Original Article

Reproductive and Developmental Medicine®

Microcephaly prevalence after the 2015 to 2016 Zika outbreak in Tangará da Serra, Brazil: a population-based study

Juliana Herrero da Silva[1,2], Ana Claudia Pereira Terças-Trettel[3,4], Juliano André Boquett[2,5,6], Giovanny Vinicius Araujo Franca[7], Augusto Cesar Cardoso-dos-Santos[2,7], Marina Atanaka[4], Marcelo Zagonel Oliveira[5,8], Anna Pires Terra[2], Viviane Karoline Vivi[4], Lucia Andreia Nunes de Oliveira[9], Lucia Schaedler[10], Ronaldo Fernandes Santos Alves[7], Lavinia Schuler-Faccini[2,5,6,*]

Abstract

Objective: Prenatal infection with the Zika virus (ZIKV) can lead to congenital Zika syndrome (CZS), characterized by microcephaly and brain injury. However, there are questions regarding the prevalence of microcephaly/CZS after the ZIKV outbreak in defined geographic areas. This study aimed to identify adverse outcomes in live births of fetuses exposed in utero to the ZIKV, compared to unexposed births, as well as maternal sociodemographic, delivery, and birth characteristics.

Methods: Here, we conducted a cross-sectional observational study to investigate the characteristics of all live births in the city of Tangará da Serra, Mato Grosso, Brazil, in 2016, after the outbreak of ZIKV infection in late 2015. All live births of children to women residing in the municipality of Tangará da Serra between January 1 and December 31, 2016, were evaluated, and head circumference was measured at birth and after 24 hours. Children born with microcephaly or a maternal history of confirmed or suspected prenatal ZIKV infection were evaluated by a multidisciplinary team. The outcomes of the exposed and non-exposed children were compared. Prevalence ratios and their respective 95% confidence intervals were calculated for sociodemographic, delivery, and live birth characteristics.

Results: Of 1,441 live births, 106 (7.3%) were from mothers with confirmed or highly probable exposure to ZIKV. The prevalence of severe congenital microcephaly (41.7/10,000) in Tangará da Serra in 2016 was ten-fold higher than that in Latin America before 2015.

Conclusion: This study may serve as a model to investigate possible outbreaks of infections in a defined geographical space in the future.

Keywords: Epidemiology, Live births, Microcephaly, Zika virus

[1] Prefeitura Municipal de Tangará da Serra, Secretaria de Saúde, Vigilância Epidemiológica, Tangará da Serra, Brazil; [2] Programa de Pós-Graduação em Genética e Biologia Molecular, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; [3] Universidade do Estado de Mato Grosso, Tangará da Serra, Brazil; [4] Programa de Pós-Graduação em Saúde Coletiva, Universidade Federal de Mato Grosso, Cuiabá, Brazil; [5] Instituto Nacional de Genética Médica Populacional – INaGeMP, Serviço de Genética Médica, Hospital de Clinicas de Porto Alegre (HCPA), Porto Alegre, Brazil; [6] Programa de Pós-Graduação em Saúde da Criança e do Adolescente, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; [7] Secretaria de Vigilância em Saúde, Ministério da Saúde, Brasília, Brazil; [8] Laboratório de Visualização Avançada e Geoinformática (VIZLab), Programa de Pós-Graduação em Computação Aplicada, Universidade do Vale do Rio dos Sinos, São Leopoldo, Brazil; [9] Programa de Pós-Graduação em Ciência da Informação, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; [10] Clínica Santa Luzia, Tangara da Serra, Brazil.

[*] Corresponding to: Lavinia Schuler-Faccini, Departamento de Genética, Universidade Federal do Rio Grande do Sul, Caixa Postal 15053 – Agencia Campus UFRGS, Brazil. E-mail: lavinia.faccini@ufrgs.br

Reproductive and Developmental Medicine (2022) 6:2

Received: 21 November 2021 **Accepted:** 17 April 2022

http://dx.doi.org/10.1097/RD9.0000000000000020

Introduction

In 2015, after the first confirmed outbreak of the Zika virus (ZIKV) in the Americas, there was a rapid and significant increase in the number of births of children with microcephaly. In 2016, the association between prenatal ZIKV infection and the development of congenital brain anomalies with consequent microcephaly was formally confirmed, and congenital Zika syndrome (CZS) was described[1–6]. Studies indicate that the majority of individuals infected with ZIKV can be asymptomatic or have mild symptoms, making clinical diagnosis difficult with low sensitivity. In addition, the symptoms can be confounded by other febrile diseases and allergic reactions[7–11].

