering the Poisson probability distribution were better adjusted to the data than those that considered a zero-inflated distribution. Figure 2 shows the posteriors means of the temporal random effects, interpreted after exponentiation as RR, and illustrates that these values were above the unit in 2010 and 2011 and between 2013 and 2016; 2015 was the most notable year, at 14.1. Figure 3 shows the posterior means of the predicted SMR for the 645 municipalities in SP between 2007 and 2017. Between 2007 and 2009, the SMR was below the unit in almost all municipalities in SP, although higher values were observed in the Western portion of the State, and lower values in the Eastern. In 2010, many municipalities in Western SP exhibited values above the unit, along with municipalities in the center of the State and in the coastal Caraguatatuba, Itanhaem and Santos micro-regions (represented on Figure 1 as micro-regions 54, 56, and 63, respectively). This was again seen in 2013 (at a lower intensity) and 2014. In 2015, the SMR was above the unit for all municipalities, except for a few located in Sao Paulo (61) and Itapeva (41) micro-regions. Meanwhile, 2016 resembled 2010, 2013, and 2014, and 2017 was similar to 2008, with municipalities presenting the lowest RR during the study period.

The years with temporal RR values above the unit were those in which most municipalities had SMR values above the unit, culminating in 2015, when these values were high in nearly all municipalities. In comparison (with the partial exception of 2015), in the remaining years, the municipalities in the Western portion of the State generally exhibited higher SMR values than those in the Eastern.
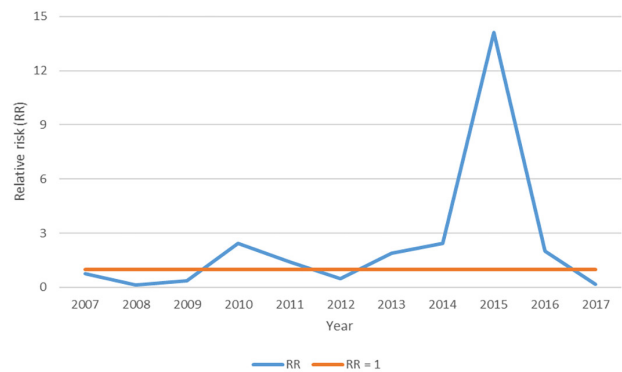

Figure 2 - Posterior means of temporal random effects (exponentiated and presented as relative risk) in the period 2007-2017, in Sao Paulo State.

