MICROCEPHALY INFANT MORTALITY IN BRAZIL BEFORE ZIKA OUTBREAK.

MORTALIDAD INFANTIL POR MICROCEFALIA ANTES DEL BROTE DE ZIKA EN BRASIL.

MORTALIDADE INFANTIL DEVIDO À MICROCEFALIA ANTES DO SURTO DE ZIKA NO BRASIL.

José Edgardo Dipierri[1], José Lavinia Schuler-Faccini[2], Valeria Fernanda Chapur[3], Rubén Adrián Bronberg[4].

1- Universidad Nacional de Jujuy. Instituto de Biología de la Altura; Jujuy, Argentina.

2- Universidade Federal do Rio Grande do Sul. Departamento de Genética; Porto Alegre, Brasil. Hospital de Clínicas de Porto Alegre. Serviço de Genética Médica; Porto Alegre, Brasil.

3- Universidad Nacional de Jujuy. Instituto de Ecoregiones Andinas. Instituto de Biología de la Altura, Consejo Nacional de Investigaciones Científicas y Técnicas; Jujuy, Argentina.

4- Hospital General de Agudos Dr. José María Ramos Mejía. Área de Genética Médica y Poblacional, Unidad de Neonatologia; Buenos Aires, Argentina. Email de contacto: rabronberg@intramed.net

Conceptos clave:

A) What is known about the subject?
As from 2015, an increase in Zika cases and infants with microcephaly has been recorded in Brazil. However there is scarce information on microcephaly in Brazil before the Zika outbreak.
B) What does this work contribute?
The analysis of the temporal and spatial distribution pattern of child deaths from microcephaly may provide evidence about the behavior of microcephaly in the Brazilian population before the Zika outbreak.

Abstract:

Introduction: We present temporal and spatial variation of deaths from microcephaly in children under 1 year of age is analyzed at regional, state, and municipal level in the pre-Zika period in Brazil.
Materials and Methods: Data on births and deaths of infants with microcephaly was obtained from DATASUS from 1996 to 2013. Infant mortality rate from microcephaly (IMR-M) was estimated at Region, Federative Unit (UF), and Municipality level. Secular trend (ST) and risk of death variation were estimated using a Poisson regression model. Satscan software was used to obtain a statistic spatial scan for the Poisson model.
Results: IMR-M shows a non-significant negative ST in the Southeast, South and Central West Regions of Brazil. A greater IMR-M risk of death variation is found in the North and Northeast Regions. Most UFs in the Southeast, South and Central West Regions showed a negative ST, in contrast to what occurs in the UFs of the North and Northeast Regions showed a positive ST. Six high risk significant clusters were found: 3 in the North-Northeast and 3 in the South-SouthWest-Center-West.
Conclusions: The North and Northeast Regions showed positive ST for IRM-M and higher death risk, which was not observed in the other regions. Cluster distribution for higher IMR-M and risk resembles the distribution of the microcephaly and Zika cases in the outbreak period.

Keywords: infant mortality; microcephaly; Brazil.

Resumen:

Introducción: Presentamos la variación temporal y espacial de las muertes por microcefalia en niños menores de 1 año de edad que se analizan a nivel regional, estatal y municipal en el período pre-Zika en Brasil.
Materiales y métodos: Los datos sobre nacimientos y muertes de niños con microcefalia se obtuvieron de DATASUS de 1996 a 2013. La tasa de mortalidad infantil por microcefalia (TMI-M) se estimó a nivel de Región, Unidad de Federativa (UF) y Municipio. La tendencia secular (TS) y la variación del riesgo de muerte se estimaron utilizando un modelo de regresión de Poisson. El análisis estadístico espacial fue realizado por un modelo de Poisson utilizando el software Satscan.
Resultados: La TMI-M muestra un TS negativo no significativo en las regiones sudeste, sur y centro-oeste de Brasil. Una mayor variación de riesgo de muerte se encuentra en las regiones Norte y Noreste. La mayoría de las UF en las regiones Sureste, Sur y Centro-Oeste mostraron un TS negativa, en contraste con lo que ocurre en las UF de las Regiones Norte y Noreste mostraron una TS positiva. Se encontraron seis agrupamientos significativos de alto riesgo: 3 en el Norte-Noreste y 3 en el Sur-Sur-Oeste-Centro-Oeste.
Conclusiones: Las regiones Norte y Noreste mostraron una TS positiva para la TMI-M y un mayor riesgo de muerte, que no se observó en las otras regiones. La distribución de los agrupamientos de mayor TMI-M y riesgo se asemeja a la distribución de los casos de microcefalia y Zika en el período del brote.