Population-based studies estimating the prevalence of congenital microcephaly due to ZIKV infection after an outbreak in a defined geographical area and at a specific time are scarce. Here, we investigated all live births in a city in Brazil during and after an outbreak of ZIKV, seeking to identify adverse outcomes in exposed live births compared to unexposed births.

Patients and methods

Sample

This was a cross-sectional observational study with data obtained from the Live Birth Information System (SINASC),

Information System on Notifiable Diseases (SINAN), and Public Health Event Registry (SP-Microcephaly). SINASC is a database containing newborn data for all live births in Brazil, and SINAN is a surveillance information system for reportable diseases. The reporting of Dengue virus (DENV), Chikungunya virus, and ZIKV cases is compulsory. RESP-Microcephaly is an online form for reporting suspected cases of microcephaly.

The study was conducted in the municipality of Tangará da Serra, located in the southwest region of the state of Mato Grosso, Brazil, 240 km from Cuiabá, the state capital. The estimated population in 2016 was 96,932 inhabitants (3% of the inhabitants of Mato Grosso), which is the central city of the region. Of the inhabitants, 90% resided in the urban areas with 25,581 permanent households. The average annual number of births is 1,400; deliveries are distributed across three maternity centers (all private), one of which is linked to the Unified Health System (SUS, for its acronym in Portuguese). Cases of ZIKV infection were reported in Tangará da Serra in November 2015, peaking from December 2015 to March 2016, with 1475 cases reported. In April 2016, only a small number of cases were notified[1].

All live births of children to women residing in the municipality between January 1 and December 31, 2016, were evaluated. The data were extracted from SINASC on September 1, 2017, and categorized into two groups: 1. EXPOSED GROUP: probable or confirmed exposure to ZIKV according to the following criteria: (a) mothers with ZIKV-positive polymerase chain reaction (PCR) during pregnancy (laboratory criterion; confirmed exposure); (b) mothers with clinical symptoms compatible with ZIKV infection despite not having undergone PCR or undergoing it outside the sensitive period (clinical-epidemiological criterion; probable exposure); (c) phenotype characteristic of CZS and exclusion of a genetic syndrome or another STORCH (syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpes virus) infection in the newborn, and 2. UNEXPOSED GROUP: remaining live births.

Data sources

Data on sociodemographic, delivery, and birth characteristics were extracted from the SINASC database. The SINASC is organized based on data in the certificate of live birth (DNV, for its acronym in Portuguese) completed by a healthcare professional. The following maternal variables were selected: age (years), schooling (years), skin color (white, brown, or black), and gestation length (weeks). The following variables related to the newborns were also recorded: sex, birth weight (Z-score), birth length (Z-score), birth head circumference (HC) (Z-score), neonatal death, and congenital anomaly.

From the SINAN and RESP databases, the following variables related to the gestational period were extracted: diagnosis of acute ZIKV infection, presence of rash or fever, date of symptom onset, trimester of symptom onset, and results of STORCH and Zika tests.

Clinical evaluation

HC was initially measured at birth and 48 hours later, according to the criteria established by the Ministry of Health, using the InterGrowth^{21st} standards[12] for preterm infants and the World Health Organization curves for term infants. Microcephaly was operationally defined as an HC of <2 Z-scores below the mean for gestational age at birth and sex.

All children with microcephaly and those considered exposed were evaluated by a multi-professional team (medical geneticists, neurologists, and pediatricians). Imaging (cranial ultrasound, brain computed tomography, or brain magnetic resonance imaging) and laboratory tests (serology or real-time PCR for STORCH and ZIKV infections) were performed.

Laboratory analysis

Real-time PCR for ZIKV in symptomatic pregnant women was performed using peripheral blood collected from symptomatic pregnant women on the day that the disease was suspected. The samples were centrifuged and aliquoted in the epidemiological surveillance sector of the municipality, preserved, and transported in a cryogenic liquid nitrogen container (–196°C), and stored in an ultra-freezer (–80°C) until the tests were performed by the Central Laboratory of Public Health (LACEN, for its acronym in Portuguese).

