

Descriptive report of cases of congenital syndrome associated with Zika virus infection in the state of São Paulo, Brazil, from 2015 to 2017

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Abstract

Objective: to characterize cases of congenital syndrome associated with Zika virus infection (CZS) and other infectious etiologies, resident in the state of São Paulo, Brazil, from October 30, 2015, to June 30, 2017. **Methods:** this was a descriptive study of suspected cases of CZS and other infectious etiologies notified on the Public Health Events Registry. **Results:** 960 cases were investigated up to epidemiological week 26/2017, and 146 were confirmed for congenital infection; of these, 59 (40.4%) were confirmed for congenital infection without etiological identification and 87 (59.6%) with laboratory confirmation, of which 55 were congenital syndrome associated with Zika virus and 32 were congenital syndrome associated with other infectious agents. **Conclusion:** this study enabled the detection of 23.9% CZS cases among suspected cases of infectious etiology.

Keywords: Microcephaly; Zika Virus; Congenital Abnormalities; Epidemiology, Descriptive.

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Introduction

Zika virus (ZIKV) is an emerging arbovirus belonging to the Flaviviridae family, along with yellow fever, dengue, West Nile and Japanese encephalitis viruses. Zika virus was first isolated in a Rhesus monkey in the Zika forest in Uganda in 1947, thus receiving the name of its place of origin.^{1,2} Human disease caused by ZIKV was recognized for the first time in Niger in 1953, when viral infection was confirmed in three persons.^{1,2} The first documented outbreak occurred in 2007, on Yap Island, in the Federated States of Micronesia (Western Pacific). It was followed by a larger epidemic in French Polynesia, South Pacific, in 2013 and 2014.³⁻⁵

In Brazil, a cluster of an unknown exanthematous disease was observed in several states in the country's Northeastern region in July 2014 and was reported by state health departments in February 2015.⁵⁻⁷ On 29 April 2015, ZIKV was identified for the first time when a similar outbreak occurred in the state of Bahia.^{8,9}

With evidence of a possible association between the change in the pattern of microcephaly occurrence and the recent outbreak of ZIKV infection, the spread of the disease in the Brazilian territory and worldwide, as well as the confirmation of ZIKV circulation by laboratory tests performed in various Brazilian Federative Units and in other countries, the event was classified as a Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO).

In October 2015, the Brazilian Ministry of Health confirmed an increase in the prevalence of microcephaly in newborn babies in the Northeastern region, compared to previously recorded estimates (approximately 0.5/10,000 liveborn infants), based on information registered on the National Birth Information System (SINASC).^{7,10} In view of the change in the pattern of microcephaly occurrence in Brazil, the Ministry declared a Public Health Emergency of National Concern (PHENC) via Ordinance No 1813/2015.¹¹

With evidence of a possible association between the change in the pattern of microcephaly occurrence and the recent outbreak of ZIKV infection,^{12,13} the spread of the disease in the Brazilian territory and worldwide, as well as the confirmation of ZIKV circulation by laboratory tests performed in various Brazilian Federative Units and in other countries, the event was classified as a Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO).¹⁴

The end of PHEIC was declared in November 2016. Notwithstanding the end of the emergency situation, WHO considered that ZIKV continues to be a challenge for Public Health. In Brazil, the declaration of the Public Health Emergency of National Concern remained in force until May 2017.¹⁵

Traditionally, microcephaly cases were accompanied only via SINASC. From November 2015, case monitoring was implanted via the Public Health Event Registration Form (RESP), this being an electronic form created by the Brazilian Ministry of Health for the compulsory notification of cases which fulfill current case definitions.¹⁶

Following the reporting of cases of congenital Zika virus syndrome in several states and following the implementation of RESP, an increase in the notification of suspected cases of congenital syndrome associated with Zika virus infection was seen in São Paulo state. An investigation was undertaken to verify whether this fact reflected surveillance system sensitivity or the increase in the number of suspected cases of CZS.

The objective of this study was to characterize cases of congenital syndrome associated with Zika virus infection (CZS) and other infectious etiologies resident in the state of São Paulo, Brazil, between 2015 and 2017.

