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EPIDEMIC OF DENGUE AND THE OCCURRENCE OF EARLY NEONATAL DEATH: AN ECOLOGICAL STUDY

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ABSTRACT

The aim of the present study was to evaluate the effects of dengue virus infection in pregnancy from 2007 to 2016. For this study we used data from the notification systems for live births and mortality in a Brazilian municipality of approximately 900 thousand inhabitants. Epidemic years were compared to endemic years, with rates related to clinical-obstetric and pediatric outcomes being calculated. Statistical difference was found for the coefficient of early neonatal mortality, which presented higher values in the epidemic years for dengue compared to the endemic years. There was no statistical difference in the coefficients of early neonatal deaths between epidemic and endemic years according to the following ICD-10 categories: neoplasias; cardiomyopathies; disorders, infections or conditions of the perinatal period; congenital malformations, deformities and chromosomal abnormalities; and external causes of morbidity and mortality. However, there was a greater notification of congenital syphilis in the epidemic years. There was an association between early neonatal mortality and the epidemic level. The results obtained in this paper are consistent with other studies on the effects of dengue infection during pregnancy and obstetric and pediatric risks.

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INTRODUCTION

Dengue is an infectious and non-contagious viral disease, transmitted by vectors, the main transmitter in urban areas being the mosquito of the genus Aedes. It is the vector disease with the highest incidence in the world reaching tropical and subtropical regions, which includes the Brazilian territory where dengue has become endemic. Epidemics occur periodically according to the alternation of circulating virus serotypes and climatic conditions (Araújo *et al*., 2017). It has a broad clinical spectrum and in most cases is asymptomatic or oligosymptomatic. Susceptibility to infection is universal, reaching both sexes at any age, race or social insertion. This disease can worsen and lead to death, especially children and the elderly. In Brazil the incidence has been higher in adults, young and in women of childbearing age (Araújo *et al*., 2017; Nascimento *et al*., 2017).

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Infection in pregnant women has been the object of study and controversy, regarding its effects on the evolution of pregnancy, childbirth and the puerperium as well as on vertical transmission and the effects that may result in the concept (Pouliot *et al.*, 2010; Leite *et al.*, 2014; Yi-Quan *et al.*, 2017). The physiological changes that occur in the body of pregnant women are similar to some of the changes caused by infection with one of the dengue viruses, which may lead to the non-perception of dengue infection and to incorrect or insufficient care (Seabra *et al*., 2010). A clinician should be particularly attentive in the treatment of a pregnant woman infected with dengue, since physiological hematological changes provide greater volume compensation and in dengue hemorrhagic there is a significant loss of volume, causing shock (Singla *et al.,* 2016; Hariyanto *et al.,* 2016). The pregnant woman has a greater risk of developing severe dengue fever and dying. The risk of dengue death is approximately 3.5 times higher in the pregnant population than in the population of women of childbearing age who are not pregnant (Machado *et al*., 2013; Nascimento *et al*., 2017). Due to the relevance of this issue mentioned above, as of 2006, the occurrence of gestation and

gestational age were variables included in the dengue investigation file in Brazil (Brasil, 2006). Dengue transmission during the first trimester is associated with an increased risk of postpartum haemorrhage, premature births, and low birth weight (Friedman *et al*., 2014; Nascimento *et al*., 2017). The association between dengue infection in pregnancy and the occurrence of abortions (Tan *et al*., 2012) and fetal death (Paixão *et al*., 2017) is also observed.In view of the above, the objective of this study was to evaluate the effects of dengue virus infection in pregnancy using data from the notification systems of live births and dead. The study was conducted in a Brazilian municipality of approximately 900 thousand inhabitants. A comparison between the epidemic and endemic years was also made based on the calculations of the rates related to clinical-obstetric and pediatric outcomes for a period of 10 years.