Statistical analyses

This study was conducted within the scope of the municipality's epidemiological surveillance department. Data collection was performed using a specific form for this study, and a database for analysis was created using an Excel® (Microsoft Corporation) spreadsheet through Epi Info® v7.2 software (Centers for Disease Control and Prevention - CDC). A small number of records had missing or unreported information and were not considered in the sample calculation. Prevalence ratios and their respective 95% confidence intervals ($CI_{95\%}$) were calculated for sociodemographic, delivery, and live birth characteristics.

Since the mosquito vector for ZIKV, *Aedes aegyptii*, has a limited range of dispersion and usually reproduces in spots with still water, litter, and a higher concentration of people, it was decided to assess the presence of hotspots in cases of infection in the city. The mothers' home addresses during pregnancy were georeferenced based on latitude and longitude. The following data were georeferenced: number of live births, number of live births exposed to ZIKV, and number of microcephalic births in 2016. Hot spot analysis was performed using the *Getis-Ord Gi** method[13,14] for the total number of live births and group of exposed live births. Georeferencing and hotspot analyses were performed using ArcGis® v10.3 software (ESRI).

Ethical approval

The project was approved in terms of its methodological and ethical aspects by the Research Ethics Committees of the Clinical Hospital of Porto Alegre (HCPA, acronym in Portuguese) and the State University of Mato Grosso (UNEMAT, acronym in Portuguese), and it was approved by the Brazilian Platform under CAAE number 56176616.2. 1001.5327.

Results

Between January 1 and December 31, 2016, 1,441 live births of women living in Tangará da Serra were recorded. Of these, 106 (7.3%) births were to mothers with probable or confirmed exposure to ZIKV: 36 (34%) had laboratory confirmation (positive real-time PCR), and 70 (66%) were included based on the clinical and epidemiological criteria. The latter group included infants with microcephaly, clinical characteristics, and imaging diagnosis of CZS or mothers who had clinical

Table 1

Live births in Tangará da Serra-MT-Brazil in 2016 according to exposure to ZIKV and diagnostic criteria.

Class	*n* (1,441)	(%)
Without known exposure; asymptomatic mothers	1,335	92.6
Exposed	106	7.4
PCR + during pregnancy	36	2.5
Clinic and epidemiologic criteria	70	4.9

ZIKV: Zika virus.

symptoms of ZIKV but did not undergo PCR and/or serology (Table 1).

The highest number of reports of pregnant women with clinical suspicion of ZIKV infection occurred between November 2015 and April 2016, which coincides with the period of highest circulation of the virus in the municipality[1]. The highest number of births in children whose mothers were exposed to ZIKV occurred between March and July 2016.

The main maternal and newborn characteristics in the groups categorized as exposed or unexposed to ZIKV are shown in Table 2. Seven cases of live births with microcephaly were recorded; five of them were diagnosed with CZS (4.8%), and two were in the unexposed group (0.2%). In addition to microcephaly, increased head circumference (higher than 2 Z-scores above average) was also more prevalent among those exposed to ZIKV (29.5% *vs.* 18.6%). Neonatal deaths were more frequent among those exposed (3.8% *vs.* 1.3%). The only demographic characteristic that differed between the two groups was skin color; white women were more frequently found in the exposed group (30.2% *vs.* 20.4%).

Table 3 shows the clinical data of the seven newborns with microcephaly. All patients diagnosed with CZS had a head circumference at birth equal to or less than 3 Z-scores below the average and had brain images characteristic of the syndrome. Among the two newborns in the unexposed group, one was diagnosed with holoprosencephaly and the other was small for gestational age. Thus, the prevalence of severe microcephaly at birth was 41.7/10,000 live births, with a rate of 34.7/10,000 due to congenital infection.

All children diagnosed with CZS had a negative STORCH test (syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpes). Serological ELISA tests for maternal IgG were performed for 71 women considered exposed using blood collected at the time of delivery, and 90.1% were positive.

Table 2

Maternal and newborn characteristics in Tangará da Serra-MT, Brazil, 2016.

