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Major Article

Prevalence of self-reported dengue infections in Manaus Metropolitan Region: a cross-sectional study

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Abstract

Introduction: Dengue is an endemic and epidemic disease in Brazil, with a high burden of disease. Amazonas State has a high risk of transmission. This study aimed to assess the self-reported prevalence of dengue in adults living in Manaus Metropolitan Region. **Methods:** A cross-sectional study was conducted with adults living in Manaus Metropolitan Region in 2015. We performed a three-phase probabilistic sampling to collect participants' clinical and sociodemographic data. Self-reported dengue infection in the previous year was the primary outcome. Descriptive statistics and Poisson regression analysis with robust variance were used to calculate the prevalence ratio (PR) of dengue infections with 95% confidence intervals (95% CIs). Multilevel analysis including city and neighborhood variables was calculated. All analyses considered the complex sampling. **Results:** Among the 4,001 participants, dengue in the previous year was self-reported by 7.0% (95% CI 6.3%–7.8%). Dengue was more frequent in women(PR 1.51; 95% CI 1.06–2.13), elderly participants (≥60 years old, PR 2.54; 95% CI 1.19–5.45), White and Asian participants (PR, 1.57; 95% CI, 1.11–2.23), and individuals who had not received endemic agent visits (PR, 2.28; 95% CI, 1.31–3.99). After multilevel analysis, sex was no longer a significant variable, with the remaining associations still significant. **Conclusions:** Seven out of 100 inhabitants of Manaus Metropolitan Region reported dengue in the previous year. Dengue was predominantly observed in women, elderly individuals, White and Asian individuals, and individuals who did not receive endemic agent visits. The setting plays an important role in dengue infections.

Keywords: Dengue. Prevalence. Amazon. Cross-sectional study. Self-report. Brazil.

INTRODUCTION

Dengue is a viral infection with both endemic and epidemic transmission cycles and has an estimated global incidence of 390 million cases per year, of which 96 million manifest symptoms of any severity[1]. The global burden of dengue is high, with 9,221 estimated deaths annually, resulting in 576,900 years of life lost to premature mortality in 2013[2]. In Brazil, the incidence was 813.1 cases per 100,000 inhabitants in 2015[3]. Workforce absenteeism caused by dengue produced a total loss of approximately 260 million dollars in 2013[4].

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Due to its environmental characteristics and inadequate sanitary and living conditions, an increase in the number of dengue cases was observed in Brazil[5-7]. The management, planning, and execution of dengue control policies is one of the competencies of the national, state, and municipal spheres of the Brazilian National Health System (*Sistema Único de Saúde*)[8].

Decreased governmental investments worldwide in public health and a lack of effective preventive actions have led to increased risks of infection in several countries[9]. In Brazil, overall, vector control programs have not produced satisfactory results; hence, the effectiveness of these interventions is still very limited[10-12]. Investments in the implementation of a rigorous and continuous national program and effective management of public services such as garbage collection and structured sanitation networks are required to reduce the prevalence of the disease in the country[13,14]. The identification of high-risk areas

is necessary for the implementation of directed public health policies and basic services to reduce the burden of dengue[15].

Amazonas, characterized by elevated temperature and precipitation and humidity rates, is located in the North Region of Brazil[16]. These climatic and environmental conditions favor the breeding, replication, and survival of dengue vectors, increasing the risk of transmission[17,18]. Previous studies have evaluated the clinical and epidemiological factors of dengue patients in Amazonas State[18-24]. Prevalence and risk factor data for dengue in the general population are scarce in Brazil. This study aimed to assess the self-reported prevalence of dengue and associated factors in adults living in Manaus Metropolitan Region.

METHODS

Study design

This was a population-based cross-sectional study conducted between May and August 2015 with adults living in Manaus Metropolitan Region in the Amazonas State, Brazil. This study is part of a larger study that intended to evaluate the use of healthcare services and resources in this region[25].

Setting

Manaus Metropolitan Region is composed of Manaus, the capital city of Amazonas State, and the following seven adjacent cities: Careiro da Várzea, Iranduba, Itacoatiara, Manacapuru, Novo Airão, Presidente Figueiredo, and Rio Preto da Eva. Over 60% of the 3,483,985 inhabitants of Amazonas live in this region[26]. The predominant climate is equatorial, which is characterized by elevated temperature and rainfall rate[16]. Regions with extremely elevated temperature and humidity rates are at increased risk for dengue transmissions between mosquitos and humans[27].

Participants

Adults ≥18 years old were eligible for the study and were recruited by probabilistic sampling in three stages by cluster and stratified by age and sex[25]. The first stage consisted of randomly selecting 400 primary and 20 secondary tracts from the 2,647 urban census tracts of Manaus Metropolitan Region. The second phase consisted of a systematic sampling of households from each tract. The third stage consisted of the registration of all adults ≥18 years old who were present at the residence, and one participant was randomly selected for the interview according to the predefined quotas of age and sex.