The exploratory analysis of covariates revealed collinearity between the covariates "number of years with dengue cases" and "time interval since dengue introduction," and of these, we opted to use the former in the modeling. Table 2 presents the posterior means and 95% credibility intervals for the fixed effects, which were interpreted as RRs. The covariates considered important in explaining the risk of death from dengue were "degree of urbanization" (one standard deviation increase in the degree of urbanization was associated with an increased in the risk of death of 45%), "number of years with dengue cases" (one standard deviation increase in this covariate was associated with a 35% increase in the risk of death) and "number of serotypes in the micro-region" (one unit increase in the number of circulating serotypes was associated with a 75% increase in the risk of death due to dengue). At the same time, the covariates "population density," "GDP per capita" and "hospital bed ratio in the micro-region" were not found to be associated with the risk of dengue-related deaths in SP, between 2007 and 2017.
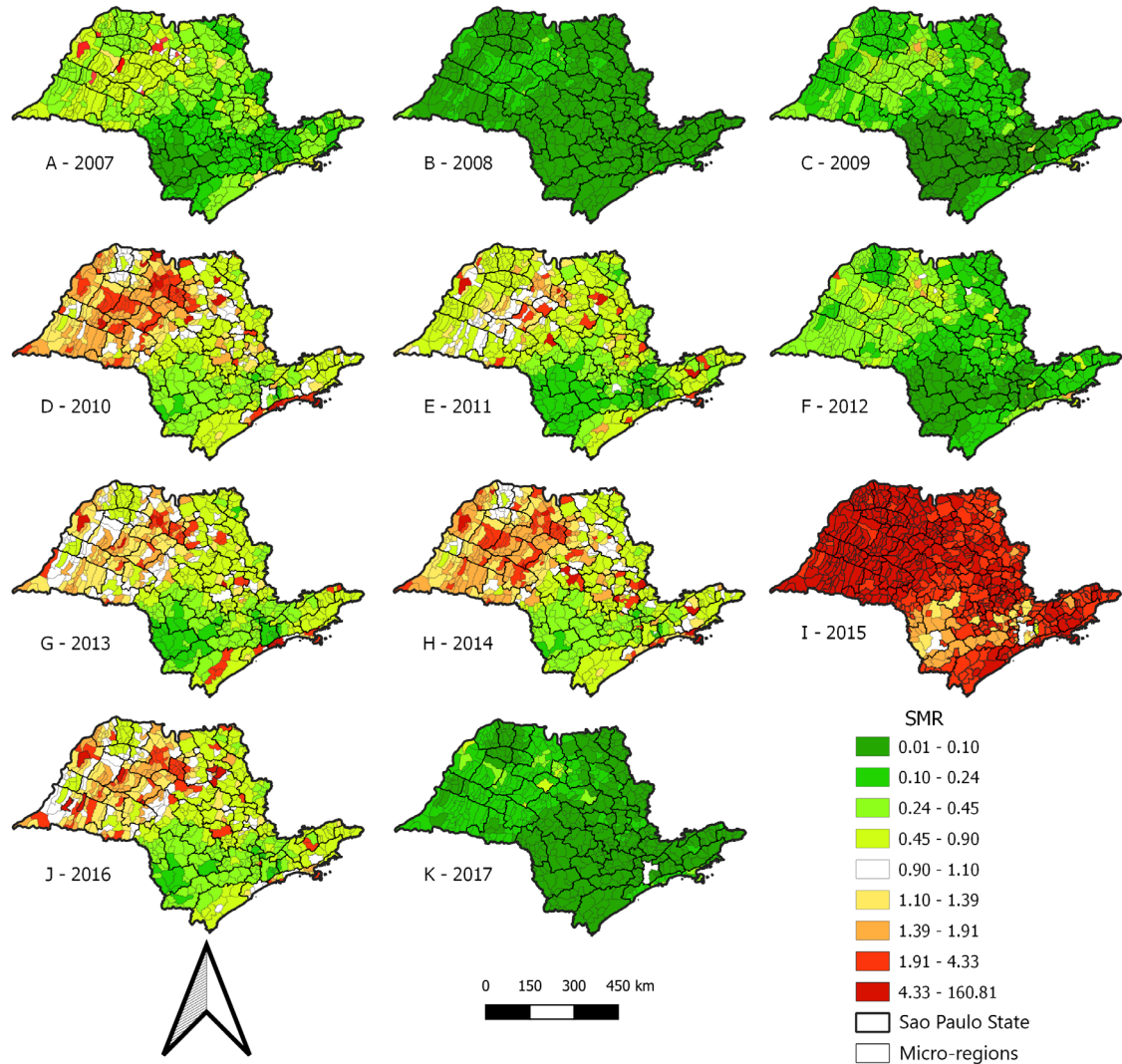
Figure 3 - Posterior means of standardized mortality ratios (SMR) of dengue in the period 2007–2017 and municipalities in Sao Paulo State.

Figure 4 shows the number of circulating serotypes per year in the State's micro-regions and their evolution over time. Between 2007 and 2010, the viral circulation pattern remained stable, with three serotypes circulating annually in approximately 60% of the regions. In 2011, the pattern changed, with circulation of an additional serotype, initially in limited areas but, increasing to one-third of the micro-regions in 2012, and rapidly extending to nearly 60% as

Table 2 - Posterior means of fixed effects presented as relative risks and their respective 95% credibility intervals for municipalities in the Sao Paulo State, 2007–2017.

