

## Mortality from Coronary Artery Disease during Dengue Epidemics

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### Abstract

**Background:** The possibility of increased mortality from coronary artery disease (CAD) during dengue epidemics is frequently taken into account to create extra cardiologic beds.

**Objective:** Describe a possible association between the mortality from CAD and the reported cases of dengue virus infections in the state of Rio de Janeiro.

**Methods:** Two time series were developed. The first series of CAD mortality comprised 313,503 patients between January 1996 and December 2010. The disease codes used were all from I20 to I25 (ICD-10). The second series comprised 275,227 cases of dengue fever reported between January 1994 and December 2010. The Box-Jenkins methodology was employed for modeling the series; and both cross correlation and intervention analysis were used to evaluate such association.

**Results:** The time series of CAD mortality best fits into the model SARIMA (1,1,1) × (1,0,1)<sub>365</sub> where annual seasonality is reflected by an increase in the number of cases in winter months. The intervention analysis showed absence of influence of cases of dengue fever in CAD mortality with a correlation coefficient of 0.0018.

**Conclusions:** There is no correlation between CAD mortality and the number of dengue fever cases. CAD mortality is higher in winter.

**Keywords:** Time series studies; Dengue; Coronary disease

### Introduction

Dengue fever is an arbovirus infection caused by virus of same name and transmitted by mosquitoes of genus *Aedes*. Today, there are four different serotypes of dengue virus, namely DENV-1, DENV-2, DENV-3 e DENV-4, from family *flaviviridae*, genus *flavivirus*<sup>1-3</sup>. With highest incidence in Southeast Asia, India and the American tropics, the World Health Organization classifies dengue as a major global health threat. Historically responsible for epidemics restricted to developing countries, nowadays it sweeps the world, virtually hitting all countries with tropical and warm climates. Therefore, it is deemed as a health issue of major social and economic impact. Every year around 50 to 100 million new cases are expected to occur worldwide, where 500,000 take its severe form.

The association between cardiovascular mortality and dengue virus infection has been scarcely debated in medical literature. Moreover, when this association is exclusively limited to coronary artery disease (CAD), such evidence vanishes altogether. There are few works reporting direct cardiac involvement in dengue fever patients<sup>4-7</sup>. However, given the high prevalence of CAD in Brazil, and the high incidence of dengue fever during epidemics, it is possible to presume that the emergence of the latter will influence the evolution of CAD.

Based on this reasoning, there is a precept, almost dogmatic, however not based on epidemiological studies or others of any kind that mortality from coronary heart disease increases during dengue fever outbreaks.

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**ABBREVIATIONS AND ACRONYMS**

- *ACF* – Autocorrelation function
- *CAD* – Coronary artery disease
- *FPACF* – Partial autocorrelation function
- *ICD-10* – International Classification of Diseases and Related Health Problems, 10<sup>th</sup> edition
- *SESDEC* – State Secretariat of Health and Civil Defense (currently called Health State Secretariat - SES)
- *SIM* – Mortality Information System
- *SINAN* – Notifiable Diseases Information System
- *WHO* – World Health Organization

This is explained by the assumption that any acute inflammatory state can theoretically unsettle stable coronary disease, either by anatomical changes in atherosclerotic plaques, or by increased cardiac oxygen demand in face of fixed pre-existing injuries. It follows, therefore, that cardiovascular mortality would be unexpectedly higher in times when there is a significant increase in cases of dengue, a disease known to trigger systemic inflammatory response syndrome<sup>3</sup>. To test this hypothesis, an ecological study was developed focusing on time series modeling based on data from the Mortality Information System (SIM)<sup>8</sup>, and data kindly provided to the authors by the Department of Environmental and Epidemiological Surveillance of the State Secretariat of Health and Civil Defense (SESDEC) of Rio de Janeiro.

The second objective of this work is to describe the series of deaths from coronary disease between January 1996 and December 2010.

## Methods

The work consists of an ecological study based on two historical series covering the period from 1996 to 2011. The population of the study is the inhabitants of the state of Rio de Janeiro, Brazil, from both genders and over 40 years old.

Two sets of data were collected for this research. The first set was extracted from the Mortality Information System (SIM)<sup>8</sup>, related to CAD mortality between January 1996 and December 2010, covering a total of 15 years. Death causes were defined according to ICD-10<sup>9</sup>, in force since 1996, year chosen to begin this series. The Health State Secretariat has kindly provided the second set of data to the authors, through the Notifiable Diseases Information System (SINAN), consisting of the number of cases of dengue fever reported between January 1994 and December 2011. The choice for this period is explained by a significant increase in the number of cases registered since 1996. It is noteworthy mentioning that the data used herein is of public domain and is not identified.

