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Conditions of the household and peridomicile and severe dengue: a case–control study in Brazil

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Introduction: The potential influence of high-vector-density environments where people are supposedly more exposed to mosquito bites may have a relation to the clinical severity of dengue fever, an association that has been poorly discussed in the literature.

Objective: This study aimed at analyzing the association between anthropic environmental factors, particularly those related to the conditions of domicile and peridomicile, and the occurrence of severe dengue cases during the 2008 epidemic in the state of Rio de Janeiro.

Methods: We conducted a retrospective case–control study with a sample of 88 severe patients aged 2–18. They were selected through chart review in four children's tertiary care centers. The 367 controls were neighbors of the cases, paired by age. Data were collected through interviews and systematic assessment of house conditions as well as peridomicile area conditions, and they were later analyzed by conditional logistic regression.

Results: The presence of three or more high-volume capacity containers, which were without a lid or were inadequately sealed (water tanks, wells, cisterns, cement tanks, and pools), was significantly more frequent in households with severe cases when compared with households of controls ($OR = 1.6$; CI $95\% = 1.36–20.01$; $p = 0.015$).

Discussion: The presence of such larger reservoirs that could potentially produce more adult forms of the vector is consistent with a situation where people are more exposed to mosquito bites, and consequently are more prone to have multiple infections over a short period of time.

Conclusion: The emergence of severe dengue cases in a high-transmission context underpins the importance of constant vigilance and interventions in those types of reservoirs, which result from precarious household structures and irregular water supply services.

Keywords: *environmental health*; *severe dengue*; *breeding sites*; *premise conditions index*

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Dengue is one of the most important arbovirus diseases in the world. It is prevalent in over 100 countries across tropical and subtropical regions, particularly in Southeast Asia, Northern Australia, the Pacific Islands, and the Caribbean and Latin America (1, 2).

In Brazil, it is becoming increasingly more important as a public health issue due to successive epidemics in several cities across the country, especially in Rio de Janeiro State, where there has been a significant increase in hospital admissions and deaths affecting younger individuals in recent years (3, 4).

The first severe cases of the disease (dengue hemorrhagic fever and dengue shock syndrome) in Rio de Janeiro were reported in the early 1990s during an epidemic caused by the introduction of DENV2 (5). However, it was in 2008 during caused by one DENV2 variant that the increase of severe clinical forms became evident (6, 7). In that year, around 322,000 cases and 240 deaths were reported. In addition, 42% of deaths affected individuals younger than 15 years old (7). Previous major epidemics hit the city in 1986, 1991, and 2001–2002, in which DENV1, DENV2, and DENV3 were the most dominant serotypes, respectively (7).

It is believed that a combination of different factors contributes to increasing the risk of progression to severe forms of dengue fever (2, 6, 8, 9). A previous study has shown the association between dengue severity and virus load as reflected in viremia titer in patients with secondary DENV1 and DENV2 infections (8). This suggests that high-vector-density environments where people are more exposed to mosquito bites might influence the clinical severity of disease, an issue that has been poorly discussed in the literature.

Thus, the objective of this study was to analyze the relation between anthropic environmental factors, particularly those related to the conditions of domicile and peridomicile area, and the occurrence of severe dengue cases during the 2008 epidemic in the state of Rio de Janeiro.

Material and method

We conducted a case–control study in 88 individuals aged 2 to 18, who were hospitalized with severe dengue from 1 November 2007 to 30 April 2008 in four children's tertiary care centers in the city of Rio de Janeiro: Instituto de Puericultura Martagão Gesteira (IPPMG/UFRJ), Instituto Fernandes Figueira (IFF/FIOCRUZ), Hospital Infantil Pronto Baby, and Hospital Municipal Menino Jesus. They were selected through chart review. Controls were selected from the same neighborhood as the cases and were matched for age (7).