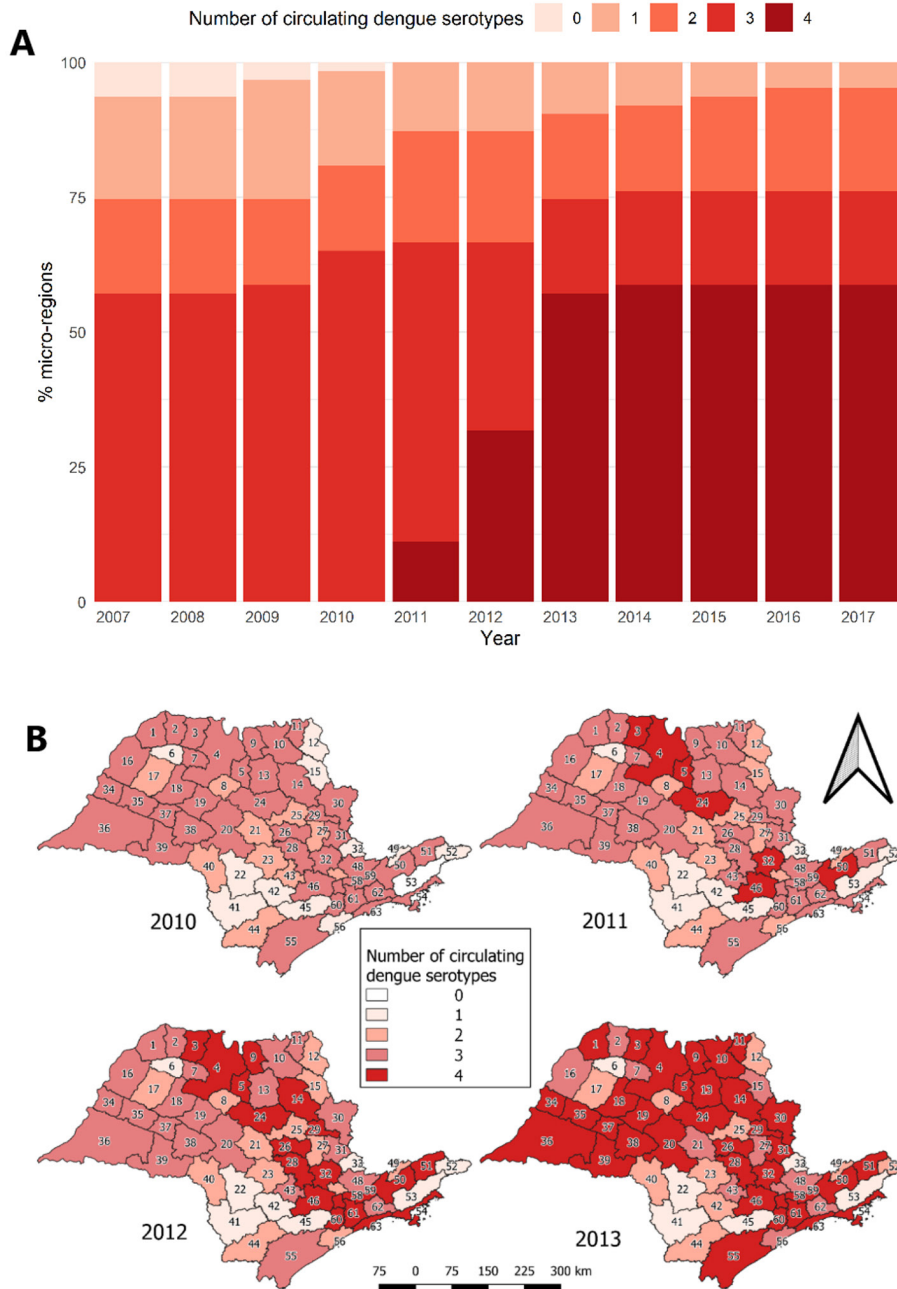| Covariates	Mean	Quantile 0.0250	Quantile 0.0975
Intercept	0.02	0.01	0.05
Demographic density	0.95	0.85	1.06
Degree of urbanization	1.45	1.06	1.98
Per capita GDP	0.97	0.87	1.08
Number of years with dengue cases	1.35	1.12	1.63
Number of serotypes in the micro-region	1.75	1.32	2.29
Hospital bed ratio in the micro-region	1.09	0.88	1.32

GDP = gross domestic product (per capita).

Figure 4 - A) Percentage of micro-regions and number of dengue virus serotypes circulating per year in Sao Paulo State, 2007-2017; B) Dengue serotypes circulating in the micro-regions of Sao Paulo State in 2010-2013. Numbers in the maps represent the micro-regions shown in Figure 1.

early as 2013, and from 2013 onwards it remained stable until 2017.