Data collection was followed by modeling and analysis of two time series, one based on CAD mortality data and the other on reported cases of dengue. The behavior of both series is described through this analysis, regarding their trend, cycles and seasonal variations, as well as the influence of the second series on the first.

The program R version 2.15.114<sup>10</sup> was used in the modeling and analysis of data.

## Time series analysis

Time series is a set of quantitative observations on a certain phenomenon chronologically ordered and distributed in a period. When it comes to studies of populations, the main reason for this analysis, time is considered as a discrete variable.

An intrinsic and unique quality of time series lies on the serial correlation of observations, which means that every observation depends on prior observations. The essence and properties of such dependence are paramount to its own analysis. The systematic, reasonable and organized process of research built to expose more simply and accurately the mechanisms generating the series, as well as the influence suffered by external factors is described below by the statisticians George Box and Gwilym Jenkins. The methods used in analyses are only appropriate for discrete data systems, in which observations occur equidistantly in time<sup>11</sup>.

In general, time series can be broken down into segments to be interpreted as a combination of the components below:

1. A trend or long-term movement
2. Fluctuations on trend of lower or higher regularity
3. A deterministic cycle (seasonality)
4. A residual, irregular or random effect

A series' trend denotes its behavior around an average value. Thereby, it may be either stationary, if its structure varies around a fixed value; otherwise, it may go upward or downward, according to the increase or decrease of averages. Seasonality shows the repetition of a pattern in a fixed time interval.

If the prediction of future values of a given series can be accurately determined by a mathematical function, then the series is deterministic. In this particular case, given any set of observations, the subsequent observation will always be the same (precision); that does not mean it will be correct (accurate) – one could always find the same wrong value! On the other hand, if values are described

as result of a stochastic (probabilistic) process, then the time series will be non-deterministic or stochastic. Therefore, the series  $Z_{\tau}$ , hereof will be expressed as shown below by a function of both observable (trend, seasonality) and random components:

$$Z_{\tau} = f(T_{\tau}, S_{\tau}, \varepsilon_{\tau})$$

where  $T_{\tau}$  is the trend component;  $S_{\tau}$  is the seasonality component, and  $\varepsilon_{\tau}$  is the random component<sup>10-12</sup>.

### The Box-Jenkins Methodology

The method chosen for analyzing the series, as described, presumes time correlation between each term of the series and their precursors. In this scenario, the foundation of the entire analytical process lies on the linear regression of each value of time series on their own past values.

Such approach, detailed in the ground-breaking work of George Box and Gwilym Jenkins<sup>10</sup>, a landmark in time series studies, encompasses the series in a model class named ARIMA (autoregressive, integrated and moving averages), used to model time-correlated data and to provide forecasts<sup>11-13</sup>. Their work's relevance later called "Box-Jenkins models" or "ARIMA modeling" is reinforced in other fields, such as Economics, Industry and Medical Sciences<sup>14</sup>.

### Cross-correlation analysis

In cross correlation analysis, it is assumed that an exceptional event, called intervention event (reported cases of dengue fever), could somehow affect the series under study (CAD mortality). In such circumstances, transfer function models are used to explore the impact of one intervention event both in quantitative and qualitative terms. The relation between the two time series is determined by the cross-correlation function. This function determines the correlation between two series according to time.

### CAD mortality

The time series developed based on CAD mortality data covers the years between 1996 and 2011. The study considered the deaths of men and women over 40 living in the state of Rio de Janeiro. The underlying causes of death - described by the International Classification of Diseases and Related Health Problems (ICD)<sup>9</sup> -, are in accordance with the codes of the 10<sup>th</sup> edition. The codes

regarding the underlying causes of deaths selected in the study were those of coronary syndromes – ICD 10: I20 to I25.

All data retrieved from SIM<sup>8</sup> related to CAD mortality is taken from death certificates filled out by the certifier physician. The criterion used for modeling the series was the underlying cause of death, defined according to ICD 10<sup>th</sup> Revision<sup>9</sup> - as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury"<sup>9</sup>.