The definition of severe dengue cases used was the shock syndrome (a clinical syndrome resulting from tissue perfusion) – in other words, the presence of either hypotension (defined as systolic pressure <80 mmHg for patients aged <5 years and <90 mmHg for those aged ≥ 5 years) or narrow pulse pressure (difference between systolic and diastolic pressure ≤ 20 mmHg), combined with at least one of the following signs: cold and clammy skin, slow capillary refill, and/or impalpable pulse (10). The following were inclusion criteria: patients with a clinical–epidemiological dengue diagnosis who were aged 2–18, classified as severe dengue cases, and hospitalized from 1 November 2007 to 30 April 2008. It is worth noting that due to operational reasons, routine serological confirmation testing (immunoglobulin M, or IgM) is not performed in all suspect cases during epidemic periods. Therefore, it was not possible to consider this test as criteria for inclusion, although 49 out of 88 cases tested positive (IgM) when hospitalized. In addition, we noticed that all severe cases tested positive for immunoglobulins (IgG) specific for the dengue virus, as a form of validation of the clinical–epidemiological dengue diagnosis. We considered as eligible controls children in an age range of up to 3 years older or younger than the respective reference case if they came from the same neighborhood as the severe cases, regardless of their history of prior dengue infection. Children with hematologic or neoplastic diseases; those with autoimmune diseases and immunodeficiencies, including transplant recipients and HIV-positive individuals; as well as deaths from dengue were not included in the study (7, 10).

Two previously trained field teams conducted household surveys with legal guardians of the children or adolescents, as well as systematic inspections in domiciles, from February to May 2009. For each severe case, we selected at least four controls from different households.

The questionnaire consisted of three sets of questions: a set of questions about the participant (sex, age, yellow fever immunization status, and history of prior dengue infections), a set of questions about household characteristics (such as the number of rooms, the number of individuals or inhabitants, how long individuals had been living at their current address, water storage habits and types of containers used, and house condition), and also questions about some characteristics of the peridomicile area (the cleanness and degree of shading).

Some of the variables related to the household and peridomicile area were collected in order to create a Premise Condition Index (PCI), based on an index proposed by Tun-Lin et al. (11) to make premise inspection more efficient. Each house was photographed, assessed, and classified by the interviewer according to the following criteria: conditions of household (well maintained, reasonably well maintained, or poorly maintained), conditions of peridomicile area (well maintained, reasonably well maintained, or poorly maintained), and degree of shading in peridomicile area (very little or no shade, some shade, or plenty of shade) (Chart 1).

PCI scores ranged from 3 to 9 and were calculated for each house assessed in the survey. Calculations were made by summing up the three scores for each variable. Since categories 1 and 3 represent opposites, they were relatively easy to score. Premises that did not fit into categories 1 and 3 were assigned to category 2 (Chart 1).

We inspected 455 houses (88 of cases and 367 of controls) from February to May 2009. In addition, we collected data on the number of larger reservoirs in terms of volume capacity (water tanks that were without a lid or inadequately sealed, cisterns, barrel that were without a lid or inadequately sealed, cement tanks, shallow wells,

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Chart 1. Description of components and scores used to create the PCI

	PCI		
Score	Conditions of household	Conditions of peridomicile area	Degree of shading in peridomicile area
3	**Poorly maintained** (Poor structure, peeling walls, broken or improvised items, little organization or cleanliness)	**Poorly maintained** (Disorganized, waste or scrap, unkempt grass, tires, bottles)	**Plenty of shade** (External area with over 50% of shade, large trees, a sunblind-like structure, and layers of shrubs with a greenhouse effect)
2	**Reasonably well maintained** (Poor or simple structure, but well organized and clean)	**Reasonably well maintained** (Moderately well-kept or poor structure, but well organized and clean)	**Some shade** (Degree of shade in external area ranging from 25 to 50%)
1	**Well maintained** (Structure in good condition, new paint, place is visibly clean and well maintained)	**Well maintained** (Organized, no apparent waste or scrap, grass is short, yard well maintained)	**Little or no shade** (External area with less than 25% of shade, no large trees or any other structure that works as a sunblind)

Adapted from Tun-lin and colleagues (11). PCI = Premise Condition Index.

and pools) and the number of smaller reservoirs (those with an average volume of 20 liters).

The estimated sample size was based on a simple logistic regression model, considering a 95% confidence level, a power of 80%, a case–control ratio of 1:4, and an unknown prevalence of 40% of explanatory variables. Assuming these parameters, it would be possible to detect an odds ratio of 2.0 or greater in a sample of 82 cases and 328 controls (12).