A comparison between the dengue-related death occurrence patterns (Figure 3) and the distribution patterns of circulating dengue virus serotypes (Figure 4) confirmed the positive association found between these two variables in the model. A partial coincidence between micro-regions in which three serotypes circulated, and municipalities with SMR above the unit in 2010 was found in the Western part of SP, as well as in some central and coastal micro-regions. The death patterns followed the same pattern in 2013 and 2014, despite the addition of the fourth serotype in 2011. However, in 2015, the pattern of deaths followed the distribution of circulating serotypes from 2013 onwards, and the micro-regions in the Central/Southern portion of the State in which one or two serotypes circulated, corresponded to the areas with the lowest SMRs, as seen in Figure 3. In most other areas of the State, four serotypes circulated in 2015, and the SMR values were also above the unit.

A comparison of the number of years between 2007 and 2017 in which dengue cases occurred in SP municipalities (Supplementary Figure S1) and the SMR values (Figure 3) confirmed the positive association between these two variables. The behavior of this covariate in specific years (2007, 2010 and 2015; Supplementary Figure S2) in relation to the SMRs values (Figure 3) has also confirmed this association. The number of years in which dengue cases occurred increased, and there was a correlation between areas with higher values for this variable and higher SMRs. As the degree of urbanization in the municipalities of SP did not change significantly during the study period, for purposes of comparison with the SMRs, Supplementary Figure S3 maps this variable for 2012 (the midpoint of the study period). A correlation in the regions in the Central/Southern portions of the State between lower SMR and lower degrees of urbanization can be seen. This phenomenon has also occurred in 2015, when the highest SMR values were found throughout the entire study period.

DISCUSSION

The year 2015 was the one with the highest dengue-related mortality in SP State, coinciding with the year in which most deaths from this disease occurred throughout the entire country, approximately 1,000, with those in SP accounting for half of that number[5]. The number of dengue-related deaths in SP between 2007 and 2017 was approximately ten times that found between 1998 and 2006. This increase occurred in parallel with the development of the disease in Brazil: mortality rates, which had already increased between 2001 and 2011[17], increased even more in the period from 2011 to 2017 in relation to the period of 2001 to 2010[5].

Some studies in Brazil[8,14] and Panama[27] observed higher dengue-related mortality rates among older people, similar to the results of the present study, which have been associated with a greater presence of comorbidities[8,13,27]. Although we did not identify any differences in mortality rates between genders, when the entire age range was considered, a higher risk of death was observed in males over the age of 70. As such, the results of the present study partially agree with those of previous studies in which differences between genders[8] were either not identified or a higher risk of death in males was found[14].

The heterogeneous pattern of the spatial distribution of dengue-related mortality in the municipalities of SP was not associated with per capita GDP in the model obtained in the present study. Other studies, however, showed a relationship between higher dengue-related mortality and poor local socioeconomic conditions, indicating the need to obtain variables that can more comprehensively characterize the determinants of this relationship in future models[16,18,28]. The hospital bed ratio in each micro-region was also considered not important to explain the risk of death from dengue, which was also observed in a study that sought to associate mortality with contextual factors using Brazilian municipalities as units of analysis[17]. It is possible that the measure of health care capacity in relation to severe cases of dengue provided by this variable does not reflect the quality and punctuality of care offered to patients, factors that have been indicated as relevant for the reduction of dengue-related mortality.

The relationship between demographic changes and the spatial heterogeneity of dengue-related mortality in the municipalities of SP was assessed via the degree of urbanization and population density, and it was found that only the degree of urbanization was associated with a higher risk of death due to the disease. The association between urbanization and dengue-related deaths was also verified in another study involving Brazilian municipalities[17]. Lack of infrastructure and sanitation, in addition to significant social inequality and environmental degradation, are causes of accelerated and unplanned urbanization processes that are related to vector-borne diseases[29]. For this reason, the risks of dengue may be higher in municipalities in which urbanization is disordered and the health care network may be less effective, which would increase the risk of death due to this disease, as has already been hypothesized in a study that considered contextual factors to assess dengue-related mortality in LAC[16]. Urbanization, among other factors, has also been associated with an increase in vector-borne diseases that have been occurring around the world in recent decades, dengue in particular[29].