### Reported cases of dengue fever

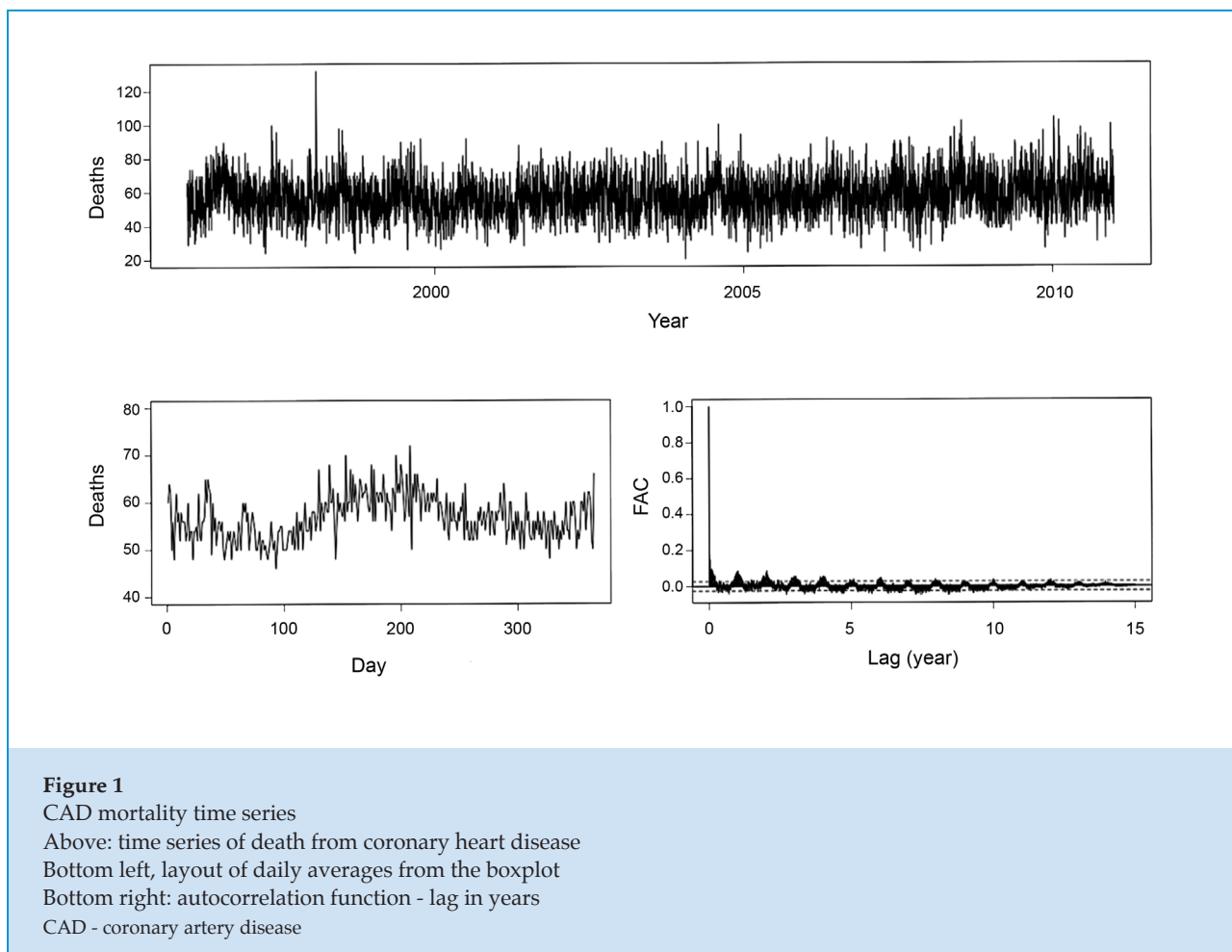
The dengue fever time series was developed based on data kindly provided by SESDEC, comprising the number of dengue fever cases reported to SINAN per day in the state of Rio de Janeiro. Reports from February 29 were not included in the preparation of the series. However, it is complicated to model the dengue series, as shown below – the concentration of cases during summer months and the irregularity of outbreaks occurrence makes it more difficult. On the other hand, as this study aims to understand the influence of dengue fever epidemics on coronary artery death through the intervention analysis, applying the modeling method on dengue series turns out to be unnecessary.

## Results

### CAD series

The CAD series comprised 5,475 days, from January 1, 1996 to December 31, 2010. The total number of deaths in this period was of 313,503, an average of 57.3±11.9 deaths per day. It was necessary to perform differentiation to make the series stationary in order to model it.

Graphical techniques were applied to provide insight into the time series behavior. Figure 1 (bottom left) shows a median built up from the total number of cases per day, from the first day to the 365<sup>th</sup> day, during the 15 years comprised in the series, taken from the daily boxplot. It is noticeable that the series shows an annual seasonality, with higher number of deaths during winter months. The mortality peak takes place around the 180<sup>th</sup> to the 190<sup>th</sup> day of the year, equivalent to the beginning of winter. In Brazil, the austral winter starts with the winter solstice, from around June 21 to September 23, the spring equinox, i.e. from the 171<sup>th</sup> to the 263<sup>th</sup> day of the year. The autocorrelation plot and the time series are also shown in Figure 1.