The search for households with children eligible for the control group followed this order: 1) first household to the right of the visited home, 2) first household to the left of the visited home, 3) first household in front of the visited home, 4) second household to the right of the visited home, 5) second household to the left of the visited home, and so on until the total number of controls had been reached. As for apartments, control identification was made the same way on the same floor, and the procedure was repeated one floor below and one floor above until the necessary number had been reached.

We conducted a descriptive analysis of the epidemiological profile of cases and controls, and also of the characteristics of domiciles and peridomiciles. The data were analyzed by conditional logistic model analysis. All statistically significant variables ($p \leq 0.05$) identified in the univariate analysis were tested in the multivariate analysis using forward selection logistic regression. A likelihood ratio test (LRT) was used to choose the best-fit model. The analysis was carried out in the R software environment (R Development Core Team, 2011).

As for the spatial distribution of severe cases, we chose not to limit our sample to the city of Rio de Janeiro in order to obtain a larger sample. Study participants therefore came from eight municipalities in the Metropolitan Region of Rio de Janeiro State.

The research was approved by the Research Ethic Committee of the City of Rio de Janeiro Municipal Health Secretary, by the Research Ethic Committee of the Martagão Gesteira Institute of Pediatrics and Child Development at Federal University of Rio de Janeiro, and also by the Research Ethic Committee of the Evandro Chagas Institute of Clinical Research at the Oswaldo Cruz Foundation.

Results

Of all 128 cases initially selected in our patient chart review, 88 were located and joined the study, totaling 68.8% of adherence. The highest loss rate (7.0%) occurred among cases that lived in violent areas, which made access by the field teams difficult. The same percentage of loss occurred among cases that no longer lived at the address provided in the patient chart. In addition, 5.5% of cases were excluded because incorrect or nonexistent addresses were recorded or because of lack of information in charts. Cases that had passed away for reasons other than dengue made up 5.5% of the initial sample. We also excluded two children (1.6%) who lived in other states and were on vacation in the city when they fell ill. There was only one patient whose legal guardian refused to take part in the study. The average age of cases and controls was 10 years.

We found a low prevalence of reported prior dengue infections and yellow fever immunization among both cases and controls, with non-significant statistical differences. On the other hand, the prevalence of other family members who also became ill with dengue fever during the epidemic period was higher in severe-case households than in control households, a statistically significant difference ($p < 0.05$).

With respect to domicile variables, the habit of storing rainwater in cisterns was more frequent in case households when compared with those of controls, with an odds ratio *p*-value on the borderline of statistical significance (OR $=2.25$; $p=0.061$).

In addition, the odds of having severe dengue fever were 5.2 times higher in households that had at least three large-capacity reservoirs that were without a lid or inadequately sealed (water tanks, wells, barrels, cement tanks, cisterns, and pools), which are regarded as potential breeding sites with greater productivity for winged forms of *Aedes aegypti* ($p=0.015$).

For the component related to peridomicile area conditions, households with severe cases had better conditions when compared with controls. Although the difference was not statistically significant, it is worth pointing out that the odds ratio *p*-value estimated for the category 'poorly maintained' in relation to the category 'well maintained' (reference layer) is on the borderline of statistical significance (OR $=0.51$; $p=0.071$) (Table 1).

On the other hand, an intermediate degree of shading in the peridomicile area was positively associated with severe outcome. The odds of severe dengue fever were 2.8 times higher in households whose peridomicile area had some shade when compared with those whose peridomicile area had little or no shade ($p=0.007$). It is worth noting that the analysis of those components according to the Premise Conditions Index was not significantly associated with disease severity (Table 1).

We compared the fit of three models that had eligible variables in the univariate analysis ($p<0.05$). According to the LRT, the most adequate model is the one with the following variables: the presence of other household inhabitants with dengue, and the presence of three or more improperly sealed high-volume-capacity reservoirs (Table 2).

Discussion

The relevance of high-volume-capacity containers (that were without a lid or inadequately sealed) as *A. aegypti* breeding sites has already been discussed in previous studies (13–15). Although the Brazilian Ministry of Health recommends equal attention to all preferential *A. aegypti* breeding sites, there are questions regarding how efficient small containers (barrels, gallons, water plant vases, and plant saucers) are in terms of producing winged forms of the vector. Although they are often identified as *A. aegypti* larvae deposit sites, the fact that those containers hold a small amount of water makes them very unstable and transitory in their environments, resulting in low production of adult vector specimens (14).