	Exposed *n* (%)	Non-exposed *n* (%)	PR ($CI_{95\%}$)	*P* value
Maternal variables				
Age (years)				
≤35	97 (91.5)	1,236 (92.6)	1.00	0.33
≥36	9 (8.5)	99 (7.4)	1.14 (0.59–2.20)	
Schooling (years)				
≤7	1 (0.9)	12 (0.9)	1.03 (0.15–6.83)	0.44
8–11	11 (10.4)	159 (11.9)	0.87 (0.47–1.58)	0.33
≥12	94 (88.7)	1,164 (87.2)	1.00	
Skin color				
White	32 (30.2)	263 (20,4)	1.00	
Black + Brown	74 (69.8)	1,028 (79.6)	0.69 (0.42–0.92)	0.02
Newborn				
Pregnancy duration (weeks)				
<37	19 (17.9)	168 (12.6)	1.46 (0.91–2.34)	0.06
≥37	87 (82.1)	1,167 (87.4)	1.00	
Sex				
Male	47 (44.3)	648 (48.5)	1.00	0.08
Female	59 (55.7)	687 (51.5)	1.30 (0.90–1.88)	
Birth weight (Z-score)				
≤−2	1 (0.9)	21 (1.6)	0.62 (0.90–4.22)	0.35
–1.99 to +1.99	98 (90.1)	1,230 (92.1)	1.00	
≥+2	7 (7.0)	84 (6.4)	0.96 (0.46–2.00)	0.44
Birth length (Z-score)				
≤−2	4 (3.8)	48 (3.6)	1.03 (0.39–2.69)	0.45
−1.99 to +1.99	92 (86.8)	1,138 (85.2)	1.00	
≥+2	10 (9.4)	149 (11.2)	0.84 (0.44–1.58)	0.30
Head circumference (Z-score)				
≤−2	5 (4.8)	2 (0.2)	11.94 (7.08–20.1)	<0.0001
−1.99 Z to +1.99	69 (65.7)	1,084 (81.2)	1,0	
≥+2	31 (29.5)	249 (18.6)	1.85 (1.24–2.77)	0.002
Neonatal death				
Yes	4 (3.8)	18 (1.3)	2.53 (1.02–6.26)	0.05
No	102 (96.2)	1,317 (98.7)	1.00	

$CI_{95\%}$: 95% confidence interval; PR: Prevalence ratio.

Table 3

Clinical characteristics of microcephalic (-2 Z-score) live births in Tangará da Serra, MT, Brazil.

ID	MA	GA	Sex	HC Z	Weight Z	Length Z	Trim	CZS	Neuro CZS	CT-scan
1	27	39	M	−5.3	−1.7	−2.4	–	+	+	C, V, A, Vol.
2	28	39	F	−5.0	−1.1	−1.9	–	+	+	C, V, A, Vol.
3	24	37	M	−3.1	−1.7	−1.6	1	+	+	C, V, A, Vol.
4	27	34	M	−4.2	−1.5	−2.1	1	+	+	C, V, A, Vol.
5	27	39	F	−3.0	−2.4	−2.1	1	+	+	C, V, A, Vol.
6	21	35	M	−5.0	−1.6	0	–	–	–	Holoprosencephaly
7	23	36	M	−2.0	−2.7	−0.5	–	–	–	No abnormalities

Cases 1 to 5 were exposed to ZIKV; 6 and 7 not exposed.

ID: Identity code; MA: Maternal age; GA: Gestational age in weeks; HC: Head circumference; Z: Z-score according to Intergrowth 21st; Trim: Trimester of maternal symptom onset; CZS: Congenital Zika syndrome. Clinical Diagnosis of CZS: Microcephaly; craniofacial disproportion; closed fontanels; ridged and overlapped skull sutures; narrow forehead; occipital prominence; prominent supraorbital bone; nuchal, forehead, and scalp redundant skin; Neuro CZS: Irritability, poor interaction with the environment, hypertonia, dystonic movements, persistent primitive reflexes, increased deep tendon reflexes; C: Calcifications; V: ventriculomegaly; A: Atrophy; Vol: Volume; ZIKV: Zika virus; +: Presence; –: Absence.

The geographical distribution of maternal residences according to the neighborhood of residence during pregnancy is shown in Figure 1. This figure shows the total number of live births, the number of live births exposed to ZIKV, and the home of the mothers of the five microcephalic infants born in 2016 in the urban area of Tangará da Serra divided by the census region in 2016. It is possible to observe that the total number of births varied considerably among the regions, ranging from zero births to the maximum range of 81 to 100 live births. A similar observation can be made regarding live births of mothers exposed to ZIKV, ranging from zero to eight per region. The residence of the five microcephalic infants' mothers also varied, and it was impossible to identify any clusters in areas indicating greater exposure and, consequently, risk. Geographic observation and hotspot analysis of live births exposed to ZIKV and microcephalic infants did not indicate areas of higher risk for births with CZS in the municipality.