Following the differentiation, the autocorrelation function (ACF) and the partial autocorrelation function (PACF) plots suggest an ARIMA (1,1,1) model, as shown in Figure 2. For seasonality analysis, ACF and PACF are applied with a 365 days lag (Figure 3). The model suggested by the correlation plot analysis is a SARMA (1,1) with annual seasonality. In summary, the model that best parsimoniously met the CAD death data was a SARIMA (1,1,1)  $\times$  (1,0,1)<sub>365</sub>. The series presents annual seasonality, with higher number of deaths occurring in winter. By breaking down the series, the number of deaths from coronary heart disease tend to decrease up to the year 2000, from which a subsequent increase in annual mortality rate can be noticed (Figure 4).

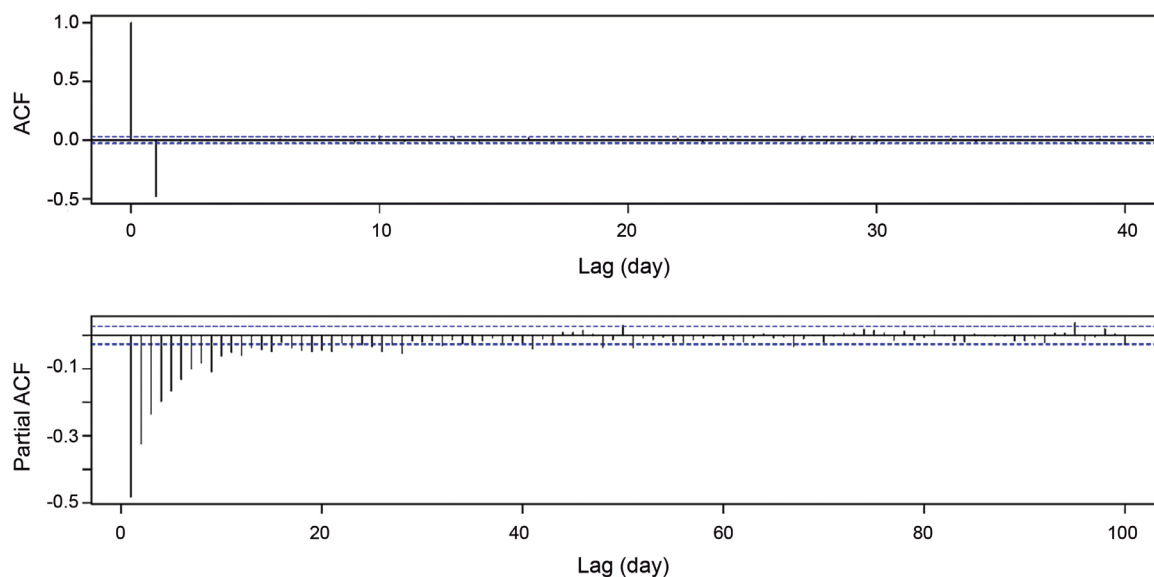
Applying the Ljung-Box test on the series broken down, we obtain  $p = 0.9216$ , that shows that the model is appropriate, dismissing the hypothesis of temporal dependence – the residue is similar to the white noise.