Variables

The primary outcome was defined as the self-reported prevalence of dengue infections in the previous year. Individual variables included sex (male, female), age group (18–24, 25–34, 34–44, 45–59, and ≥60 years old), marital status (single, separated/divorced, widowed, married), educational level (higher education or above, high school, middle school, elementary schoolor less), ethnicity (non-White, White and Asian, where non-White included Black, Brown [Brazilian mixed race], and Indigenous), socioeconomic status (A/B, C, D/E, where A refers to the wealthiest and E to the poorest[28]), health status (very good or good, fair, bad or very bad), health insurance coverage (yes, no), self-reported chronic diseases (yes, no), pregnancy status (yes, no), usage of healthcare services in the last 12 months (yes, no), hospitalization in the last 12 months (yes, no), visits from a family health agent in the last 12 months (2–12 visits, 1 visit, no visit), and visits from an endemic disease control agent in the last 12 months (2–12 visits, 1 visit, no visit).

The variable at the city level was the primary care package (*Piso da Atenção Básica*, PAB) per capita in the Brazilian currency, and at the neighborhood level (according to the neighborhood where the household was located), the Gini index was used.

Data source and measurements

Individual variables were collected from face-to-face interviews conducted by trained interviewers who registered the participants' responses in electronic tablets (Tab 3 SM-T110 Samsung® Galaxy). The prevalence of self-reported dengue infections was assessed through the following question: "In the last 12 months, has any doctor diagnosed you with dengue?" The following two response options could be filled: "yes" or "no". PAB per capita was obtained from the Brazilian Ministry of Health[29]. The Gini index was obtained from the Brazilian Development Atlas[30].

Bias

To ensure the quality of the study, a pretest was performed with 150 participants who were included in the final sample. A hired company audited 20% of these interviews through telephone contact to confirm the responses, and parts of the interviews were recorded on the electronic tablet.

Study size

The sample size was calculated based on a conservative estimate of a 50% prevalence of dengue infection in a population of 2,106,322 adults living in the region, considering a 95% confidence interval (95% CI), an absolute precision of 2%, and a design effect of 1.5. We included an additional 10% in the sample to compensate for losses, with a total of 4,000 individuals to be interviewed.

Statistical methods

Variables were analyzed using descriptive statistics with 95% CIs. Prevalence ratios (PRs) were calculated using Poisson regression with robust variance to identify factors associated with self-reported dengue. A multilevel Poisson regression analysis with random intercept was performed to assess continuity and variables at the individual, neighborhood, and city levels. We initially used an empty model to determine the clustering of continuity by city and neighborhood levels to obtain the variance. City and neighborhood variables that reduced the variance at each level were maintained in the final model, whereas those that increased the variance were excluded. If high collinearity was observed among the variables ($r>0.9$), a latent variable was created by multiplying both variables.

The multilevel Poisson analyses were used to calculate the PR and 95% CIs, which were adjusted by latent variables at the city level (PAB per capita), neighborhood level (Gini index), and individual level (all variables) of self-reported dengue.

Associations were considered statistically significant if p was <0.05. Data analyses were performed using Stata V.14.2 (Stata) with consideration of the complex sampling design (svy command).

Ethics

The Ethics Research Committee from the Federal University of Amazonas approved this study on March 3, 2015, with the report no. 974,428 (Certificate of Presentation for Ethical Appreciation 42203615.4.0000.5020). Before performing any procedure, all participants provided written informed consent for inclusion in the study.

RESULTS

We included 4,001 participants, of whom 281 self-reported dengue infections in the previous year (prevalence: 7.0%; 95% CI 6.3%–7.8%).

Half of the individuals were women (52.8%), aged from 25 to 44 years old (49.9%), single (54.3%), and had an educational level up to high school (47.5%; **Table 1**). Most belonged to the lower socioeconomic status (C, D/E; 84.2%) and ethnically identified themselves as Brown, Black, or Indigenous (80.7%); 63.5% of the participants had received at least one visit from a family health agent. The frequency of visits from endemic disease control agents increased as the number of family health agent visits increased (71.9%) and was higher among the wealthier population (43.8%). Regarding the participants who were hospitalized (6.8%) in the previous year, one was hospitalized due to dengue.

The frequency of dengue infections was higher in women (8.3%) and adults aged 45 to 59 years (10.6%) and ≥60 years (9.4%), individuals who completed elementary school or less (9.0%), White and Asian individuals (9.0%), individuals belonging to the lower socioeconomic status (9.2%), individuals with bad or very bad health statuses (8.9%), individuals with chronic diseases (8.1%), women who were pregnant in the last 12 months (11.2%), and individuals without any visit from a family health agent in the last year (10.7%).

Dengue was associated with female sex (PR 1.51; 95% CI 1.06–2.13), older age (25–34 years old: PR 1.93, 95% CI 1.06–3.51; 35–44 years old: PR 2.59, 95% CI 1.41–4.78; 45–59 years old: PR 2.73, 95% CI 1.44–5.20; ≥60 years old: PR 2.54, 95% CI 1.19–5.45), White and Asian ethnicity (PR 1.57; 95% CI 1.11–2.23), and a lack of visits from endemic disease control agents in the last 12 months (PR 2.28; 95% CI 1.31–3.99; **Table 2**).