Palabras clave: mortalidad infantil; microcefalia; Brasil.

Resumo

Introdução: Apresentamos a variação temporal e espacial das mortes por microcefalia em crianças menores de um ano de idade analisadas nos níveis regional, estadual e municipal no período pré-zika no Brasil.
Materiais e métodos: Os dados sobre o nascimento e morte de crianças com microcefalia é obtido DATASUS 1996 a 2013. A taxa de mortalidade infantil por microcefalia (IMR-M) foi estimada região nível, UF (UF) e município. A tendência secular (ST) e a variação do risco de morte foram estimadas usando um modelo de regressão de Poisson. A análise estatística espacial foi realizada por um modelo de Poisson utilizando o software Satscan.
Resultados: O IMR-M mostra um ST negativo não significativo nas regiões sudeste, sul e centro-oeste do Brasil. Uma maior variação no risco de morte da IMR-M é encontrada nas regiões Norte e Nordeste. A maioria das UF nas regiões Sudeste, Sul e Centro-Oeste apresentou um ST negativo, ao contrário do que ocorre na UF das Regiões Norte e Nordeste, que apresentou um ST positivo. Seis grupos significativos de alto risco foram encontrados: 3 no Norte-Nordeste e 3 no Sul-Sul-Oeste-Centro-Oeste.
Conclusões: As regiões Norte e Nordeste apresentaram um ST positivo para RM e um aumento do risco de morte, o que não foi observado nas demais regiões. A distribuição dos grupos de maior IMR-M e risco assemelha-se à distribuição dos casos de microcefalia e zika no período do surto.

Palavras-chave: mortalidade infantil; microcefalia; Brasil.

Recibido: 2019-08-15 **Aceptado:** 2019-09-14

DOI: http://dx.doi.org/10.31053/1853.0605.v76.n4.25172

Introduction

In March 2015, Campos et al.[1] identified a Zika virus infection - a flavivirus transmitted by Aedes mosquitoes - in Brazil, associated with a recent ongoing outbreak in Camaçari, Bahia, Brazil. This outbreak appeared in the dengue virus dispersal area. Since then, its spread has been confirmed in the five regions of the country, thus featuring an outbreak[2]. The Brazilian national authorities estimate that up to a 1.5 million cases of Zika virus infection have occurred since the outbreak began[3].

In September 2015, reports about an increase in the number of children born with microcephaly in the areas of the country affected by the Zika virus began to appear[4]. In November 2015, the Brazilian Ministry of Health suggested a relationship between Zika virus and the microcephaly outbreak in the Northeast. The Evandro Chagas Institute in Belen forwarded the results of tests carried out on a baby born in Ceará with microcephaly and other congenital malformations. The presence of the Zika virus was identified in blood and tissues of this baby[5].

Acknowledging the magnitude of the problem, a register of new cases of microcephaly was established by the government of Brazil through the Ministry of Health[6], and a Scientific Working Group on Zika Virus through the Ministry of Science Technology and Innovation. An epidemiologic report of the Ministry of Health on suspected cases of microcephaly related to Zika virus ZIKV, updated as at August 27, 2016, details that 9,172 suspected cases were reported until that date in newborns from 1639 municipalities from 27 Federative Units[7]. According to one report[8], 5,909 suspected cases of microcephaly were reported between July 2015 and February 2016, including newborns and fetal losses (6%), where 1501 cases completed clinical, laboratory and image examinations. Of these 1501 cases, 40.1% (n=602) were classified as confirmed cases of microcephaly, the remaining 899 cases were ruled out, and 3670 suspected cases continue under evaluation. In this communication[8], Zika virus or IgM positive results in cerebrospinal fluid (CSF) were detected in 76 babies, including two fetal losses.

In February 2016[9], WHO states that the recent cluster of microcephaly cases and other neurological disorders reported in Brazil, following a similar cluster in French Polynesia in 2014, constituted a Public Health Emergency of International Concern (PHEIC).