In contrast, permanent and higher-volume-capacity reservoirs used by the population to store water are difficult to remove and have greater potential to produce winged forms of *A. aegypti.* They operate as key breeding

Table 1. Relative frequency (%) and OR of parameters related to domicile and peridomicile conditions that were used to form the PCI

Conditions of the household and peridomicile area	Severe cases ($n=88$)	Controls ($n=367$)	OR	95% CI	*p*
Conditions of household					
• Visibly well maintained	47.7	41.4	1+	–	–
• Reasonably well maintained	29.5	34.2	0.70	[0.37–1.33]	0.28
• Poorly maintained	22.7	24.4	0.70	[0.35–1.40]	0.32
• Missing	1.3	0	–	–	–
Conditions of peridomicile area					
• Visibly well maintained	39.2	29.0	1+	–	–
• Reasonably well maintained	20.3	24.9	0.51	[0.22–1.19]	0.12
• Poorly maintained	40.5	46.1	0.51	[0.24–1.06]	0.07**
• There is none	0	0	–	–	–
Degree of shading in peridomicile area					
• Little or no shade	18.9	31.5	1+	–	–
• Some shade	48.6	36.7	2.81	[1.31–6.02]	0.00*
• Plenty of shade	32.4	31.8	1.93	[0.86–4.29]	0.10
• There is none	–	–	–	–	–
PCI					
• ≤ 3	20.6	18.4	1+	–	–
• >3 and ≤ 6	45.9	46.2	0.83	[0.37–1.86]	0.66
• >6 and ≤ 9	33.3	35.4	0.79	[0.34–1.84]	0.59

Rio de Janeiro (RJ), Brazil (2009). 95% CI = confidence interval of 95%; PCI = Premise Condition Index; OR = odds ratio.
+Reference category.
*p-value statistically significant.
**Borderline p-value.

Table 2. Comparative analysis of multivariate models, according to the LRT

Variables	Adjusted OR	CI 95%	*p*
Model 1			
• Household inhabitants with dengue	1.86	[1.01–3.45]	0.04*
Model 2			
• Household inhabitants with dengue	1.99	[1.06–3.72]	0.03*
• Three or more larger volume reservoirs*	1.41	[1.01–1.99]	0.04*
Model 3			
• Household inhabitants with dengue	1.99	[1.06–3.73]	0.03
• Three or more larger volume reservoirs*	1.42	[1.01–2.01]	0.04*
• Degree of shading in peridomicile area	1.01	[0.99–1.01]	0.18

LRT results for models 1 and 2 were significant ($p = 0.046$). H_{null} rejected: the partial model is superior to the full model of overall model fit. LRT results for models 2 and 3 were not significant ($p = 0.184$). Therefore, H_{null} not rejected: the partial model is superior to the full model of overall model fit.
LRT = likelihood ratio test; OR = odds ratio.

sites that feed smaller peripheral ones (grates, plant saucers, etc.), supporting large epidemics (11, 13–16). This situation is often worsened by intermittent water distribution in endemic areas, where water storage practices favor domestic breeding of *A. aegypti* and thus the risk of infection by dengue virus (17, 18).

The results of a pioneering study that tested the reactivity of serum samples from hospitalized children, classified in groups according to different clinical levels of dengue fever, and proteins in the saliva of *A. aegypti* (mosquito salivary protein, or MSP) showed significant differences in the pattern of immune response in different groups of patients (19). MSPs are considered highly immunogenic and are also noted as deregulators of inflammatory and hemostatic responses during blood feeding. By connecting to the mediators of the inflammatory process, MSPs antagonize the host's defense and make blood suction easier. This increases cell susceptibility and virus transmission, which are both associated with increased severity in several arboviruses (20–22).

Other studies suggest that in situations where individuals had been previously highly exposed to vector bites and consequently had high antibody titers against MSPs, infected mosquitoes tend to take multiple and prolonged bites, increasing the risk of virus inoculation (23). This process could lead to an increase of inoculated viral load in the host, of the amount of cells initially infected, and of viremia titers, all of which are factors associated with dengue severity (8, 19).