After performing multilevel analyses, dengue infections were associated with older age (25–34 years old: PR 1.98, 95% CI 1.05–3.74; 35–44 years old: PR 2.47, 95% CI 1.28–4.75; 45–59 years old: PR 2.65, 95% CI 1.35–5.21; ≥60 years old: PR 2.52, 95% CI 1.10–5.79), White and Asian ethnicity (PR 1.57; 95% CI 1.07–2.31), and not receiving a visit from an endemic disease control agent (PR 2.07; 95% CI 1.23–3.55; **Table 3**). Pregnancy increased the variance and was excluded from the final multilevel analysis (data not shown).

DISCUSSION

Seven out of 100 inhabitants of Manaus Metropolitan Region self-reported a diagnosis of dengue in the past year; the frequency of self-reported dengue was higher in women, elderly individuals, White and Asian individuals, and individuals whose households did not receive a visit from an endemic disease control agent. After adjusting for the funding of primary care by the municipality and inequalities in the neighborhoods, the association between dengue and female sex was not significant.

Despite the large number of participants, the study has limitations inherent in cross-sectional designs[31]. The self-reported outcome may not include participants who had symptoms of dengue but did not seek medical assistance or who presented with subclinical dengue. In 2008, a study conducted in Rio de Janeiro found that out of the 337 participants who had a molecular confirmation of dengue, only 23.3% presented with symptomatic infections[32]. Dengue may result in a variety of symptoms that can be easily confused with other pathologies, such as malaria[33], and only a low proportion of affected individuals seek treatment, leading to fewer diagnoses[1]. Misclassification due to memory bias or confusion with another disease is also possible. Selection bias may have influenced the results because only individuals who were present at the residences at the time of the interviews were invited to participate. Due to the vector's indoor characteristics and preference for feeding on humans during daylight hours[34], transmission occurs mainly at home[35], so it is possible that the interviewees were more frequently exposed to the infection.

In 2015, 34,110 probable cases of dengue infections were registered in the North Region of Brazil, of which 4,131 were reported in Amazonas State, leading to a prevalence of 0.12%, taking the state population as the denominator[3,26]. This official prevalence was lower than we estimated in the present analysis, probably due to the underreporting of cases to the Brazilian Ministry of Health[36]. A study conducted between 2009 and 2011 in a public emergency unit in Salvador, Bahia, showed that one out of 12 dengue cases was actually reported to the health authority, which suggests an underreporting of the disease[36].

Dengue infections were more frequent in women, which was similar to the results of an epidemiological study conducted in Amazonas State in 2009, in which 54% of the 1,003 notifications occurred in female patients[24]. The same pattern was observed in a study conducted in the Southeast Region of Brazil from 1998 to 2006, in which 57% of the 1,212 notified cases were found in women[37]. A plausible explanation is that women tend to seek health services more than men, resulting in more diagnoses in this group[38]. A large study conducted in Rio Grande do Sul State from 2014 to 2016 analyzed 13,420 blood samples from patients with suspected dengue fever and reported that the infection was equally distributed between both sexes[39]. In a cross-sectional study conducted in rural Amazonia in 2004, after the analysis of the participants' blood samples, male sex was a predictor of

TABLE 1: Sociodemographic characteristics of participants, prevalence of dengue infections in the previous year, and frequency of endemic disease control agent visits in Manaus Metropolitan Region, 2015.

Variables	Total		Frequency of dengue	Endemic disease control agent visits*					
				None		One visit		2–12 visits	
	n	%	%	n	%	n	%	n	%
Sex									
Female	2,113	52.8	8.3	660	31.4	744	35.2	709	33.4
Male	1,888	47.2	5.6	640	34.0	636	33.7	612	32.3
Age group (years)									
18–24	838	20.9	4.8	362	43.3	252	30.2	224	26.5
25–34	1,152	28.8	5.5	414	36.0	354	30.7	384	33.2
35–44	843	21.1	7.1	223	26.6	344	40.7	276	32.7
45–59	772	19.3	10.6	209	27.3	298	38.5	265	34.2
≥60	396	9.9	9.4	92	23.5	132	33.2	172	43.3
Marital status									
Single	2,173	54.3	5.6	738	34.1	714	32.9	721	33.0
Separated/divorced	260	6.5	9.6	104	40.2	74	28.3	82	31.5
Widowed	159	4.0	11.9	46	28.8	53	33.6	60	37.6
Married	1,409	35.2	8.3	412	29.4	539	38.1	458	32.4
Educational level									
Higher education or above	158	4.0	4.4	46	28.9	55	35.2	57	35.8
High school	1,903	47.5	6.0	642	33.8	624	32.8	637	33.4
Middle school	649	16.2	6.9	241	33.2	219	33.7	212	33.1
Elementary school or less	1,291	32.3	9.0	398	31.1	482	37.2	411	31.7
Skin color									
Non-White	3,227	80.7	6.6	1,012	31.5	1,115	34.5	1,100	34.0
White or Yellow	774	19.4	9.0	288	37.3	265	34.3	221	28.5
Socioeconomic status									
A/B	629	15.7	3.5	152	24.2	201	32.1	276	43.8
C	2,285	57.1	7.0	741	32.6	796	34.8	748	32.6
D/E	1,087	27.1	9.2	407	37.6	383	35.2	297	27.2
Health status									
Very good or good	2,646	66.1	6.1	924	35.1	804	30.4	918	34.5
Fair	1,108	27.7	8.8	306	27.7	472	42.6	330	29.8
Bad or very bad	247	6.2	8.9	70	28.4	104	42.2	73	29.5
Health insurance									
Yes	523	13.0	6.1	139	26.7	156	29.8	228	43.5
No	3,478	87.0	7.2	1,161	33.5	1,224	35.2	1,093	31.3
Chronic diseases									
Yes	2,289	57.2	8.1	643	28.2	865	37.8	781	34.0
No	1,712	42.8	5.6	657	38.6	515	30.1	540	31.4
Pregnancy*									
Yes	223	10.5	11.2	83	37.3	83	37.4	57	25.4
No	1,890	89.5	8.0	577	30.7	661	34.9	652	34.4
Medical visit*									
Yes	3,066	76.6%	7.2	883	28.9	1,090	35.6	1,093	35.6
No	935	23.4%	6.7	417	44.9	290	30.9	228	24.2
Hospital admission*									
Yes	273	6.8%	9.9	78	28.7	94	34.5	101	36.9
No	3,728	93.2%	6.8	1,222	32.9	1,286	34.5	1,220	32.6
Family health agent visits*									
2-12 visits	861	42.8%	4.3	66	7.8	174	20.3	621	71.9
One	416	20.7%	7.9	67	16.2	281	67.5	68	16.4
None	729	36.5%	10.7	437	60.2	204	27.8	88	12.0