Rasmussen et al. recognized the association between prenatal exposure to ZIKV and brain disruption[10]. Martines et al.[11] describe evidence of a link between Zika virus infection and microcephaly and fetal demise through detection of viral RNA and antigens in brain tissues from infants with microcephaly and placental tissues from early miscarriages. Calvet et al.[12] detected the Zika virus genome in the amniotic fluid of two pregnant women. Although an association between microcephaly and congenital infection by Zika has been confirmed, the real magnitude of this increase is still controversial. In addition, apparently there is evidence of a seasonal increase in microcephaly in newborns in Paraiba (Northeast Brazil), one of the nine States within the epicenter of the epidemic, before the 2015 Zika outbreak. Sousa Soares de Araújo et al.[13] collected the occipital-frontal head circumference from 16,208 neonates born between January 1st, 2012 and December 31st, 2015 in 21 different public health centers from Paraíba. In this study, regardless of the classification criteria used, a higher incidence of microcephaly between 2012 and 2015 was demonstrated.

Considering this issue, Barreto et al.[14] deems necessary to enlarge the basis of evidence of infection, diseases, and potential outcomes, among other aspects, to go deeper into the epidemiologic understanding of microcephaly and Zika. Since no sufficient information on microcephaly prevalence in newborns in Brazil before the Zika outbreak exists, reference to other apparently unrelated data sources that might also contain important information is necessary[15].

This study analyzes temporal (1996-2013) and spatial variation of deaths from microcephaly in children under one year old in Brazil at Region, Federative Unit, and Municipality level. The analysis of the temporal and spatial distribution pattern of child deaths from microcephaly may provide evidence about the behavior of microcephaly in the Brazilian population before the Zika outbreak.

Materials and Methods

This ecological and population study gathers information from databases of births and infant deaths that occurred in Brazil, collected by the Ministry of Health Information Department of the Unified Health System (*Sistema Único de Saúde*, Ministério de Saúde) of Brazil (Datasus) (http://www2.datasus.gov.br/DATASUS/index.php?area=01) between 1996 and 2013. Information on infant deaths due to microcephaly came specifically from the Mortality Information System, (*Sistema de Informações sobre Mortalidade,* SIM).

Data were analyzed with reference to the maternal place of residence. The variables used were: a) number of live births (NLB), b) number of infant deaths (<1 year old) from microcephaly coded by ICD-X (Q002 Code). Based on these figures and regardless of gender, the Infant Mortality Rate by Microcephaly (IMR-M) (infant deaths from microcephaly / 10000 LB) was computed at temporal and spatial levels. At space level calculations were performed for the whole country, 5 geographic regions (North, Northeast, Southeast, South and Central West), 27 States (Rondonia, Acre, Amazonas, Roraima, Pará, Amapá, Tocantins, Maranhão, Piauí, Ceará, Rio Grande do Norte, Paraíba, Pernambuco, Alagoas, Sergipe, Bahia, Minas Gerais, Espirito Santo, Rio de Janeiro, Sao Paulo, Paraná, Santa Catarina, Rio Grande do Sul, Mato Grosso do Sul, Mato Grosso, Goiás, Federal District) and 5600 municipalities[16]. Temporal secular trend (ST) and risk of death variation for the entire country was evaluated at regional and state levels, with rates and percentages calculated using a Poisson regression model. In order to realize the temporal analysis and the applied mathematical model, the total period was subdivided into three subgroups: 1996-2001 (baseline), 2002-2007 and 2008-2013. In order to detect areas with rates and percentages of death from microcephaly significantly different from the nationwide rates and percentages, a cluster analysis was performed at municipal level using SaTScan v5.1 Software that allows identification of clusters and verifies whether these are statistically significant[17].

Results

As evidenced in Table 1, IMR-M shows a non-significant negative ST throughout Brazil, as well as in the Southeast, South and Central West Regions. In contrast, ST is positive in the North and Northeast regions, but only significant in the North Region, with an IMR-M for 2008-2013 (0.267) almost duplicating the baseline for 1996-2001 (0.152). The highest death risk from microcephaly was found in the North Region, followed by the Northeast, South, Southeast, and Central West Regions; but the risk is only significant in the North Region, compared to the baseline (1996-2001). All the Federative Units of the Southeast, South, and Central West Regions, except Minas Gerais, showed a non-significant negative ST. In contrast, almost all the Federative Units of the North and Northeast Regions, except Acre, Maranhao, Ceará, and Rio Grande do Norte, showed a positive ST only significant in the States of Amazonas and Bahia. None of the Federative Units, except the State of Bahía, showed a statistically significant death risk from microcephaly in children under 1 year of age, compared to the baseline; however, higher risks (>2) were found in the States of Rondonia, Amazonas and Piauí, in the Northeast Region. The lowest risk was found in the Federal District (Table 1).