It is logical to assume that the more experience a municipality is with subsequent dengue epidemics, the more prepared will be its health teams to recognize the first cases, identify severity and reduce deaths, while in municipalities in which the disease is a more recent development, an increased number of deaths would be more likely. However, based on the findings of the present study (which are in accordance with the results of a relevant study involving LAC countries), an increased number of years with dengue cases was associated with a higher risk of dengue-related mortality[16]. Considering the entire population as being previously susceptible, and the number of years with dengue cases as an approximation of the virus transmission time in the municipality, its increase is accompanied by accumulated immunity among those exposed, and therefore, a progressively greater chance of sequential infections over the years. According to the

results of the model obtained in the present study, there was an increase in the risk of dengue-related death. For this reason, municipalities are possibly able to improve their capacity to organize and manage services in the face of serial dengue epidemics, but the mechanisms that determine the severity of the disease will continue to be present, and the training of professionals in each seasonal period should be encouraged as a strategy to reduce mortality. The association between the number of years with dengue cases and a higher risk of dengue-related mortality points to an increase in the severity of cases and an increased rate of mortality in an inadequate health care condition. Therefore, in addition to the generalized improvement in healthcare throughout SP, the time of dengue transmission could be a criterion for prioritizing the allocation of resources to improve care in the municipalities.

Previous reports have pointed to an association between viral serotype replacement and increased severity or mortality due to dengue, based on descriptive temporal or spatio-temporal relationships[8,30,31]. An ecological study investigating the effects of environmental, demographic, socioeconomic and biological factors on dengue-related mortality observed an increased risk of death due to the disease when DENV2 was circulating, but the emergence and re-emergence of different serotypes were not analyzed[16]. For this reason, the finding of the present study of the existence of a relationship between the number of circulating serotypes and an increased risk of death from dengue is an unprecedented demonstration of the effect of hyper endemicity on dengue-related mortality in the literature, in ecological terms.

Given the potential use of serotyping in defining risk areas for dengue-related deaths, viral circulation monitoring should be more widely used, with representative sample form geographical regions that permit targeted and timely actions. However, the number of DENV serotyping that can be performed by the Brazilian laboratory infrastructure is still insufficient to develop an appropriate regional viral monitoring according to the needs of the country[4], so that investments in this area are essential.

Molecular epidemiology studies have associated the presence or absence of symptoms in infected people with DENV and their frequencies, as well as the increase in the number of dengue cases and their severity, with circulation of different serotypes and diversity of DENV genotypes[27,32-34], indicating the importance of a genotypic surveillance alongside other epidemiological surveillance activities. In a case reported in Brazil, in 2019, the occurrence of death from dengue was associated with a viral lineage that had not been detected in the country before[35].

This type of information, when available in space and time, could be useful in modifying the ecological modeling used in the present study and improve the process of identifying areas of risk for deaths.

The limitations of the present study include the use of data from secondary sources based on passive epidemiological surveillance, which is consequently subject to underreporting and underestimation of the magnitude of both, morbidity and dengue-related mortality[36]. As an ecological study, we were careful to interpret our findings at the level of the analysis units used, rather than extrapolating our results to the individuals.

Modeling by regression of variables with spatial and temporal distribution (such as dengue-related mortality) could violate the basic assumption of independence between the observed values[37]. To avoid this, we considered the existence of spatial and temporal dependence in the phenomenon studied, which has not been the rule in spatio-temporal studies on dengue[38]. To this end, spatially and temporally structured random effects were included in our models, in addition to the interactions between them, which allowed the self-correlation found in the data to be incorporated into the structure of the models[22,39]. Additionally, the hierarchical Bayesian models used in the present study are recognized as suitable for investigating spatiotemporal disease patterns[40].

The growing number of dengue cases and deaths worldwide has shown the poor effectiveness of control measures, a situation requiring urgent attention[5]. Using tools to identify risk areas for the occurrence of severe cases and increased deaths could make dengue surveillance and control systems more effective. Despite its limitations, the strengths of the present study ensure its validity, so its findings can contribute to the improvement of this system.

CONCLUSION

The overall mortality rate due to dengue in SP during the study period was 0.22 deaths per 100,000 inhabitant-years, increasing with age, with higher values observed in people aged 70 years and over (1.41 per 100,000 inhabitant-years). Mortality rates did not differ between genders when considering all age groups; however, among people aged 70 years or more, the risk of death was higher in males. The distribution of dengue-related deaths was found to be heterogeneous in space and time. The highest SMR values were observed in the Northern, Northwestern, Western, and coastal regions of the State. The mortality rate was highest in 2015, and the SMR was above the unit in nearly all municipalities in SP during that year. The number of circulating serotypes, number of years with dengue cases,

and degree of urbanization were associated with a higher relative risk of dengue-related mortality.

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