Methods

This is a descriptive study of notified suspected cases of CZS and other infectious etiologies resident in São Paulo state. This state has 645 municipalities, distributed over an area of 248,221,996 km², with an estimated population of 44,749,699 inhabitants in 2016. The state's municipalities are divided into 27 Epidemiological Surveillance Groups the role of which is to guide surveillance action in municipalities in their area of coverage. The Public Health Event Registration Form (RESP) was used as the data source for suspected cases of CZS and other etiologies.

All suspected cases notified on RESP in the period from 30 October 2015 to 30 June 2017 were included in the study. The database used was downloaded on 7 August 2017. Only cases notified up to epidemiological week 26 (up to 30 June 2017) were considered.

The operational definitions recommended by the Brazilian Ministry of Health were used.¹⁶ Initially we adopted the more sensitive 33cm head circumference measurement for both sexes. This was later reduced to 32cm for full-term babies of both sexes following new evidence from field studies. Finally, in March 2016, we adopted the international standard definition of microcephaly in full-term children, aligned with WHO guidelines,¹⁷ namely 31.5cm for girls and 31.9cm for boys. On 30 August 2016, WHO recommended that countries should adopt as a reference for the first 24-48h of life the anthropometric parameters defined by the INTERGROWTH¹⁸ study for both sexes.¹⁶

The following definitions¹⁶ were used for case notification and classification, according to the Public Health Emergency of National Concern integrated health surveillance and care guidelines:

- a) Newborn (first 48 hours of life) to be notified as a suspected case: any newborn baby (full-term or pre-term) with head circumference less than or equal to -2 standard deviations, according to the Intergrowth table,¹⁸ according to gestational age at birth and sex; or with craniofacial disproportion; or with limb joint malformation (arthrogryposis); or having ultrasound (USG) results with altered patterns during pregnancy.
- b) Miscarriage to be notified as a suspected case: any miscarriage occurring within the first 22 weeks of gestation in which the pregnant woman presented one or more symptoms - rash and/or fever without a defined cause; pregnant women with a positive laboratory test result for STORCH (syphilis, toxoplasmosis, other infections, rubella, cytomegalovirus, herpes) or Zika; USG results with altered patterns during pregnancy.
- c) Fetal death or stillbirth to be notified as a suspected case: any fetal death or stillbirth in pregnant women with one or more symptoms – head diameter or circumference less than or equal to -2 standard deviations for gestational age and sex, according to the INTERGROWTH table, measured during pregnancy by means of ultrasound or measured soon after birth; craniofacial disproportion; limb joint malformation (arthrogryposis); rash and/or

fever without defined etiology -; positive test result for STORCH or Zika while pregnant or within 48 hours postpartum.

- d) Early neonatal death to be notified as a suspected case: any early neonatal death, occurring up to the 7th day of life, having one or more symptoms - mother reporting rash and/or fever without a defined cause in pregnancy; with a positive or reactive laboratory result for STORCH+Zika while pregnant or within 48 hours postpartum.

Following epidemiological and laboratory investigation, reported suspected cases were classified as probable, confirmed, discarded or inconclusive:

- a) Confirmed case of congenital infection: without etiological identification: any case having an imaging exam report describing two or more signs and symptoms (imaging examination or clinical examination)¹⁶ WITH report of rash or fever without a defined cause during pregnancy AND without laboratory result for STORCH+Zika; OR with negative or inconclusive laboratory result for STORCH+Zika in a sample taken from the mother or newborn baby; and as a probable case of congenital infection without etiological identification, any case of mothers WITHOUT reported rash or fever without a defined cause during pregnancy.
- b) Confirmed case of congenital STORCH infection: any suspected case with two or more signs and symptoms (imaging examination or clinical examination),¹⁶ with positive or reactive result for at least 1 of the STORCH diseases in a sample taken from a newborn baby or its mother (during pregnancy); and confirmed case of congenital Zika infection, any suspected case with positive or reactive Zika virus result in a sample taken from a newborn baby or its mother.
- c) Discarded case: any case which, following investigation, does not comply with the definitions of confirmed, probable or inconclusive cases; and inconclusive case, any case which does not comply with the definitions and when it was no longer possible to investigate the case.