Table N°1: Infant mortality rate from microcephaly (IMR-M), Secular trend and Relative Risk in sub-period 2008-2013, compared to basal sub-period 1996-2001 by Regions and Federative Units.

Region /FU	Microcephaly	Sub-Periods			Secular trend	Relative risk
	(n)	1996-2001	2002-2007	2008-2013	(1996-2013)	
Brazil	**911**	**0.17**	**0.18**	**0.16**	**-0.001**	**0.96**
North	**105**	**0.15**	**0.16**	**0.27**	**0.046***	**1.75***
Rondônia	12	0.11	0.25	0.38	0.071	3.45
Acre	8	0.34	0.20	0.29	-0.022	0.85
Amazonas	26	0.14	0.16	0.31	0.089*	2.22
Roraima	2	0.38	0.00	0.00	0.364	-
Pará	46	0.14	0.17	0.25	0.032	1.75
Amapá	2	0.00	0.00	0.22	0.678	-
Tocantins	9	0.19	0.13	0.27	0.048	1.39
Northeast	**247**	**0.13**	**0.18**	**0.16**	**0.019**	**1.24**
Maranhão	24	0.13	0.13	0.10	-0.066	0.53
Piauí	19	0.11	0.21	0.30	0.086	2.87
Ceará	40	0.16	0.21	0.13	-0.008	0.82
Rio Grande do Norte	21	0.29	0.26	0.10	-0.052	0.35
Paraíba	15	0.06	0.27	0.09	0.003	1.36
Pernambuco	38	0.11	0.18	0.13	0.010	1.14
Alagoas	13	0.10	0.11	0.15	0.05	1.52
Sergipe	2	0.00	0.00	0.10	0.519	-
Bahia	75	0.12	0.20	0.23	0.047*	1.90*
Southeast	**328**	**0.17**	**0.16**	**0.13**	**-0.019**	**0.79**
Minas Gerais	85	0.16	0.18	0.19	0.014	1.22
Espírito Santo	22	0.26	0.22	0.19	-0.010	0.74
Rio de Janeiro	81	0.25	0.16	0.15	-0.033	0.61
São Paulo	140	0.14	0.13	0.10	-0.031	0.71
South	147	**0.19**	**0.25**	**0.16**	**-0.012**	**0.81**
Paraná	68	0.21	0.32	0.16	-0.008	0.79
Santa Catarina	23	0.14	0.18	0.12	-0.007	0.83
Rio Grande do Sul	56	0.21	0.23	0.17	-0.017	0.83
Central West	**84**	**0.26**	**0.18**	**0.17**	**-0.022**	**0.65**
Mato Grosso do Sul	24	0.28	0.50	0.20	-0.011	0.72
Mato Grosso	16	0.24	0.14	0.17	-0.027	0.70
Goiás	32	0.26	0.11	0.20	-0.004	0.79
Federal District	12	0.28	0.07	0.08	-0.092	0.27

Reference: *p≤0.05, significant level

Fig. 1 shows the distribution of the 6 clusters with a IMR-M significantly higher than the countrywide, three in the North and Northeast Regions, and 3 in the South and Southeast Regions. Deaths from microcephaly in children under 1 year of age were found in only 581 randomly distributed municipalities of the total of 5568 in Brazil, but there are only 232 (40%) high risk cluster municipalities distributed in the North and Center-South part of the country. Table 2 shows details about IMR-M, risk, Regions, States, and number of Municipalities included for each cluster.