Discussion

Despite the unequivocal causal association between congenital ZIKV infection and abnormal brain development leading to microcephaly, the prevalence of exposure and adverse outcomes in defined populations remains unclear, as are the possible

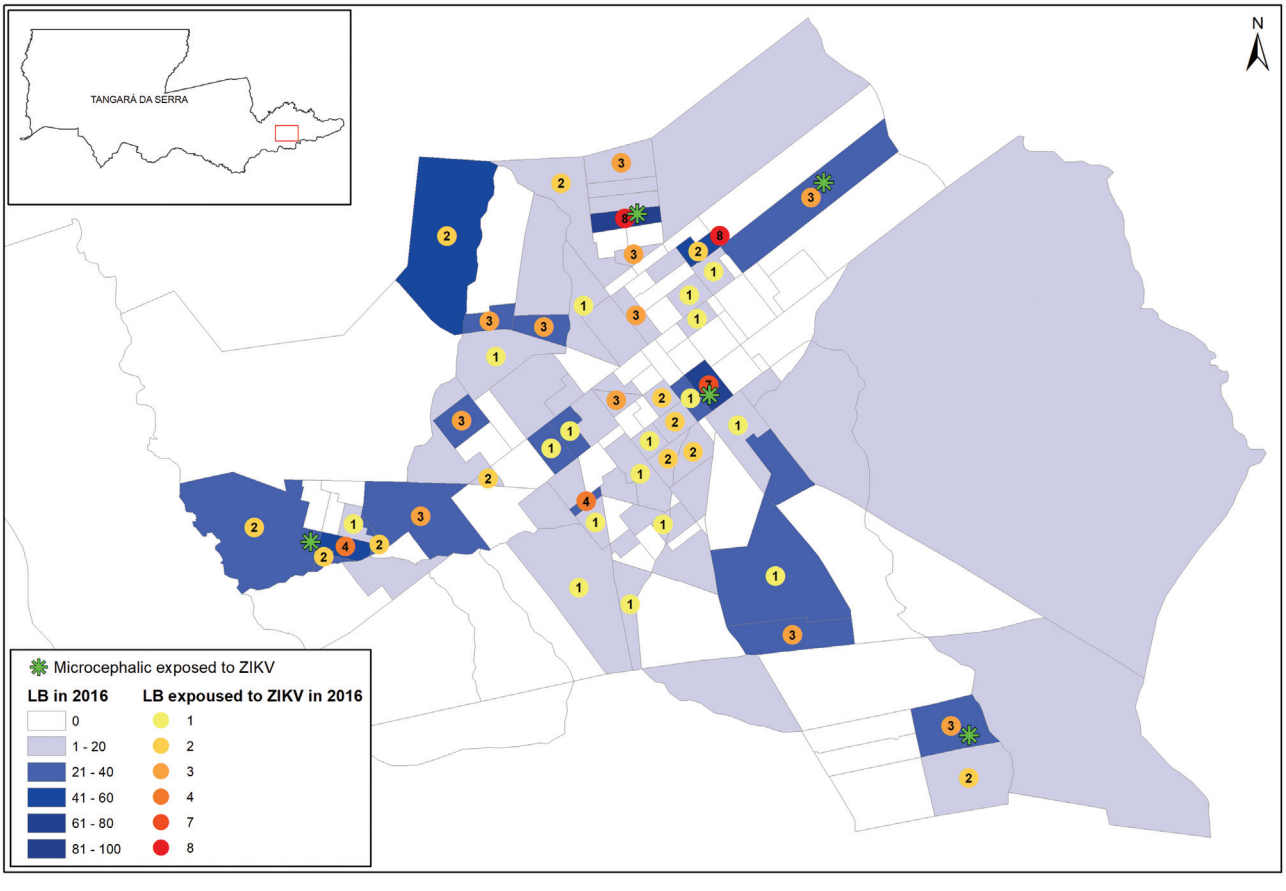

Fig. 1. Distribution of live births from mothers exposed to ZIKV and microcephalic livebirths in the urban area of Tangará da Serra-MT, 2. ZIKV: Zika virus.

cofactors that can modify these risks[15]. The present study, which used a population-based approach covering all births in a medium-sized city for 1 year during and after the ZIKV epidemic, sought to answer some of these questions. According to data extracted from SINAN in September 2017, the period of highest ZIKV transmission in the municipality occurred between epidemiological weeks 44/2015 and 16/2016 (November 2015 and April 2016). A total of 1,235 cases were confirmed using laboratory or clinical-epidemiological criteria.