### Time series of reported cases of dengue fever

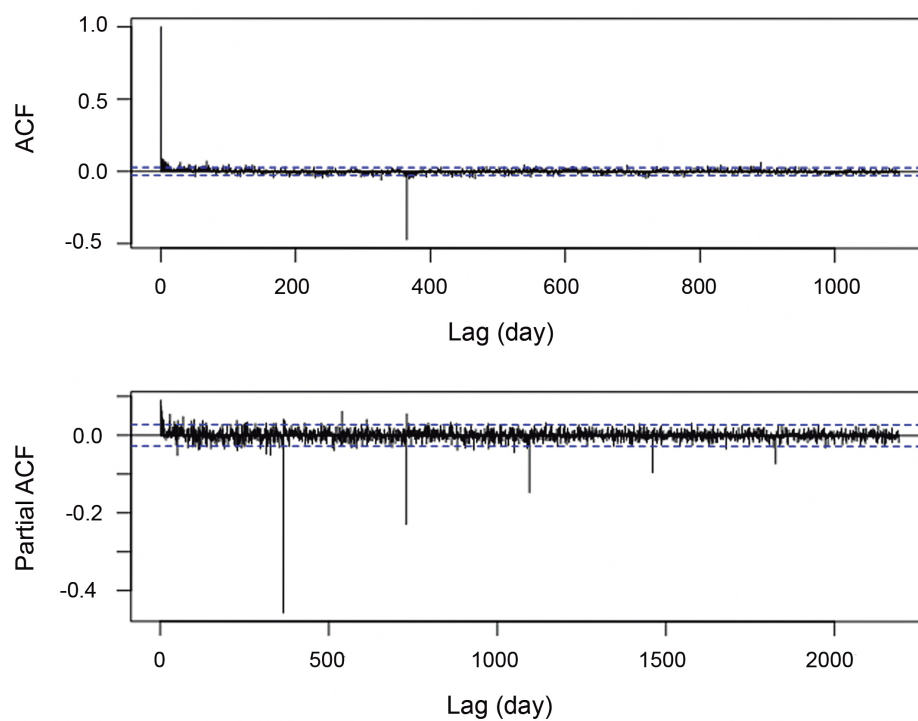
The dengue series was developed based on 6,205 cases distributed from January 1, 1994 to December 31, 2010. Figure 5 highlights that within the period studied, the first cases of dengue reported are in 1995. The first major epidemic of which we have records occurred in 1998, with about 900 cases reported – the same year of the worldwide spread of the disease. The boxplot, developed based on the number of cases of each day of the year, presents the disease behavior: almost all of the cases occur in the warmer months of the year, from January to May, peaking in late February and early March (Figure 6) Thus, in certain months there are no reports of the disease, when the series reaches the baseline.

### Intervention analysis

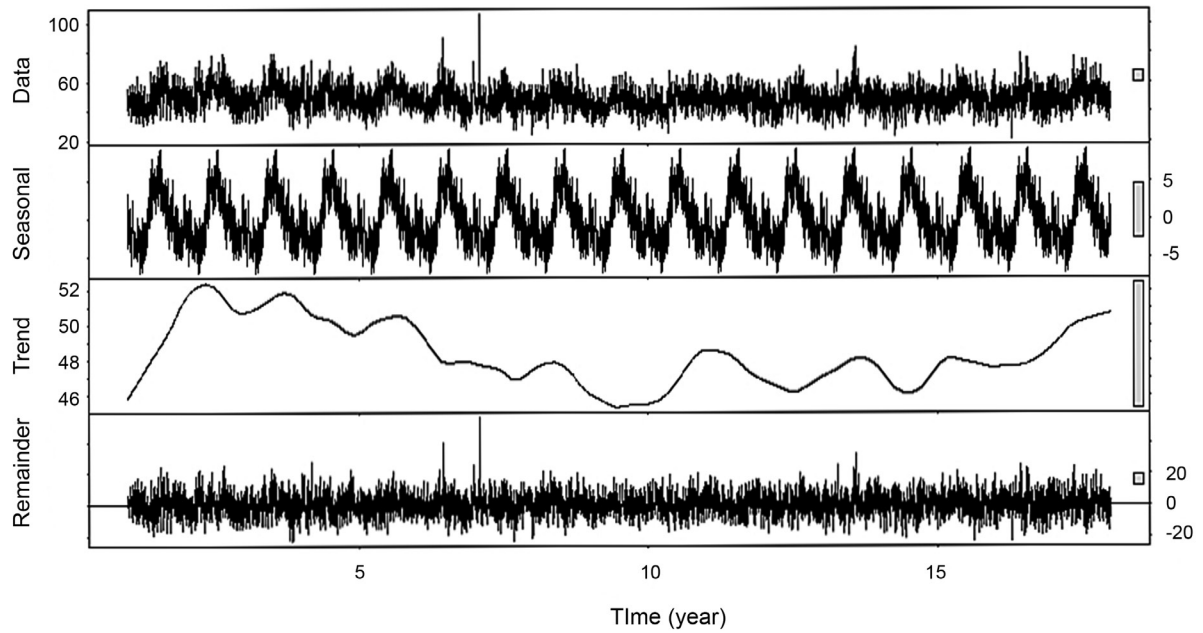
The intervention analysis (Table 1) shows no influence of cases of dengue fever in the CAD mortality series. A slight variation is noticed when considering the setting values of CAD mortality series with and without the influence of the series on the number of reported cases of dengue.