*In the previous 12 months.

TABLE 2: Prevalence ratios and adjusted prevalence ratios with 95% confidence intervals and p-values for the factors associated with self-reported dengue infections in Manaus Metropolitan Region, 2015.

Variables	PR (95% CI)	p-value	aPR (95% CI)	p-value
Sex		0.001		0.021
Male	1.00		1.00	
Female	1.49 (1.18–188)		1.51 (1.06–2.13)	
Age group (years)		<0.001		0.268
18–24	1.00		1.00	
25–34	1.14 (0.78–1.68)		1.93 (1.06–3.51)	
35–44	1.48 (1.01–2.19)		2.59 (1.41–4.78)	
45–59	2.22 (1.54–3.20)		2.73 (1.44–5.20)	
≥60	1.97 (1.28–3.03)		2.54 (1.19–5.45)	
Marital status		<0.001		0.473
Single	1.00		1.00	
Separated/divorce	1.72 (1.14–2.59)		1.55 (0.87–2.78)	
Widowed	2.14 (1.35–3.38)		1.38 (0.68–2.80)	
Married	1.50 (1.17–1.91)		1.20 (0.84–1.72)	
Educational level		0.006		0.461
Higher education or above	1.00		1.00	
High school	1.37 (0.65–2.88)		1.07 (0.48–2.39)	
Middle school	1.58 (0.72–3.43)		1.41 (0.61–3.27)	
Elementary school or less	2.06 (0.98–4.33)		1.02 (0.45–2.28)	
Skin color		0.016		0.011
Non-White	1.00		1.00	
White or Yellow	1.37 (1.06–1.78)		1.57 (1.11–2.23)	
Socioeconomic status		<0.001		0.165
A/B	1.00		1.00	
C	2.00 (1.29–3.10)		1.42 (0.80–2.53)	
D/E	2.65 (1.69–4.15)		1.81 (0.96–3.41)	
Health status		0.007		0.175
Very good or good	1.00		1.00	
Fair	1.44 (1.13–1.84)		1.37 (0.97–1.93)	
Bad or very bad	1.46 (0.95–2.23)		1.02 (0.51–2.06)	
Health insurance		0.380		0.848
No	1.00		1.00	
Yes	0.85 (0.60–1.22)		0.95 (0.59–1.78)	
Chronic diseases		0.003		0.186
No	1.00		1.00	
Yes	1.45 (1.14–1.84)		1.26 (0.89–1.78)	
Pregnancy*		0.096		0.130
No	1.00		1.00	
Yes	1.40 (0.94–2.10)		1.65 (0.86–3.13)	
Medical visit*		0.649		0.841
No	1.00		1.00	
Yes	1.07(0.81-1.40)		0.96 (0.64-1.44)	
Hospital admission*		0.054		0.800
No	1.00		1.00	
Yes	1.45 (0.99–2.11)		1.08 (0.59–1.54)	
Family health agent visits*		<0.001		0.364
2-12 visits	1.00		1.00	
One	1.85 (1.17–2.91)		1.33 (0.77–2.29)	
None	2.49 (1.70–3.64)		1.45 (0.87–2.42)	
Endemic agent visits*		<0.001		0.012
2–12 visits	1.00		1.00	
One	1.56 (0.94–2.58)		1.57 (0.93–2.67)	
None	2.07 (1.21–3.55)		2.28 (1.31–3.99)	

*In the previous 12 months.