Of the 1,441 births in 2016, 7.5% of the mothers reported symptoms consistent with ZIKV infection. Less than half of the symptomatic pregnant women had laboratory confirmation by PCR because of blood collection after the viremic period or because the test was not performed. In 2014, during the outbreak in French Polynesia, 11.5% of the population sought treatment for symptoms suggestive of ZIKV fever, of the 741 samples sent for PCR analysis, 51% were positive. On Yap Island, Micronesia, in 2017, a population-based study with home visits estimated that a ZIKV outbreak may have affected approximately 75% of the population, but only 19% were symptomatic[8]. Flamand *et al.*[16], when studying pregnant women in French Guiana, observed that only 17%–35% were symptomatic, depending on the region studied. Mitchell *et al.*[17], using Bayesian models and seropositivity data obtained on Yap Island, in French Polynesia, and Puerto Rico, reevaluated estimates of the proportion of asymptomatic cases, which ranged from 50% (Puerto Rico) to 73% (Yap Island).

Thus, considering the estimated number of asymptomatic cases of between 50% and 80% of individuals infected with ZIKV, we could infer that in Tangará da Serra, in the sample of mothers of children born in 2016, between 15% and 38% were infected with the virus. Interestingly, two of the five newborns with classic CZS in Tangará da Serra in 2016 (severe microcephaly, craniofacial disproportion, prominent occiput with excess skin folds, brain ultrasound and magnetic resonance imaging showing enlarged ventricles, simplified gyral pattern, decreased cortex, and coarse calcifications) were born to asymptomatic mothers. When they were retrospectively investigated in the laboratory, the ELISA test showed positive IgG.

A population-based seroprevalence study in Bahia showed IgG positivity in 63% of the population in 2016[11], almost the same rate observed in French Polynesia (66%) after the 2013 and 2014 outbreaks.[18] During the 2015 to 2016 outbreak in Martinique, 50% of the population were seropositive[19]. In a subsample of 71 pregnant women considered exposed in our study, 90.1% were positive for anti-ZIKV IgG in samples collected at the time of delivery. This result should be interpreted cautiously because IgG levels may indicate a past infection and not necessarily an infection during pregnancy. It may also reflect cross-reactivity with other flaviviruses, especially DENV, which is also endemic in the region.

These findings lead to a discussion on the risk of congenital anomalies in infants born to mothers with ZIKV infection during pregnancy and the impact of ZIKV on the prevalence of these anomalies at birth. In the present study, microcephaly associated with phenotypic changes characteristic of CZS and brain images showing severe damage was observed in 4.7% of the group considered exposed, with a prevalence of 34/10,000 live births. Hoinen *et al.*[20] observed a 4% prevalence of microcephaly in 442 completed pregnancies with laboratory-confirmed exposure to ZIKV in North American states. Reynolds *et al.*[21], updated this estimate with the finding of 972 completed pregnancies with laboratory evidence of ZIKV infection, observing a 5% rate of congenital defects related to the virus for all gestational periods and a rate of 11% when the analysis was restricted to infections in the first trimester of pregnancy. Comparatively, the prevalence of microcephaly in European countries surveyed by EUROCAT (the European Surveillance of Congenital Anomalies) was 1.74/10,000 births ranging from 0.86% to 2.93%.[22] ECLAMC (The Latin American Study of Congenital Malformations) registered a prevalence of 3.0/10,000 in the years before 2015 in South America[23]. Our study was restricted to clinical observations up to the time of discharge. Therefore, it did not include anomalies that may be present in the absence of microcephaly, such as anomalies on brain imaging or in the fundus of the eye.[24,25]