METHODS

The present work was carried out from 2007 to 2016 in the city of Campo Grande, central western region of Brazil. As an analysis tool, the use of the ecological or aggregate study was chosen. The advantage of using the ecological study is due to its easy execution, low relative cost and the overcoming of ethical issues (Almeida Filho and Barreto, 2017). Secondary data available were used in the following databases: Mortality Information System (SIM); Notifiable Disease Information System (Sinan); Live Birth Information System (Sinasc). The databases used in this research are available at the Department of Information Technology of the National Health System / Datasus (www.datasus.gov.br) and Health Department of the State of Mato Grosso do Sul, Brazil (www.saude.ms.gov.br). Firstly, a survey was made of the number of new cases of dengue in the period 2007 to 2016, and the calculated incidence rates per 100,000 inhabitants were also calculated. In order to demonstrate which years would be epidemic and endemic, a control diagram was constructed, consisting of graphical representation of annual incidence rates, arithmetic mean of these rates (calculated with exclusion of epidemic year rates) and endemic threshold (values corresponding to average incidence rate plus or minus 1.96 standard deviations) in the study period. Then, observed incidence rates that exceeded the maximum limit of the expected variation (endemic threshold) correspond to the epidemic years.

Subsequently were calculated the coefficients of maternal, fetal, neonatal and infant mortality. This calculation is necessary to verify if there has been a change in the years of dengue incidence. The calculation of the coefficients considers the basic health indicators available in the Inter-Agency Health Information Network (Ripsa) (Pan American Health Organization, 2008), i.e:

- Maternal mortality: ratio between maternal death (death occurring during pregnancy or 42 days after its termination, other than accidental or incidental causes) and number of live births, in which this division is multiplied by 100,000;
- Fetal mortality: ratio between total fetal deaths and total births (live births and fetal deaths), in which it is multiplied by 1,000;
- Early neonatal mortality: ratio between total deaths from 0 to 6 days of life and total live births, which is multiplied by 1,000;
- Late neonatal mortality: ratio between total deaths from 7 to 27 days of life and total live births, which is multiplied by 1,000;
- Post-neonatal mortality: ratio between the number of deaths from 1 to 11 months of life and the total number of live births, which is multiplied by 1,000;
- Infant mortality: the ratio between the number of deaths of children under one year of age and the number of live births, multiplied by 1,000.

In this manuscript, the descriptive statistics of the collected data were performed using graphical and tabular representation, consisting of absolute and relative frequency. The statistical tests used were the Student's t-test and Mann Whitney. Statistical tests were performed at a significance level of 5%. The data were analyzed by the Statistical Package for Social Science (SPSS for Windows, version 24.0, SPSS Inc, Chicago, IL, USA).

RESULTS

In Figure 1 it is possible to observe the seasonal variation of the incidence rate of dengue in residents from 2007 to 2016 in the city of Campo Grande, Brazil. In fact, there was a high incidence in the years 2007, 2010, 2013 and 2016, which varied from 3,104 to 5,967 cases per 100,000 inhabitants. For the years 2009, 2011, 2012 and 2015, there was a variation from 776 to 1868 cases per 100,000 inhabitants. On the other hand, in 2008 and 2014 the rate was 499 cases per 100,000 inhabitants. The years 2007, 2010, 2013 and 2016 had rates above the endemic threshold, so are the epidemic years.

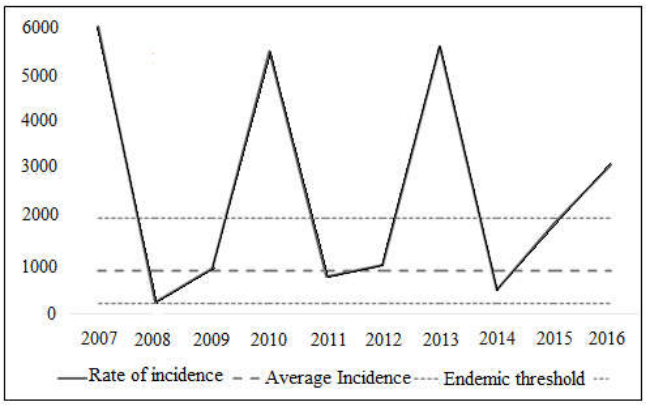

Figure 1 - Rates of incidence of dengue in residents from 2007 to 2016, Campo Grande / MS / Brazil. The mean incidence represents the arithmetic mean of the incidence rates of the endemic years (2008, 2009, 2011, 2012, 2014 and 2015). The endemic threshold represents the values corresponding to the mean incidence of more or less than 1.96 standard deviations.