TABLE 3: Prevalence ratios and 95% confidence intervals of self-reported dengue infections in Manaus Metropolitan Region (2015) adjusted in the multilevel multivariate Poisson regression model.

Variables	PR (95% CI)	p-value
Sex		0.065
Male	1.00	
Female	1.42 (0.98–2.06)	
Age group (years)		
18–24	1.00	0.064
25–34	1.98 (1.05–3.74)	
35–44	2.47 (1.28–4.75)	
45–59	2.65 (1.35–5.21)	
≥60	2.52 (1.10–5.79)	
Marital status		0.649
Single	1.00	
Separated/divorce	1.46 (0.80–2.72)	
Widowed	1.26 (0.57–2.76)	
Married	1.13 (0.77–1.66)	
Educational level		0.505
Higher education or above	1.00	
High school	1.07 (0.45–2.55)	
Middle school	1.47 (0.58–3.70)	
Elementary school or less	1.06 (0.43–2.61)	
Skin color		0.022
Non-White	1.00	
White or Yellow	1.57 (1.07–2.31)	
Socioeconomic status		0.329
A/B	1.00	
C	1.34 (0.72–2.49)	
D/E	1.65 (0.83–3.29)	
Health status		0.213
Very good or good	1.00	
Fair	1.41 (0.96–2.07)	
Bad or very bad	1.19 (0.57–2.49)	
Health insurance		0.640
No	1.00	
Yes	1.14 (0.67–1.94)	
Chronic diseases		0.248
No	1.00	
Yes	1.26 (0.85–1.87)	
Medical visit*		0.936
No	1.00	
Yes	1.02 (0.66–1.58)	
Hospital admission*		0.916
No	1.00	
Yes	1.04 (0.55–1.96)	
Family health agent visits*		0.651
2–12 visits	1.00	
One	1.27 (0.75–2.16)	
None	1.20 (0.73–1.96)	
Endemic agent visits*		0.030
2–12 visits	1.00	
One	1.56 (0.94–2.58)	
None	2.07 (1.21–3.55)	

Note: Pregnancy status was excluded from the table as it increased the variances. *In the previous 12 months.

baseline dengue seropositivity[40]. Dengue was not significantly more common in women in the multilevel analysis than in men, which indicates that the risk of dengue based on sex may be influenced by the setting.

Older individuals had a higher prevalence of dengue, which was consistent with the results from a previous study conducted in Araraquara, Sao Paulo, which assessed 16,431 cases of dengue reported between 1991 and 2015. The authors concluded that the frequency of dengue was higher in individuals aged 20–59 years old[41]. A household survey performed in 2005 and 2006 in the Northeast Region of Brazil also found that older age was a risk factor among 2,833 individuals who were examined and assessed for dengue antibodies[42]. Dengue seropositivity tends to increase with age due to cumulative exposure over time, especially in endemic locations, leading to increased susceptibility to infections[43]. However, severe dengue and dengue hemorrhagic fever are most common in children[44-46]. In 2008, individuals below 15 years old were the most affected individuals during an epidemic in Rio de Janeiro State, accounting for 47% of dengue hospitalizations[46-48].

In our study, Whites and Asians self-reported more dengue than non-White individuals. Studies performed with Cuban (2017) and Colombian (2014) individuals reported the protective effects of African ancestry genes against dengue infections after the analysis of the genotypes from 274 and 287 diagnosed patients, respectively[49,50]. In 2018, another epidemiological study conducted in Tanzania included 431 dengue patients with different self-reported ethnicities and found similar results, suggesting a lower risk of dengue among individuals of African ancestry than other ethnicities[51]. A study from Rio de Janeiro City indicated that self-declared Black individuals had higher incidence rates of severe dengue than other individuals, based on an analysis of 59,395 reported cases during an epidemic in 2008, probably due to the historical socioeconomic vulnerability of this group[52].

Not receiving a visit from an endemic disease control agent in the previous year increased the risk of dengue by twofold. This association was maintained after adjustment in the multilevel analysis. Our findings suggest that visits from these agents are effective methods of reducing the incidence of dengue regardless of the status of the other determinants assessed. In 2010, endemic disease control agents were incorporated into primary care to strengthen the surveillance, prevention, and control strategies for endemic diseases[53]. Despite their relevance, endemic disease control agents are still experiencing difficulties in integrating with the population and family health agents in Brazil[54,55]. Visits from family health agents did not reduce the frequency of infections. Family health agents are also dealing with obstacles that potentially reduce their availability to the population, such as low salaries, low recognition of their function, a lack of limits on their attributions, barriers in their relationship with the community, weak professional training, and bureaucracy[56,57]. These results highlight the importance of endemic disease control agents in the prevention and control of diseases, particularly endemic ones.

Dengue was not associated with the presence of chronic diseases or with self-reported health status. Comorbidities such as diabetes and renal, infectious, and pulmonary diseases increase the risk of mortality by approximately 11 times in Brazil[58]. These patients also seem to be at higher risk of developing severe complications compared to healthier individuals[59]. Although our study showed no associations between these variables, the presence of concomitant chronic diseases, which leads to lower health-related quality of life[60], increases mortality rates and severe complications of dengue.