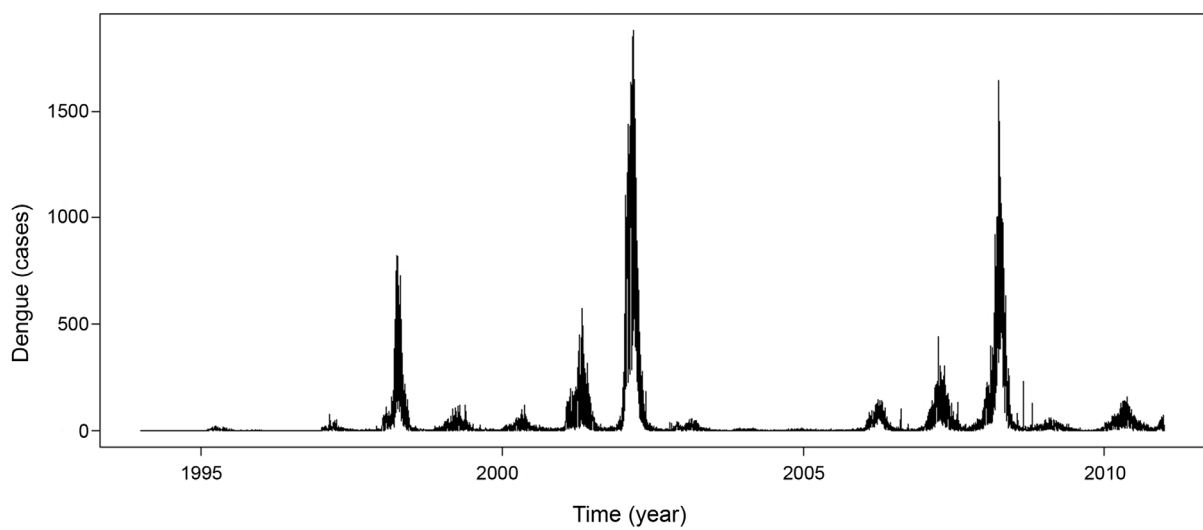
**Figure 2**  
Autocorrelation and partial autocorrelation functions of CAD mortality series - lag in days  
CAD - coronary artery disease; ACF - autocorrelation function



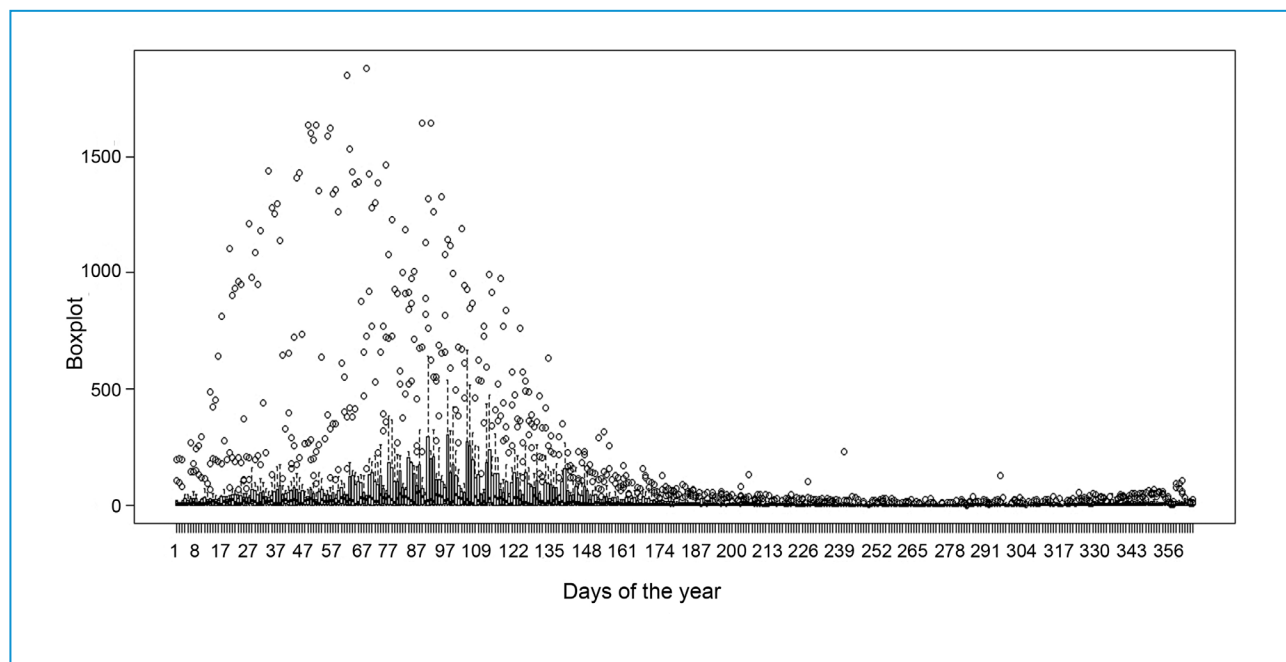
**Figure 3**  
Autocorrelation and partial autocorrelation functions of CAD mortality series - lag in 365 days  
CAD - coronary artery disease; ACF - autocorrelation function