Initially, the relative frequencies of suspected cases of CZS and other infectious etiologies (discrete quantitative variable) were described according to their classification. The temporal distribution of the absolute frequency of cases of CZS was plotted according to their classification, while spatial distribution was

plotted according to municipality and Epidemiological Surveillance Group of residence (nominal qualitative variable). Confirmed cases of CZS were described by means of absolute and relative frequency, according to the following variables: sex (male; female), head circumference (Z score according to INTERGROWTH), rash in pregnancy (yes; no) and imaging exam (yes; no).

The proportion of cases of congenital infection syndrome, congenital syndrome associated with Zika virus infection and congenital syndrome associated with other infectious agents investigated in pregnancy (STORCH) was calculated:

- a) Proportion of congenital infection syndrome: number of confirmed cases confirmed of congenital infection with infectious etiology divided by the total number of suspected cases of congenital syndrome with infectious etiology.
- b) Proportion of congenital syndrome associated with Zika virus infection: number of laboratory-confirmed cases of CZS divided by the total number of suspected cases of congenital syndrome with infectious etiology.
- c) Proportion of congenital syndrome associated with other infectious agents: number of confirmed cases of congenital syndrome associated with any STORCH disease divided by the total number of suspected cases of congenital syndrome with infectious etiology.

Microsoft Excel 2010 and Epi Info 7 were used for data storage and analysis. An open access secondary database was used, without any nominal data that enabled the identification of the subjects. As such, there was no requirement for the study to be registered and assessed by the Research Ethics Committee/National Committee for Ethics in Research (CONEP) (Resolution No. 510 of 7 April 2016).

Results

From 30 October 2015 to 30 June 2017, 1,151 suspected cases of CZS and other infectious etiologies were reported on the RESP system. The investigation of 83.4% (960) of these suspected cases had been completed as at epidemiological week 26.

Of the 960 cases with complete investigation as at epidemiological week 26/2017, 50.6% (486) were discarded; of these, 29.0% (141) did not meet the current case definitions and 71.0% (345) went on to have normal neurological development and head circumference for their age and sex.

Of the 474 cases that met the criteria for suspected cases of CZS and other infectious etiologies, in 51.5% (244) the alterations found were confirmed to be due to non-infectious causes; while 48.5% (230) were suspected of having infectious etiology.

Of the 230 suspected cases of congenital infection syndrome, 3.5% (8 cases) were inconclusive, 33.0% (76 cases) were classified as probable, 25.7% (59 cases) were confirmed for congenital infection without etiological identification by means of imaging examinations (ultrasound, transfontanelar imaging or tomography) and 37.8% (87 cases) were confirmed for congenital infection with etiologic identification by means of laboratory exams (reverse transcription-polymerase chain reaction [RT-PCR]). The proportion of congenital infection syndrome was 63.5% (146/230) (Table 1 and Figure 1).

Of the 87 confirmed cases of congenital infection with etiologic identification, 55 were by Zika virus infection (CZS); the remaining 32 were caused by other infectious agents: 11 by syphilis, 10 by cytomegalovirus, 8 by toxoplasmosis, 1 by herpes simplex, 1 by Coxsackie virus and 1 by parvovirus.

Among the cases of infectious etiology, the proportion of confirmed CZS cases was 23.9% (55/230); and the proportion of congenital syndrome associated with infection by a STORCH was 13.9% (32/230).

Of the 55 laboratory-confirmed ZIKV cases, 23 were in newborn infants/children, 22 in miscarriages, 5 in fetuses with alteration of the central nervous system, 3 in early neonatal deaths, and two cases occurred in stillborn infants (Table 2).