Conclusions

Dengue was reported by 7 out of 100 inhabitants from Manaus Metropolitan Region and was predominantly observed in women, elderly individuals, Whites and Asians, and individuals living in households that did not receive a visit from an endemic disease control agent. Inequality and the funding of primary care removed the effect of sex on the prevalence of dengue, indicating an influence of the setting.

Conflict of Interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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REFERENCES

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504-7.
2. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ, et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. Lancet Infect Dis. 2016;16(6):712-23.
3. Secretaria de Vigilância em Saúde. Ministério da Saúde. Monitoramento dos casos de dengue, febre de chikungunya e febre pelo vírus Zika até a Semana Epidemiológica 52, 2015 [Internet]. Brasil: Boletim Epidemiológico; 2016 [cited 2019 Apr 20]. Available from: http://portalarquivos2.saude.gov.br/images/pdf/2016/janeiro/15/svs2016-be003-dengue-se52.pdf.
4. Montibeler EE, Oliveira DR. Dengue endemic and its impact on the gross national product of BRAZILIAN'S economy. Acta Trop. 2018;178:318-26.
5. Barcellos C, Lowe R. Expansion of the dengue transmission area in Brazil: the role of climate and cities. Trop Med Int Health. 2014;19(2):159-68.
6. Almeida AS, Medronho RA, Valencia LIO. Análise espacial da dengue e o contexto socioeconômico no município do Rio de Janeiro, RJ. Rev Saude Publica. 2009;43(4):666-73.
7. Costa AIP, Natal D. Distribuição espacial da dengue e determinantes socioeconômicos em localidade urbana no Sudeste do Brasil. Rev Saude Publica. 1998;32(3):232-6.
8. Salles TS, da Encarnação Sá-Guimarães T, de Alvarenga ESL, Guimarães-Ribeiro V, de Meneses MDF, de Castro-Salles PF, et al.

History, epidemiology and diagnostics of dengue in the American and Brazilian contexts: a review. Parasit Vectors. 2018;11(1):264.