**Figure 4**  
Breakdown of series in seasonal, trend and random components



**Figure 5**  
Dengue time series



**Figure 6**  
Boxplot of dengue cases reported in each day of the year

**Table 1**  
Intervention analysis

		Series CAD (without dengue influence)						
	AR	MA	SAR	SMA	$\sigma^2$	log likelihood	AIC	
	0,0558	-0,9423	-0,0980	0,0944	129,6	-21081,58	42 171,16	
Standard error	0,0150	0,0064	0,2812	0,2722				
		Series CAD (with dengue influence)						
	AR	MA	SAR	SMA	$\sigma^2$	log likelihood	AIC	
	0,0553	-0,9415	-0,0995	0,0959	129,5	-21081,08	42 172,17	
Standard error	0,0151	0,0065	0,2502	0,2421				

AR - autoregressive; MA - mobile average; SAR - seasonal autoregressive; SMA - seasonal mobile average; AIC - Akaike information criterion;  $\sigma^2$  - variance; CAD - coronary artery disease

## Discussion

Cardiovascular manifestations in patients with dengue fever have been described throughout the history since the 1960s. The shock syndrome associated with dengue, with cardiovascular collapse and myocardial depression,

was well known and little studied. In 1972, Ivor Obeyesekere and Yvette Hermon<sup>6</sup> described 10 acute myocardial infarction cases caused by the *arbovirus* in the city of Colombo, Sri Lanka (at that time it was called Portuguese Ceylon), specifically the dengue and chikungunya fever viruses. In this case-by-case detailed

description, patients with clinical, electrocardiographic and radiological alterations leading to the diagnosis of myocarditis had high titer of antibodies specific to the *arbovirus*, besides a background of acute febrile syndrome<sup>6</sup>. In fact, this report suggests potential cardiac tropism for dengue virus in specific circumstances.

Also in Sri Lanka, during the outbreak of 2004-2005, an observation study was carried out with 133 individuals with dengue, in the *Peradeniya Teaching Hospital*, located in the central province of same name, considered by public health as an endemic area. In such survey, the cardiac involvement, defined as the elevation of cardiac enzymes, namely MB-CK and troponin, as myocardial injury markers, and NT-proBNP, as myocardial dysfunction marker, occurred in up to 20% of cases (troponin T was elevated at 0.8%, MB-CK at 12.8%, and NT-proBNP at 18.9%). No shock was reported in that series, as well as no coronary disease background of the patients studied. Besides the elevation of cardiac enzymes, particularly those with evidence of myocardial necrosis, there are other unusual manifestations ranging from rhythm disorders (atrioventricular blocks, atrial fibrillation and sinus node dysfunction), pericarditis and myopericarditis<sup>7</sup>.

Different from the cases described of potential myocardial involvement by the virus, no reference was found on CAD-specific manifestations in patients with dengue fever. Notwithstanding the occurrence of increasingly acute outbreaks, the possibility of such correlation becomes more tangible<sup>15</sup>.

Therefore, the theoretical concept to be tested was grounded on the possibility that dengue fever could cause acute coronary syndrome, either by direct action on the immune-hemostatic system or by destabilization of pre-existing disease. A third possibility, although less likely, would be the direct action of the virus causing coronary arteritis. Anyway, such an association has not been described yet.

To test the hypothesis that dengue epidemics might be associated with increased CAD mortality, an ecological study with time series modeling (exploratory study) was carried out. For this purpose, data collected in the past was analyzed, some available on Datasus<sup>8</sup> website, others kindly provided by the State Secretariat of Health Surveillance, as reported.

Two forms of immune response that somehow go in different ways are likely to result from infection by dengue virus. The first prevents infection and promotes

recovery. The second, related to the hemorrhagic syndrome and to dengue shock syndrome, is generally observed in individuals with secondary infection. In this case, the antibodies developed for the infection of one serotype may not neutralize the infection caused by a second virus of a different serotype, paradoxically amplifying the infection. Individuals with dengue shock syndrome and hemorrhagic syndrome have massively infected macrophages that cause elevated viremia. In turn, macrophages activated and destroyed by cytotoxic cells release thromboplastin and complement-activating proteases, triggering coagulation and cell lysis<sup>17</sup>. Could this scenario give rise to events that ultimately result in coronary thrombosis or atherosclerotic plaque rupture? The intervention analysis applied to time series did not confirm an association between dengue epidemics and mortality from coronary heart disease. The parameters of CAD mortality series, with or without the influence of the dengue series, are similar.