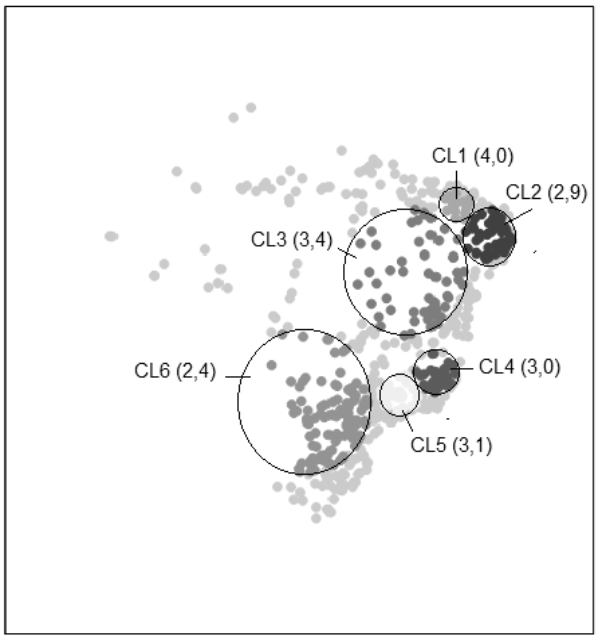

Figura N°1. High risk of rate of infant mortality from microcephaly (IMR-M) and relative risks (in parentheses) of clusters (CL) represented in a scatter plot of coordinates.

Table 2: Infant mortality rate from microcephaly (IMR-M), Secular trend and Relative Risk in Brazil by clusters.

Microcephaly (n)	Live borns (n)	IMR-M *10^4	Relative Risk	Regions	Federative Units	Municipalities (n)
16	120926	1.32	4.00	Northeast	Ceará Piauí	15
55	591388	0.93	2.89	Northeast	Ceará, Rio Grande, Paraíba, Pernambuco, Alagoas, Bahía	46
62	578507	1.07	3.36	North, Northeast Center-Western	Pará, Tocantins, Maranhao, Piauí, Pernambuco Bahia, Minas Gerais, Goiás	53
29	297680	0.97	2.97	Southeast	Minas Gerais, Espíritu Santo, Rio de Janeiro	26
35	346078	1.01	3.10	Southeast	Sao Paulo, Rio de Janeiro, Minas Gerais	32
135	1828231	0.74	2.41	Southeast, South, Center-Western	Sao Paulo, Paraná, Santa Catarina, Rio Grande do Sul, Mato Grosso do Sul, Mato Grosso, Goiás	102

Reference: *p≤0.05, significant level

Discussion

Regardless of age, 1,679 deaths from microcephaly occurred in Brazil as a whole in the analyzed period of time (1996-2013), where 54.2% (911 cases) refer to children under 1 year of age analyzed herein (Table 1). These numbers are quite different from of a total reported cases between 2015-2016 (n=10,867), of which 582 (5.3%) evolved to fetal or neonatal death[18]. These figures suggest that neonatal mortality from Zika-related microcephaly is low, and thus the mortality rates from this cause may only provide fragmentary evidence or a partial view of the occurrence of this malformation[15]. However, the percentages of neonatal mortality in suspected cases of microcephaly provided by COES contrast with the information provided by ECLAMC[19] about the lethality of this malformation, where the birth death rate in congenital microcephaly is usually high, since 6% of the cases are stillborn and 24% suffer neonatal death.

The code assigned by the CIE-10 to microcephaly (Q02) specifically identifies this malformation as a major isolated structural malformation, as defined by the International Clearing House for Birth Defect as a congenitally small cranium, with an occipito-frontal circumference 2 standard deviations below the age- and sex-appropriate distribution curves. This definition excludes microcephaly associated with anencephaly or encephalocele. However, in addition to congenital infections, microcephaly may result from other conditions (chromosomal abnormalities; exposure to drugs, alcohol, or other environmental toxins; premature fusion of the bones of the skull or craniosynostosis, and certain metabolic disorders) with which it may eventually be confused[6]. The herein provided information about deaths from microcephaly occurred in Brazil before the Zika outbreak must be understood in the context of these limitations.

Noteworthy, this analysis took into account the place of residence of the deceased child and its mother, thus preventing the hospital derivation phenomenon that occurs when a high complexity hospital starts receiving prenatally diagnosed cases for the birth, thus altering the actual prevalence in a specific town or region[18].