According to the results shown in Table 1, which includes the incidence rate of dengue fever per year, for the epidemic years the Neonatal Mortality Coefficient was 4.8 and 7.8 per thousand live births. Compared to the endemic years the coefficient of live births was 3.9 and 5.7. On the other hand, for the other coefficients the minimum and maximum values were close between the epidemic and endemic years. In the epidemic and endemic years in the study period (2007 to 2016), the comparison of the mean values obtained from the coefficients of maternal mortality, neonatal and infant mortality reveals that there was statistical difference only for the coefficient of early neonatal mortality (Table 1 and Figure 2).

Table 1. Maternal Mortality Coefficients, Neonatal and Infant Coefficients, Campo Grande /MS, from 2007 to 2016

Years *	CMM	CMF	CMNP	CMNT	CMPN	CMI
2007	32,6	7.2	7,6	2,1	4,4	14,1
2008	31,2	8.8	5,7	2,7	4,8	13,3
2009	48,5	9.7	5,3	2,3	4,7	12,4
2010	46,9	8.9	6,1	2,5	4,6	13,2
2011	46,0	9.0	5,5	2,1	2,5	10,2
2012	59,1	5.8	4,4	1,4	2,8	8,6
2013	65,7	7.7	4,8	1,5	3,0	9,3
2014	21,1	7.9	3,9	1,3	2,7	8,0
2015	48,4	8.3	4,4	1,5	2,8	8,6
2016	43,8	8.3	5,6	1,5	3,5	10,7
2007 - 2016 Mean ± Standard deviation						
Epidemic years	47,3± 13,8	8,0 ± 0,7	6,0 ± 1,2	1,9 ± 0,1	3,9 ± 0,1	11,8± 2,2
Endemic years	42,4± 13,7	8,3 ± 1,4	4,9 ± 0,1	1,9 ± 0,1	3,4 ± 1,1	10,2± 2,2
p **	0,299	0,771	0,044	0,482	0,225	0,142

Observations: data from SIM / Dis / Ses / MS.
CMM = Coefficient of maternal mortality per 100,000 resident mothers
CMF = Coefficient of fetal mortality per 1,000 total births
CMNP = Coefficient of Early Neonatal Mortality per 1,000 live births
CMNT = Coefficient of late Neonatal Mortality per 1,000 live births
CMPN = Coefficient of Post-Neonatal Mortality per 1,000 live births
CMI = Child Mortality Coefficient per 1,000 live births
* Epidemic years in bold (2007, 2010, 2013 and 2016) with a frequency of more than 3,000 cases of dengue fever per 100,000 inhabitants.
** *p* in bold indicates a statistically significant difference between the epidemic and endemic years. Student's t-test for independent samples.

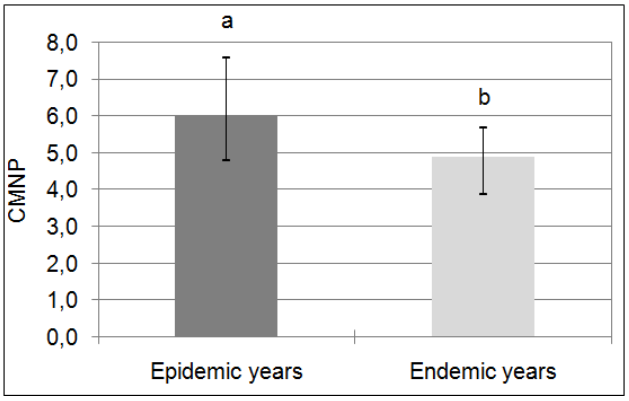

Figure 2. Mean, minimum and maximum values of the Coefficient of Early Neonatal Mortality (CMNP) according to the epidemic years (2007, 2010, 2013 and 2016) and endemic (2008, 2009, 2012, 2014, 2015) obtained in Campo Grande- MS, 2007 to 2016. The column represents the average of the CMNP; the vertical line represents the amplitude between the lowest and highest value of the CMNP. The different letters indicate a statistically significant difference (*p* = 0.044 - Student's t test for independent samples)

Table 2. Coefficient of Early Neonatal Mortality according to the ICD-10 category per 1,000 live births and the number of dengue cases *, Campo Grande, Mato Grosso do Sul, 2007 to 2016.