Although not the primary objective of this study, the modeling and description of CAD mortality time series in the state of Rio de Janeiro outlined a specific behavior during the period approached. Certainly, understanding the descriptor parameters would help grasping their generator mechanisms, and ultimately planning concrete actions and measures of public health.

The first noteworthy behavior, the annual seasonality, presents a mortality peak in winter months, as already described in other countries. In fact, these seasonal variations were associated with mortality from both coronary artery disease and cerebrovascular disease - in England and Wales, the mortality winter peak of cardiovascular diseases is responsible for 2,000 additional deaths per year<sup>18-20</sup>. In fact, the possibility of a relationship between temperature and CAD mortality is also grounded on data that associate an increased mortality with greater distance from the Equator, as it happens in England, the United States, Canada and Australia. Along the same line, data analyzed from 1,474 North American hospitals found in the *National Registry of Myocardial Infarction*, covering the period from 1994 to 1996, revealed a 53% increase in the incidence of acute myocardial infarction in winter months compared to summer months<sup>21</sup>.

A second unexpected behavior of the series, of greater epidemiological relevance, is the lack of decrease of the mortality trend in the period analyzed between 1996 and 2011. On the one hand, this could be simply explained by the population growth, especially among individuals over 40 years old. On the other hand, a similar behavior

had already been noticed in the United States<sup>21</sup>. Data presented by government institutions and published by the Statistics Committee of the American Heart Association (AHA)<sup>22</sup> shows a slowdown in CAD mortality decrease rate that, at first, seemed to be in line with the socioeconomic development of the country in the last three decades. This effect that seems to be happening in several developing countries has led to spending on health actions aimed at primary prevention, especially through the control of risk factors already known. In Brazil, regions with higher economic growth, such as São Paulo and Rio de Janeiro, experienced an increase in mortality after the 2000s, parallel to the improvement of living conditions of population<sup>23</sup>. New epidemiological analyses will be required to describe associations with prevalence of risk factors, namely smoking, diabetes and dyslipidemia.

In this context, the application of epidemiological study methods can guide SUS actions, making them more effective and efficient. One would try to understand, for example, the worsening of mortality rates from ischemic heart disease in developed countries as a power game between social and technological development, on the one hand; and the massive recruitment of new smokers among women and youth, on the other hand, combined with the prevalence of diabetics, dyslipidemics and "new" sedentary individuals.

A limitation that could be suggested, inherent to the collection of data analyzed, refers to the quality in reporting dengue cases to SINAN. Uncomplicated cases of dengue, listed in the group of diseases attached (compulsory reporting list - LNC) of Ordinance GM/MS no. 104 of 01/25/2011<sup>24</sup> (Ordinance in force at the time of data collection, revoked by article 14 of Ordinance GM/MS no. 1271 of 6/6/2014), are reported to and filed with SINAN according to the rules and routines established by the Health Surveillance Secretariat of the Ministry of Health (MS)<sup>24</sup>. On the other hand, the diseases listed in Annex II of the said ordinance (immediate compulsory reporting list - LNCI) include dengue cases with complications, dengue shock syndrome, dengue hemorrhagic fever, death from dengue and cases of DENV- 4 infection occurred in areas without endemic transmission by this serotype, which requires immediate report. Reading between the lines of such information, we presume that the unreported cases of dengue would comprise mostly those cases not diagnosed, possibly because they are mildly symptomatic or even asymptomatic. Thus, they would be occurrences with

lower theoretical potential to cause death from cardiovascular complications. On the other hand, diseases that might be diagnosed and reported as dengue, namely leptospirosis, yellow fever, leukemia, in theory have the potential to trigger unstable coronary artery disease.

The methodology applied herein tests the hypothesis at a comprehensive level, as data come from observations of phenomena determined in a population belonging to a determined geographical area. The total number of individuals exposed and the total number of cases within each group is known, while the number of cases exposed is unknown. The time series design, widely used in econometrics and meteorology, is used herein to analyze the evolution of the CAD mortality rate, along a timeline, assessing the impact of an intervention - reported cases of dengue. A limitation ascribed to studies of this kind is reflected in the inability to transfer the estimate of environmental effect, the association of variables (if any) to the individual level.

## Conclusions

The time series analysis did not prove an association between the report of dengue cases and mortality from coronary heart disease. However, the analysis of the CAD mortality series depicts annual seasonality with more cases in winter months, as shown in other countries. Moreover, there is a propensity to increase in the number of deaths from coronary heart disease, unexpected for the socioeconomic pattern of the state of Rio de Janeiro.

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## Potential Conflicts of Interest

No relevant potential conflicts of interest.

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## Academic Association

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