Taking only the number of deaths from microcephaly into account, the Southeast Region has the greatest number of cases, followed by the Northeast, South, and Central West Regions (Table 1). This distribution may be due to the effect of population size of each of the regions with the same distribution as the number of cases with microcephaly. However, when the rate between the number of children's deaths from microcephaly and the total population of the region is computed (year 2012) the highest value is found in the North region ($6.4*10^3$), followed by the Central West ($5.8*10^3$), the South ($5.3*10^3$), the Northeast ($4.6*10^3$), and the South ($4.1*10^3$) Regions.

When IMR-M between sub-periods is compared, a spatial change is found between 1996-2001 and 2008-2013, characterized by a rate increase in the North area of the country. Indeed, in the 1996-2001 period, the highest IMR-M is found in the Central West Region, followed by the South, Southeast, North, and Northeast Region; in contrast, in the 2008-2013 period, the highest IMR-M is found in the North Region, followed by the Northeast, Central West, South, and Southeast Regions (Table 1). This spatial IMR-M change is expressed by a higher and more significant increase in death risk from this malformation in the North Region, followed by the Northeast, South, Southeast, and Central West Region, and a positive ST in the North and Northeast Regions (Table 1).

Noteworthy, the State of Paraíba, where a much higher than expected incidence of microcephaly was observed (varying from 2% to 8% according to the classification criteria applied) showed a very low and non-significant ST, and a decrease in IMR-M in the 2008-2013 period, before the analyzed period[13].

Noteworthy, cluster 1, located in the Northeast and mainly comprising the municipalities of the States of Ceará and Piauí, shows higher relative risk (4.0) and IMR-M (1.32) (Table 2). One of the strongest epidemiologic evidences relating the Zika virus and Microcephaly is expressed by the temporal and spatial coincidence of the cases of Zika and microcephaly. Fig. 1 shows that the distribution of the clusters of highest risk of death from microcephaly is similar to the distribution of the microcephaly cases recorded in the period 08/11/2015 - 26/03/2016[20] and the cases of Zika recorded in the country from April 2015 to the Epidemiologic Week 8 of 2016[21].

Conclusion

The epidemiology of infant mortality from microcephaly in the 1996-2013 period is characterized by: (1) A temporal and spatial IMR-M variation; (2) compared with the South Regions, the North Regions show a negative ST of IMR-M; (3) the North Regions show higher IMR-R than the South Regions; (4) the municipal clusters with higher IMR-R risk tend to be located in the North and Central West part of the country; (5) the spatial image of the clusters with highest IMR-M and risk is similar to the distribution of the reported cases of microcephaly and Zika since mid-2015[22].

Conflictos de interés y cesión de derechos

Los autores declaran no tener conflicto de interés, siendo responsables de lo escrito y cediendo el derecho de autor a la Universidad Nacional de Córdoba para publicar en la RFCM.