Of the 23 cases of newborn infants/children with CZS, 9 had microcephaly at birth and 8 presented severe microcephaly. Rash was the most frequently reported sign during pregnancy, being reported in 18 of the 23 pregnant women with laboratory-confirmed ZIKV, 12 of them during the first trimester. The main changes in imaging examinations of confirmed cases of CZS were calcifications (11 out of 23) and ventriculomegaly (9 out of 23) (Table 2).

Confirmed CZS cases showing no change in imaging examinations were confirmed by the presence of a clinical symptom (rash and/or fever) and CZS reactive PCR laboratory test in pregnant women and/or newborn babies.

In all confirmed cases of CZS in which the child did not have microcephaly at birth, imaging examinations

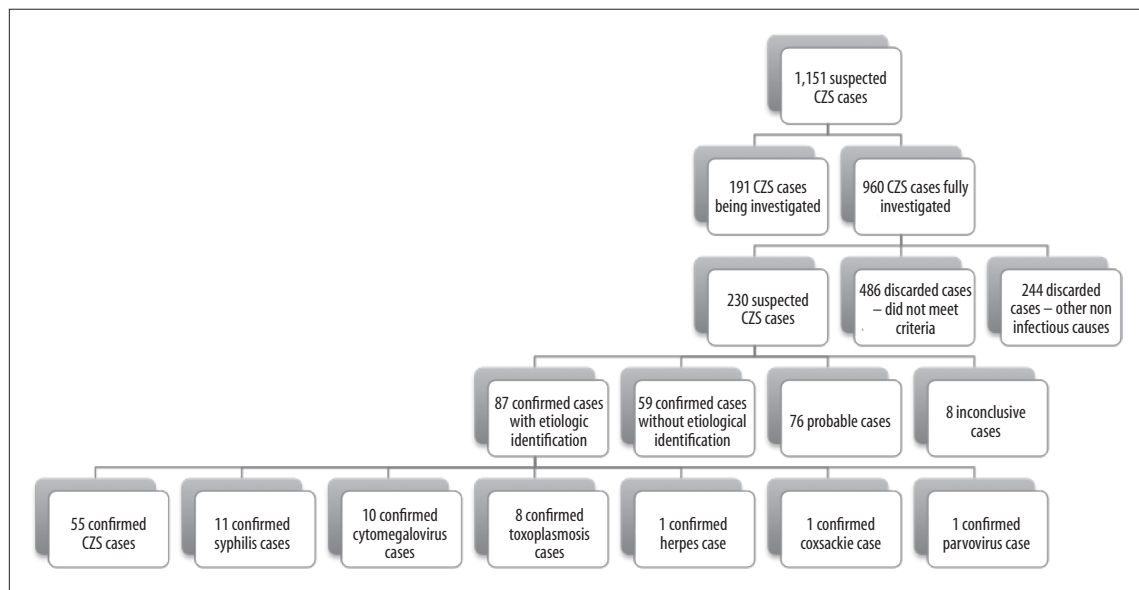
Table 1 – Distribution of suspected cases of congenital syndrome according to their classification, São Paulo state, 30 October 2015 to 30 June 2017

Case classification	2015	2016	2017	Total	
				n	%
Confirmed cases of congenital infection without etiologic identification	27	29	3	59	25.7
Confirmed cases of congenital infection by STORCH ^a with etiologic identification	3	26	3	32	13.9
Confirmed cases of congenital infection by virus with etiologic identification	–	41	14	55	23.9
Probable cases of congenital infection	7	50	19	76	33.0
Inconclusive cases	1	7	–	8	3.5
Total	38	153	39	230	100.0

a) STORCH: syphilis, toxoplasmosis, other infections, rubella, cytomegalovirus and herpes simplex.

Source: Public Health Events Registry (CPSV) / Strategic Information Center on Health Surveillance (CIEVS) / State Health Secretariat of São Paulo.

Date retrieved from database: 8/7/2017.



Source: Public Health Events Registry (CPSV) / Strategic Information Center on Health Surveillance (CIEVS) / State Health Secretariat of São Paulo.
Date retrieved from database: 8/7/2017.