In Brazil, the prevalence of microcephaly at birth associated with ZIKV in 2015 to 2016 varied considerably according to geographical region, with a peak of 49.9/10,000 in the Northeast Region in November 2015[26]. The central-west region was predominantly affected by the second wave of ZIKV. The maximum estimated risk of microcephaly due to congenital infections in this region was 14.5/10,000 live births in 2016. In the present study, Tangará da Serra recorded 34.7/10,000 cases of microcephaly compatible with congenital infection, much higher than the maximum rate estimated by Oliveira *et al.*[26] for the central-west region. Explanations for this difference may include the fact that all births in the city were evaluated and the head circumference at birth was recorded in the DNV, which was not mandatory in that year for the rest of the country. Thus, there was no lack of notification or under-reporting. However, all five cases were severe and only allowed visual identification, with differential diagnoses of genetic syndromes performed by experienced geneticists. The total number of 1,441 births was a small denominator and led to a large $CI_{95\%}$ of between 15 and 81. Even so, the lower limit of the $CI_{95\%}$ was higher than the maximum value estimated for the central-west region by other authors.

Questions regarding regional differences in adverse outcomes, particularly microcephaly, have been discussed in the literature[15]. In Tangará da Serra, we explored differences in spatial distribution and sociodemographic factors. An analysis performed to identify geographic clusters within the urban region of Tangará da Serra did not show statistically significant concentrations of maternal seropositivity or microcephaly cases. Spatial correlation showed that locations with a possibly higher concentration of cases were explained by their higher population density. There were no differences in most sociodemographic variables, except for skin color, in women who self-reported as white were likely to be present in the exposed groups. A study evaluating the spatial distribution and socioeconomic variables of births with and without microcephaly in Recife, Pernambuco, observed a strong association between precarious housing and living conditions, and a high prevalence of microcephaly[27]. This association was not observed in Tangará da Serra, perhaps because of the very small sample size or because the social and housing conditions are more uniform than those in large Brazilian capitals. Differences in skin color and exposure may be explained by the small sample size.

Another limitation of our study was that we included only live births. The prevalence of microcephaly in stillbirths is challenging to determine in Brazil and other Latin American countries because postmortem studies are not widely available in medical facilities. However, a recent meta-analysis has estimated the median absolute risk for fetal mortality in 37 studies of Zika-affected pregnancies as 6.3% (IQR 3.2%–10.6%)[28].

In conclusion, this population-based study was conducted in a defined geographic space to investigate the prevalence of

congenital microcephaly due to ZIKV after an infection outbreak in Brazil. An investigation of the socioenvironmental cofactors that can modify this prevalence is essential to better understand this problem. This study may serve as a reference or model to investigate possible outbreaks of infections in a defined geographical space in the future.

Acknowledgments

The authors wish to thank the municipality of Tangará da Serra for their help and providing health facilities during the execution of this project.

Author contributions

J.H.S., A.C.P.T-T., G.V.A.F., M.A., and L.S-F. designed the study protocol; J.H.S., A.C.P.T-T., J.A.B., A.P.T., V.K.V., and L. S-F. performed the data collection, clinical evaluation and laboratory tests; J.H.S., A.C.P.T-T., G.V.A.F., M.Z.O., L.A.N.O., R.F.S.A., and L.S-F. participated in data analysis and interpretation; J.H.S. and L.S-F. designed and drafted the manuscript. All authors contributed to the final manuscript and approved the submitted version.

Funding(s)

INAGEMP–National Institute of Population Medical Genetics grant CNPq (465549/2014-4), CAPES (88887.136366/2017-00), and FAPERGS (17/2551-0000521-0); Project: Zika vírus: Uma abordagem translacional (CNPq grant 440763/2016-9); and Project: A História Natural do Zika Vírus (Ministry of Health grant 929698560001160-02).

Conflicts of interest

All authors declare no conflict of interest

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Edited By Yong-Qing Zhu

How to cite this article: da Silva JH, Terças-Trettel ACP, Boquett JA, Franca GVA, Cardoso-dos-Santos AC, Atanaka M, Oliveira MZ, Terra AP, Vivi VK, de Oliveira LAN, Schaedler L, Alves RFS, Schuler-Faccini L. Microcephaly prevalence after the 2015 to 2016 Zika outbreak in Tangará da Serra, Brazil: a population-based study. Reprod Dev Med 2022;6(2):98–103. doi: 10.1097/RD9.0000000000000020