Fuentes de Financiamiento

Este trabajo no ha tenido fuente de apoyo alguna

References

1. *Campos GS, Bandeira AC, Sardi SI. Zika Virus Outbreak, Bahia, Brazil. Emerg Infect Dis 2015; 21(10):1885–1886.*
2. *Portal da Saúde. Confirmação do Zika Vírus no Brasil. Ministerio da Saúde 2015. Available from: http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/secretarias/svs/noticias-svs/17702-confirmacao-do-zika-virus-no-brasil.*
3. *WHO 2016. WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. Feb 1, 2016. Available from: http://www.who.int/mediacentre/news/statements/2016/ .*
4. *Schuler-Faccini L, Ribeiro EM, Feitosa IM. Possible Association Between Zika Virus Infection and Microcephaly — Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016; 65:59–62.*
5. *Portal da Saúde. Ministério da Saúde confirma relação entre vírus zika e casos de microcefalia. Ministerio da Saúde 2015. Available from: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/21014-ministerio-da-saude-confirma-relacao-entre-virus-zika-e-microcefalia.*
6. *Schuler-Faccini L, Ribeiro EM, Feitosa IM, Horovitz DD, Cavalcanti DP, Pessoa A, Doriqui MJ, Neri JI, Neto JM, Wanderley HY, Cernach M, El-Husny AS, Pone MV, Serao CL, Sanseverino MT. Brazilian Medical Genetics Society–Zika Embryopathy Task Force Possible Association Between Zika Virus Infection and Microcephaly - Brazil, 2015. Morb Mortal Wkly Rep 2016; 65(3):59-62.*
7. *Portal da Saúde 2016. Centro De Operações De Emergências Em Saúde Pública Sobre Microcefalias. Informe Epidemiológico Nº 33 – Semana Epidemiológica (Se) 26/2016 (26/06 A 02/07/2016) Monitoramento Dos Casos De Microcefalia No Brasil. Available from: http://portalsaude.saude.gov.br/images/pdf/2016/julho/08/Informe-Epidemiol--gico-n---33--SE-26-2016--05jul2016-22h30.pdf*
8. *Franca, G.V., Schuler-Faccini, L., Oliveira, W.K., Henriques, C.M., Carmo, E.H., Pedi, V.D., Nunes, M.L., Castro, M.C., Serruya, S., Silveira, M.F., Barros, F.C., Victora, C.G. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. Lancet 2016;27;388 (10047):891-7*
9. *WHO 2016. Zika situation report. Zika and potential complications. Available from: http://www.who.int/emergencies/zika-virus/situation-report/who-zika-situation-report-12-02-2016.pdf?ua=1.*
10. *Rasmussen, S, Jamieson D, Honein M, Petersen L. Zika Virus and Birth Defects Reviewing the Evidence for Causality. N Engl J Med 2016; 374:1981-1987*
11. *Martines, R, Bhatnagar J, Keating M, et al. Notes from the field: evidence of Zika virus infection in brain and placental tissues from two congenitally infected newborns and two fetal losses—Brazil, 2015. MMWR. Morbidity and mortality weekly report 2016; 65.*
12. *Calvet G, Aguiar RS, Melo AS, Sampaio SA, de Filippis I, Fabri A, Araujo ES, de Sequeira PC, de Mendonça MC, de Oliveira L, Tschoeke DA, Schrago CG, Thompson FL, Brasil P, Dos Santos FB, Nogueira RM, Tanuri A, de Filippis AM. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. Lancet Infect Dis 2016; S1473-3099(16)00095-5.*
13. *Soares de Araújo JS, Regis CT, Gomes RGS, et al. Microcephaly in northeast Brazil: a review of 16 208 births between 2012 and 2015. Bull World Health Organ E-pub 2016:*
14. *Barreto ML, Barral-Netto M, Stabeli R, Almeida-Filho N, Vasconcelos PF, Teixeira M, Buss P, Gadelha PE. Zika virus and microcephaly in Brazil: a scientific agenda. Lancet 2016; S0140-6736(16)00545-6.*
15. *Byass P, Wilder-Smith A utilising additional sources of information on microcephaly. Lancet 2016; S0140-6736(16)00519-5.*
16. *IBGE 2012. The Brazilian Institute of Geography and Statistics. Available from: http:// www.ibge.gov.br/home/mapa_site/mapa_site.php.*
17. *Kulldorff M, Huang L, Konty K. A scan statistic for continuous data based on the normal probability model. Int J Health Geogr 2009; 8:58.*
18. *COES Microcefalia 2016 (Centro de Operações de Emergências em Saúde Pública Sobre Microcefalias). Informe Epidemiológico Nº 41 – Semana Epidemiológica (SE) 34/2016 (21/08 a 27/08/2016). Monitoramento dos casos de microcefalia no Brasil. Ministerio de Saude do Brasil . Available from: www.saude.gov.br*
19. *ECLAMC 2016. DOCUMENTO ECLAMC FINAL. Resumo e conclusões dos Documentos 1-5. Bue, 30 de dezembro, 2015. Available from: http://www.eclamc.org/microcefaliaarchivos.php.*
20. *COES Microcefalia 2016 (Centro de Operações de Emergências em Saúde Pública Sobre Microcefalias). Informe Epidemiológico Nº 41 – Semana Epidemiológica (SE) 34/2016 (21/08 a 27/08/2016). Monitoramento dos casos de microcefalia no Brasil. Ministerio de Saude do Brasil . Available from: www.saude.gov.br*
21. *Boletim Epidemiológico. Secretaria de Vigilância em Saúde. Ministério da Saúde 2016; 47 (14).*
22. *COES Microcefalia 2017 (Centro de Operações de Emergências em Saúde Pública Sobre Microcefalias). Informe Epidemiológico Nº 47 – Semana Epidemiológica (SE) 52/2016 (25/12 a 31/12/2016). Monitoramento dos casos de microcefalia no Brasil. Ministerio de Saude do Brasil . Available from: www.saude.gov.br*