Figure 1 – Ranking algorithm of suspected cases reported of congenital syndrome associated with Zika virus infection, São Paulo state, 30 October 2015 to 30 June 2017

were performed to check for changes compatible with CZS, in addition to the reactive laboratory test result in pregnant women and/or children.

An increase in the number of notifications of suspected cases of CZS and other infectious etiologies was seen following the Public Health Emergency of National Concern was declared; while there was a decrease, in 2017 (Figure 2).

Confirmed cases are concentrated in the southeast and northeast of the state (Figure 3).

Discussion

From 30 October 2015 to 30 June 2017, São Paulo state investigated 960 suspected cases of CZS, of which 230 met the criterion for relationship with infectious disease during pregnancy and 87 were confirmed for congenital infection with etiologic identification, demonstrating CZS circulation in the state. After the Public Health Emergency of National Concern was declared, there was an increase in the number of

notifications, as can be observed both here and in national studies.^{7,19}

In this study, we found a proportion of 63.5% (146/230) of cases of congenital infection syndrome, including confirmed CZS cases, confirmed cases without etiological identification and confirmed cases of congenital syndrome associated with a STORCH. These data are compatible with national findings in the literature dedicated to the period of the Zika epidemic with cases of CZS.⁷

The proportion of confirmed cases of congenital syndrome associated with the infection by a STORCH was 13.9%, with syphilis, toxoplasmosis, cytomegalovirus, herpes, Coxsackie and parvovirus being identified. This finding is compatible with a national study.⁷

The proportion of confirmed CZS cases in São Paulo state was 23.9% among those suspected of having infectious etiology. If confirmed cases without etiological identification are added to confirmed ZIKV cases, this proportion is 49.5% (114/230). It can be inferred that these were ZIKV cases, because the infectious causes had been discarded and the clinical and radiological findings were compatible with ZIKV.

The main changes found in imaging examinations were calcifications and ventriculomegaly. These findings were consistent with the case series published by Aragon et al., when describing the findings of post-natal imaging examinations in 23 children with presumed ZIKV infection. Guillemette-Artur et al. reported similar findings in a three-patient series using fetal magnetic resonance imaging.²⁰⁻²²

Table 2 – Distribution of confirmed cases of live births with congenital syndrome associated with Zika virus infection (n=23) according to sex, head circumference, presence of rash and imaging exam, São Paulo state, 30 October 2015 to 30 June 2017

Variables	n
Newborn sex	
Female	12
Male	11
INTERGROWTH head circumference classification	
Without microcephaly (-1 standard deviations) ^a	6
Microcephaly (-2 standard deviations)	9
Severe microcephaly (-3 standard deviations)	8
Rash in pregnancy	
Yes	18
1 st trimester	12
2 nd trimester	4
3 rd trimester	2
No	5
Imaging changes	
Without an imaging exam	4
Image examination without changes	3
Calcification	4
Ventriculomegaly	11
Lissencephaly	9
Arthrogyposis	4
Hydrocephalus	2
Agenesis of corpus callosum	1

a) All cases without microcephaly presented changes in imaging exam.

Source: Public Health Events Registry (CPSV) / Strategic Information Center on Health Surveillance (CIEVS) / State Health Secretariat of São Paulo. Date retrieved from database: 8/7/2017.

Confirmed cases are concentrated in the southeast and northeast of São Paulo state, where there was a greater number of ZIKV infections in 2016.²³