9. Viennet E, Ritchie SA, Williams CR, Faddy HM, Harley D. Public Health Responses to and Challenges for the Control of Dengue Transmission in High-Income Countries: Four Case Studies. PLoS Negl Trop Dis. 2016;10(9):e0004943.
10. Costa EMDS, Cunha RVD, Costa EAD. National Dengue Control Program implementation evaluation in two border municipalities in Mato Grosso do Sul State, Brazil, 2016. Epidemiol Serv Saude. 2018;27(4):e2017478.
11. Teixeira MG, Barreto ML, Costa MdCN, Ferreira LDA, Vasconcelos PFC. Avaliação de impacto de ações de combate ao *Aedes aegypti* na cidade de Salvador, Bahia. Rev Bras Epidemiol. 2002;5(1):108-15.
12. Teixeira MG, Costa MdCN, Barreto F, Barreto ML. Dengue: twenty-five years since reemergence in Brazil. Cad Saude Publica 2009;25:S7-S18.
13. Godói IP, Da Silva LVD, Sarker AR, Megiddo I, Morton A, Godman B, et al. Economic and epidemiological impact of dengue illness over 16 years from a public health system perspective in Brazil to inform future health policies including the adoption of a dengue vaccine. Expert Rev Vaccines. 2018;17(12):1123-33.
14. Rodrigues NC, Lino VT, Daumas RP, Andrade MK, O'Dwyer G, Monteiro DL, et al. Temporal and Spatial Evolution of Dengue Incidence in Brazil, 2001-2012. PLoS One. 2016;11(11):e0165945.
15. Rodrigues NCP, Daumas RP, de Almeida AS, Dos Santos RS, Koster I, Rodrigues PP, et al. Risk factors for arbovirus infections in a low-income community of Rio de Janeiro, Brazil, 2015-2016. PLoS One. 2018;13(6):e0198357.
16. Alvares CA, Stape JL, Sentelhas PC, de Moraes Gonçalves J, Sparovek G. Köppen's climate classification map for Brazil. Meteorol Z. 2013;22:711-28.
17. Hales S, de Wet N, Maindonald J, Woodward A. Potential effect of population and climate changes on global distribution of dengue fever: an empirical model. Lancet. 2002;360(9336):830-4.
18. de Castro DB, Sampaio VS, de Albuquerque BC, Pinto RC, Sadahiro M, Dos Passos RA, et al. Dengue epidemic typology and risk factors for extensive epidemic in Amazonas state, Brazil, 2010-2011. BMC Public Health. 2018;18(1):356.
19. Bastos Mde S, Figueiredo RM, Ramasawmy R, Itapirema E, Gimaque JB, Santos LO, et al. Simultaneous circulation of all four dengue serotypes in Manaus, State of Amazonas, Brazil in 2011. Rev Soc Bras Med Trop. 2012;45(3):393-4.
20. Rocha LA, Tauil PL. Dengue in children: clinical and epidemiological characteristics, Manaus, State of Amazonas, 2006 and 2007. Rev Soc Bras Med Trop. 2009;42(1):18-22.
21. Pinto RC, Castro DB, Albuquerque BC, Sampaio V de S, Passos RA, Costa CF, et al. Mortality Predictors in Patients with Severe Dengue in the State of Amazonas, Brazil. PLoS One. 2016;11(8):e0161884.
22. Martins Vdo C, Bastos Mde S, Ramasawmy R, de Figueiredo RP, Gimaque JB, Braga WS, et al. Clinical and virological descriptive study in the 2011 outbreak of dengue in the Amazonas, Brazil. PLoS One. 2014;9(6):e100535.
23. De Figueiredo RM, Thatcher BD, de Lima ML, Almeida TC, Alecrim WD, Guerra MV. Exanthematous diseases and the first epidemic of dengue to occur in Manaus, Amazonas State, Brazil, during 1998-1999. Rev Soc Bras Med Trop. 2004;37(6):476-9.
24. Costa AG, Santos JD, Conceicao JK, Alecrim PH, Casseb AA, Batista WC, et al. Dengue: epidemiological aspects and the first outbreak in the Middle Solimoes Region of Coari in the State of Amazonas from 2008 to 2009. Rev Soc Bras Med Trop. 2011;44(4):471-4.
25. Silva MT, Galvao TF. Use of health services among adults living in Manaus Metropolitan Region, Brazil: population-based survey, 2015. Epidemiol Serv Saude. 2017;26(4):725-34.
26. Instituto Brasileiro de Geografia e Estatística. Censo demográfico de 2010: Amazonas [Internet]. Brasil: Instituto Brasileiro de Geografia e Estatística; 2010 [cited 2019 Feb 16]. Available from: https://censo2010.ibge.gov.br/sinopse/index.php?uf=13&dados=4.
27. Campbell KM, Haldeman K, Lehnig C, Munayco CV, Halsey ES, Laguna-Torres VA, et al. Weather Regulates Location, Timing, and Intensity of Dengue Virus Transmission between Humans and Mosquitoes. PLoS Negl Trop Dis. 2015;9(7):e0003957.
28. Associação Brasileira de Empresas de Pesquisa. Critério de Classificação Econômica [Internet]. Brasil: Associação Brasileira de Empresas de Pesquisa; 2015 [cited 2019 Feb 18]. Available from: https://censo2010.ibge.gov.br/sinopse/index.php?uf=13&dados=4.
29. DATASUS - Departamento de Informática do SUS [Internet]. Brasil: Ministério da Saúde; 2019 [cited 2019 Feb 18]. Available from: http://datasus.saude.gov.br/.
30. Atlas do Desenvolvimento Humano no Brasil - RM-Manaus [Internet]. Brasil: Programa das Nações Unidas para o Desenvolvimento; 2013 [cited 2019 Feb 18]. Available from: http://www.atlasbrasil.org.br/2013/pt/perfil_rm/manaus.
31. Thiese MS. Observational and interventional study design types; an overview. Biochem Med (Zagreb). 2014;24(2):199-210.
32. Honório NA, Nogueira RM, Codeço CT, Carvalho MS, Cruz OG, Magalhães MeA, et al. Spatial evaluation and modeling of Dengue seroprevalence and vector density in Rio de Janeiro, Brazil. PLoS Negl Trop Dis. 2009;3(11):e545.
33. Halsey ES, Baldeviano GC, Edgel KA, Vilcarromero S, Sihuincha M, Lescano AG. Symptoms and Immune Markers in Plasmodium/Dengue Virus Co-infection Compared with Mono-infection with Either in Peru. PLoS Negl Trop Dis. 2016;10(4):e0004646.
34. Gubler DJ. Dengue and dengue hemorrhagic fever. Clin Microbiol Rev. 1998;11(3):480-96.
35. Velasco-Salas ZI, Sierra GM, Guzmán DM, Zambrano J, Vivas D, Comach G, et al. Dengue seroprevalence and risk factors for past and recent viral transmission in Venezuela: a comprehensive community-based study. Am J Trop Med Hyg. 2014;91(5):1039-48.
36. Silva MM, Rodrigues MS, Paploski IA, Kikuti M, Kasper AM, Cruz JS, et al. Accuracy of Dengue Reporting by National Surveillance System, Brazil. Emerg Infect Dis. 2016;22(2):336-9.
37. Flauzino RF, Souza-Santos R, Barcelllos C, Gracie R, Magalhaes Mde A, Oliveira RM. Spatial heterogeneity of dengue fever in local studies, City of Niteroi, Southeastern Brazil. Rev Saude Publica. 2009;43(6):1035-43.
38. Levorato CD, de Mello LM, da Silva AS, Nunes AA. [Factors associated with the demand for health services from a gender-relational perspective]. Cien Saude Colet. 2014;19(4):1263-74.
39. Gregianini TS, Tumioto-Giannini GL, Favreto C, Plentz LC, Ikuta N, da Veiga ABG. Dengue in Rio Grande do Sul, Brazil: 2014 to 2016. Rev Med Virol. 2018;28(1).
40. da Silva-Nunes M, de Souza VA, Pannuti CS, Speranca MA, Terzian AC, Nogueira ML, et al. Risk factors for dengue virus infection in rural Amazonia: population-based cross-sectional surveys. Am J Trop Med Hyg. 2008;79(4):485-94.
41. Ferreira AC, Chiaravalloti Neto F, Mondini A. Dengue in Araraquara, state of Sao Paulo: epidemiology, climate and *Aedes aegypti* infestation. Rev Saude Publica. 2018;52:18.