Category ICD-10	Years		*p*
	* Epidemics	Endemics	
	Mean ± Standard deviation		
Congenital syphilis	6,03 ± 1,16	4,88 ± 0,73	** 0,044
Neoplasms	0,02 ± 0,04	0,01 ± 0,03	*** 0,375
Cardiomyopathies	0,02 ± 0,04	0,00 ± 0,00	*** 0,261
Disorders, infections or affections of the perinatal period	4,62 ± 1,26	3,58 ± 0,69	** 0,062
Congenital malformations, deformities and chromosomal abnormalities	1,29 ± 0,28	1,24 ± 0,33	** 0,399
External causes of morbidity and mortality	0,04 ± 0,04	0,05 ± 0,04	*** 0,335

Observations: The data obtained in this table comes from the SIM / Dis / Ses / MS.
* epidemic years (2007, 2010, 2013 and 2016) with more than 3,000 cases of dengue per 100,000 inhabitants.
** Student's t-test for independent samples. *p* in bold indicates a statistically significant difference between the epidemic and endemic years.
*** Mann Whitney test for independent samples.

Table 2 shows the mean and standard deviation of the coefficients of early neonatal mortality between the epidemic and endemic years in the study period (2007 to 2016) according to ICD-10 categories. Early neonatal deaths were recorded. There was a statistical difference between the coefficients between the epidemic and endemic years only for congenital syphilis. There was no record of early neonatal death due to dengue in the SIM.

DISCUSSION

In the present study, there were higher values of the coefficient of early neonatal mortality in the epidemic years for dengue compared to the endemic years. There were no statistically significant differences in maternal mortality, fetal mortality, or other mortality rates in neonates (late neonatal, post-neonatal and infant). However, the association between dengue virus infection in the gestational period and the occurrence of early neonatal deaths was observed in a cohort study involving pregnant women exposed and not exposed to the dengue virus in the period 2007-2012 in the city of Rio Branco, Acre, Brazil. The risk ratio observed for the outcome of early neonatal death was 6.8 (IC 95%: 1,61 -28,75) (Feitoza *et al.*, 2017). In fact, the associated risk apparently depends on the epidemic level (Hanf *et al.*, 2013). Asymptomatic pregnant women are not included in several studies, since do not show signs or symptoms of dengue, and serology tests for dengue are not performed and therefore are not reported. Since they are not notified, the effects resulting from infection in the concept are not attributed to dengue infection. Additionally, the notification number of dengue cases increases in the second and third trimester of pregnancy, since in the first trimester, the woman in the reproductive phase may even be unaware that she is pregnant (Friedman *et al.*, 2014; Paixão *et al.*, 2016; Carles, 2016; Brasil and Lupi, 2017).

In view of the aforementioned, the present study presents a positive aspect when using the maternal, fetal and infant mortality coefficients of the entire population, and a comparison of the values between epidemic and endemic years, which would minimize the non-notification of asymptomatic ones for dengue. However, in the ecological study it is not directly known if those exposed to a disease had a certain effect, in this sense, early neonatal mortality could have been caused by other causes and not only by dengue infection. Due to this limitation, early neonatal mortality was analyzed according to ICD-10 categories, in which there was some early neonatal death. The results showed that there was a statistical difference between epidemic and endemic years for congenital syphilis. Regarding the cause attributed to neonatal death according to the ICD-10 category, there are limitations in the use of data from health information systems related to mortality, since they are provided continuously by the information contained in the death certificates. There is a tendency to attribute maternal diseases, such as hypertensive diseases, diabetes and syphilis, as causes of fetal and neonatal death (Barbeiro *et al.*, 2015). Those circumstances may explain the higher frequency of congenital syphilis reported in the present study. The use of information generated from secondary data always requires caution, since the calculation of the selected indicators is sensitive to the limitations of Brazilian health information systems. The SIM presents as deficiencies the inadequate fulfillment of the declarations of death and the underreporting of deaths, especially with regard to stillbirths and fetal and perinatal deaths.

SINAN's main limitation is the underreporting of dengue case (Mota *et al*., 2012), which was observed in the present study, since there was no record of early neonatal dengue death.

Conclusion

The use of maternal, fetal, and infant mortality coefficients of a population and comparison between annual epidemic and endemic values minimizes the lack of notification of asymptomatic symptoms for dengue. There was an association between early neonatal mortality and the epidemic level. The results presented in this manuscript are consistent with other studies that consider the effects of dengue infection during pregnancy, obstetric and pediatric risks.

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