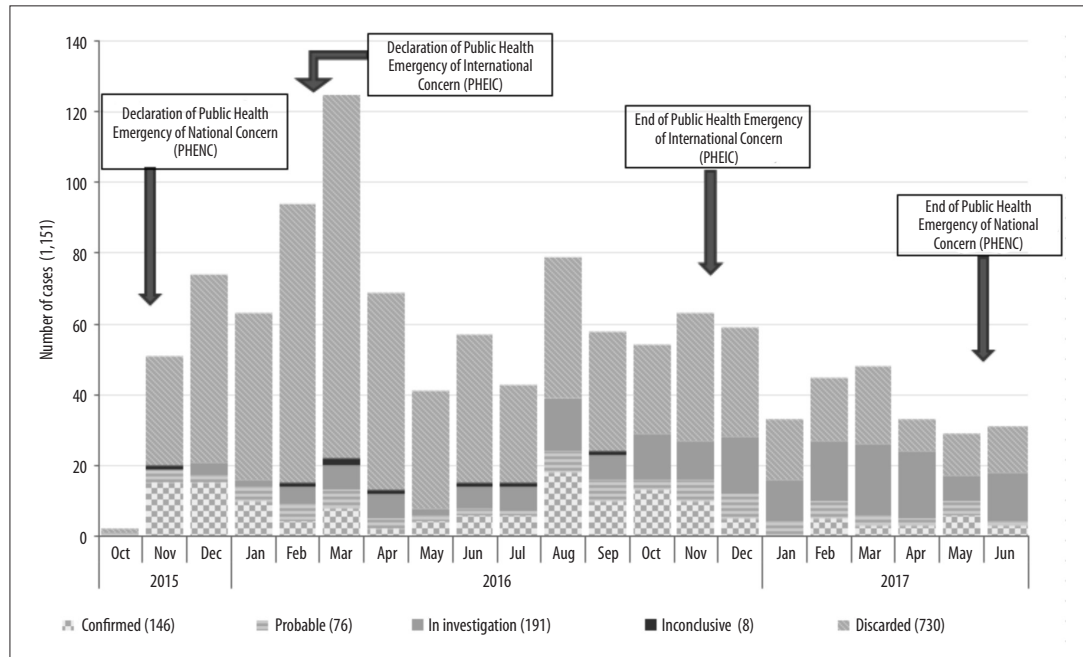
Of the 55 cases of CZS, the majority were newborn infants/children, followed by cases of miscarriage. The majority of publications on previous CZS infection have focused on changes in the central nervous system and on other congenital malformations caused by the virus to the fetus or newborn.²⁴ Few articles discuss possible adverse obstetric outcomes associated with ZIKV infection. Chibueze et al.²⁵ conducted a systematic review and concluded: of the 142 eligible articles, 18 met criteria for inclusion (13 case series studies and five observational studies), and few studies reported cases of miscarriages and stillbirths in pregnant women infected by ZIKV. Cohort studies are urgently needed with the purpose of clarifying whether ZIKV infection increases the risk of miscarriage.²⁶

As observed in other studies on microcephaly, conducted in Brazil,²¹ most of the mothers reported having rash in the first trimester of pregnancy, similarly to the results found in this study. It is known

that the embryonic period presents the highest risk for multiple complications arising from infectious processes.²⁸⁻³⁰

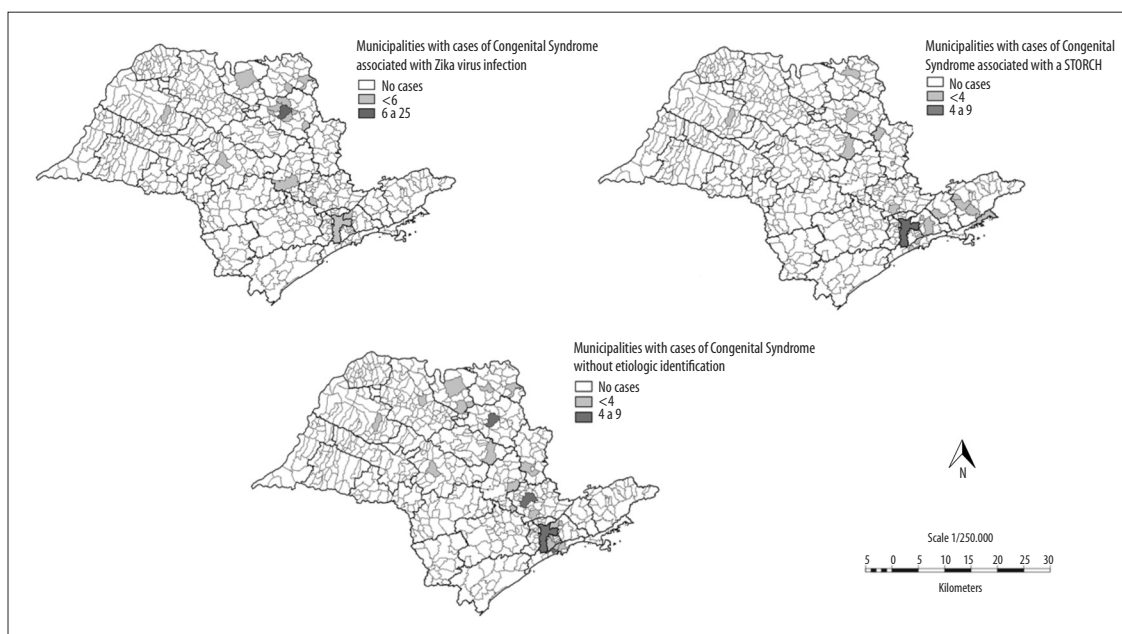
A study conducted by Johansson et al.²⁹ demonstrated that different rates of Zika virus infection in the population, underreported microcephaly rates and trimester of pregnancy in which Zika virus infection occurs are factors that determine different microcephaly prevalence rates, varying between 2 and 12 cases per 10,000 births.