Aspects involving the biological plausibility of an association between prior exposure to saliva proteins of *A. aegypti* – caused by high exposure to insect bites – and dengue fever severity shown in those studies are consistent with the results of our findings. In that sense, the presence of three or more inadequately sealed high-volume-capacity reservoirs during a period of intense transmission may have contributed to high vector density and consequently a large number of insect bites in domiciles with severe cases when compared with controls.

As for the degree of shading in peridomicile areas, although there is no evidence that this influences outcomes in our study, some authors have already documented its importance in modulating ideal conditions for producing pupae and winged forms of *A. aegypti*, and consequently for dengue transmission (11, 15, 24). Additionally, the fact that at least one household inhabitant fell ill in the same epidemic period of hospitalization of severe cases (shown by univariate and multiple analyses) reinforces a domicile context of high exposure to mosquito bites (25).

Even though our study did not focus on breeding sites but rather on vulnerable conditions of houses and peridomicile areas, our findings should be interpreted by considering potential changes in the dwellings from when the epidemic occurred to when data collection took place. However, based on on-site visits and photographs of households, most participants come from low-income families and therefore are unable to notably improve the structure of their homes. A previous study showed that domiciles that tested positive for *A. aegypti* breeding sites are 3.22 times more likely to remain positive in the following 12 months than a negative domicile becoming infested by the vector (11). Likewise, another study highlighted that the use of permanent containers (water tanks, cement tanks, and wells) to store water contributes to stable infestation indices throughout time (15).

Nevertheless, we found a contradictory protective effect for severe dengue in households whose peridomicile-area conditions were unfavorable ('poorly maintained'). We attribute this to the fact that many home interviews for cases were scheduled by phone in advance, while this procedure was often not possible for the control group. The scheduling of interviews in advance may have led some participants to clean and organize their yards, removing possible breeding sites, before the field team arrived. Furthermore, one should also consider the possibility that the trauma experienced by families of children and teenagers who have been under imminent risk of dying from dengue fever (severe cases) may have caused them to be more careful with their homes in order to avoid the risk of falling ill again. From that perspective, this may have contributed to the lack of explanatory power of the PCI in univariate and multiple analyses, since one of the components of that index was the variable 'peridomicile area conditions'.

As for the variable 'reported prior infection', our findings did not show an association between previous dengue fever episodes and disease severity, probably due to the way this variable was measured (self-reported), which takes into account only symptomatic infections. However, this finding does not exclude the occurrence of sequential infections, given that it is not possible to confirm whether cases or controls had primary or secondary infection since the study design was retrospective, and even for severe cases acute-phase sera were not available.

Another limitation is related to variable yellow fever immunization status. Since the study participants had low immunization levels (6.8% of severe cases and 7.6% of controls), we were unable to assess a potential association with dengue severity.

Among the difficulties faced by field teams when collecting data, we highlight incorrect or incomplete addresses and the fact that some participants lived in violent communities, which limited access by field teams. However, whenever possible, teams would get in touch with the local Residents Association (RA) or with the Family Health Program team (PSF) to easily locate a child's address as well as to obtain access to the community. Additionally, it was difficult at times to find children whose age was compatible with that of the case, whether because there were few children in the neighborhood, because many were at school, or even because their parents were not at home at the time of recruitment.

Conclusion

We speculate that the presence of larger reservoirs, whether open or inadequately sealed, increased exposure to mosquito bites because they have greater potential for producing *A. aegypti* adult forms.

Even assuming that factors such as a DENV-2 serotype variant and the population immunity status after previous epidemics caused by different serotypes may have contributed to the increase of dengue severity in the 2008 epidemic (6, 26), it is important to note that the context of emergence of severe cases is suggestive of intensive transmission, especially if one considers that other inhabitants in the same home were also infected during the same epidemic period.

Our findings reinforce the importance of constant vigilance and intervention regarding these types of high-volume-capacity reservoirs that are usually used to store water over long periods due to the disruptions in water supply services. Many domiciles we visited were located in slum areas and belonged to low-income families that cannot afford improvements in household structure. In this respect, it is up to the government to find a solution by reestablishing constant water supply and developing public policies concerning housing infrastructure.

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