42. Braga C, Luna CF, Martelli CM, de Souza WV, Cordeiro MT, Alexander N, et al. Seroprevalence and risk factors for dengue infection in socio-economically distinct areas of Recife, Brazil. Acta Trop. 2010;113(3):234-40.

43. L'Azou M, Assoukpa J, Fanouillere K, Plennevaux E, Bonaparte M, Bouckenooghe A, et al. Dengue seroprevalence: data from the clinical development of a tetravalent dengue vaccine in 14 countries (2005-2014). Trans R Soc Trop Med Hyg. 2018;112(4):158-68.

44. Pone SM, Hokerberg YH, de Oliveira Rde V, Daumas RP, Pone TM, Pone MV, et al. Clinical and laboratory signs associated to serious dengue disease in hospitalized children. J Pediatr (Rio J). 2016;92(5):464-71.

45. Halstead SB. Predictors of dengue severity. J Pediatr (Rio J). 2016;92(5):429-31.

46. Wakimoto MD, Camacho LA, Guaraldo L, Damasceno LS, Brasil P. Dengue in children: a systematic review of clinical and laboratory factors associated with severity. Expert Rev Anti Infect Ther. 2015;13(12):1441-56.

47. Teixeira MG, Costa MC, Coelho G, Barreto ML. Recent shift in age pattern of dengue hemorrhagic fever, Brazil. Emerg Infect Dis. 2008;14(10):1663.

48. Secretaria de Vigilância em Saúde - Ministério da Saúde. Informe Epidemiológico da Dengue: Janeiro a Junho de 2008 [Internet]. Brasília: Ministério da Saúde; 2008 [cited 2019 Apr 27]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/informe_epidemiologico_dengue_janeiro_junho_2008.pdf

49. Sierra B, Triska P, Soares P, Garcia G, Perez AB, Aguirre E, et al. OSBPL10, RXRA and lipid metabolism confer African-ancestry protection against dengue haemorrhagic fever in admixed Cubans. PLoS Pathog. 2017;13(2):e1006220.

50. Chacon-Duque JC, Adhikari K, Avendano E, Campo O, Ramirez R, Rojas W, et al. African genetic ancestry is associated with a protective effect on Dengue severity in colombian populations. Infect Genet Evol. 2014;27:89-95.

51. Boillat-Blanco N, Klaassen B, Mbarack Z, Samaka J, Mlaganile T, Masimba J, et al. Dengue fever in Dar es Salaam, Tanzania: clinical features and outcome in populations of black and non-black racial category. BMC Infect Dis. 2018;18(1):644.

52. Gibson G, Souza-Santos R, Pedro AS, Honorio NA, Sa Carvalho M. Occurrence of severe dengue in Rio de Janeiro: an ecological study. Rev Soc Bras Med Trop. 2014;47(6):684-91.

53. Ministério da Saúde. Portaria nº 1.007/GM, de 4 de maio de 2010 [Internet]. Brasil: Ministério da Saúde; 2010 [cited 2019 Apr 27]. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/gm/2010/prt1007_04_05_2010.html

54. Pessoa JP, Oliveira ES, Teixeira RA, Lemos CL, Barros NF. Control of dengue: Consensus views of Endemic Disease Control Agents and Community Health Agents on their integrated action. Cien Saude Colet. 2016;21(8):2329-38.

55. Sales FM. Health education actions for the prevention and control of dengue fever: a study at Icarai, Caucaia, Ceara State, Brazil. Cien Saude Colet. 2008;13(1):175-84.

56. Guanaes-Lorenzi C, Pinheiro RL. Is the value of Community Healthcare Agents in Brazil's Family Health Strategy receiving full recognition? Cien Saude Colet. 2016;21(8):2537-46.

57. Alonso CMDC, Béguin PD, Duarte FJCM. Work of community health agents in the Family Health Strategy: meta-synthesis. Rev Saude Publica. 2018;52:14.

58. Werneck GL, Macias AE, Mascarenas C, Coudeville L, Morley D, Recamier V, et al. Comorbidities increase in-hospital mortality in dengue patients in Brazil. Mem Inst Oswaldo Cruz. 2018;113(8):e180082.

59. Toledo J, George L, Martinez E, Lazaro A, Han WW, Coelho GE, et al. Relevance of Non-communicable Comorbidities for the Development of the Severe Forms of Dengue: A Systematic Literature Review. PLoS Negl Trop Dis. 2016;10(1):e0004284.

60. Astrom M, Persson C, Linden-Bostrom M, Rolfson O, Burstrom K. Population health status based on the EQ-5D-Y-3L among adolescents in Sweden: Results by sociodemographic factors and self-reported comorbidity. Qual Life Res. 2018;27(11):2859-71.