Microcephaly prevalence in São Paulo state, according SINASC system data, increased threefold in the period 2015-2016, passing from 3.46 cases per 10,000 live births (LB) in 2015 to 9.52 cases per 10,000 LB in 2016, as demonstrated in other studies.³⁰ This increase was more evident in some municipalities of the state, such as Campinas (8.02 cases/10,000 LB in 2015; 50.01 cases/10,000 LB in 2016), Ribeirão Preto (5.65 cases/10,000 LB in 2015; 44.14 cases/10,000 LB in 2016), Jundiaí (0.00 cases/10,000 LB in 2015; 41.22 cases/10,000 LB in 2016) and São José dos Campos (0.00 cases/10,000 LB in 2015; 14.27 cases/10,000 LB in 2016). The



Source: Public Health Events Registry (CPSV) / Strategic Information Center on Health Surveillance (CIEVS) / State Health Secretariat of São Paulo. Date retrieved from database: 8/7/2017.

Figure 2 – Distribution of notified cases of congenital syndrome, by month of notification and classification, São Paulo state, 30 October 2015 to 30 June 2017



Source: Public Health Events Registry (CPSV) / Strategic Information Center on Health Surveillance (CIEVS) / State Health Secretariat of São Paulo. Date retrieved from database: 8/7/2017.

Figure 3 – Distribution of confirmed cases of congenital syndrome associated with Zika virus infection and other infectious etiologies, and distribution of confirmed cases of congenital infection without etiologic identification according to municipality of residence, São Paulo state, 30 October 2015 to 30 June 2017

data corroborate the fact of the largest number of confirmed cases being located in the municipalities of Ribeirão Preto and Campinas.

Among the methodological limitations of this study, it is possible to mention: (i) the recording of incomplete information inherent to surveillance systems routines; (ii) the absence of timely collection of clinical samples to enable identification of ZIKV in mothers and children; (iii) high laboratory specificity using only the RT-PCR assay for ZIKV diagnosis in pregnant women, because serology is not available at the time of investigation; and (iv) the absence of full STORCH investigation for all cases.

The results presented in this report demonstrate sensitivity not only of the notification system but also of health professionals, after the Public Health Emergency of National Concern was declared, in addition to the identification of CZS cases in São Paulo state. Further studies of a prospective design need to be carried out in that state in order to better understand the circulation of Zika virus and its association with congenital syndrome.

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Authors' contributions

Martins RS, Fróes MH, Saad LdC, Ignacio Junior SM, Prado WDA, Ciccone FH, Guimarães TC and Figueiredo EM contributed to the conception and design of the study, data analysis and interpretation and critical review of the manuscript. Sato HK and Katz G contributed to the concept and outline of the study and critical review of the intellectual content of the manuscript. All the authors have approved the final version and declared themselves to be responsible for all aspects of the study, ensuring its accuracy and integrity.

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