Travel Medicine and Infectious Disease (2016) 14, 458—463

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/tmid

Commentary

Trends of the microcephaly and Zika virus outbreak in Brazil, January—July 2016

Maria Clara de Magalhães-Barbosa [a,*], Arnaldo Prata-Barbosa [a,b], Jaqueline Rodrigues Robaina [a], Carlos Eduardo Raymundo [a], Fernanda Lima-Setta [a], Antonio José Ledo Alves da Cunha [b]

[a] *Instituto D'Or de Pesquisa e Ensino (IDOR), Departamento de Pediatria, Rua Diniz Cordeiro 30, Botafogo, Rio de Janeiro, Rio de Janeiro, 22281-100, Brazil*
[b] *Faculdade de Medicina da Universidade Federal do Rio de Janeiro, Departamento de Pediatria, Rua Bruno Lobo, n° 50, Cidade Universitária, Rio de Janeiro, Rio de Janeiro, 21941-612, Brazil*

Received 24 July 2016; received in revised form 9 September 2016; accepted 13 September 2016
Available online 1 October 2016

KEYWORDS
Zika virus;
Microcephaly;
Congenital abnormalities;
Outbreak

Summary In the last two months, there have been indications that the Zika virus epidemic is on the decline in Brazil. We reviewed the surveillance data published by the Brazilian Ministry of Health to assess trends of microcephaly and neurological abnormalities suggestive of congenital infection, as well as Zika virus disease in Brazil as a whole and its various regions. From November 2015 to July 2016, 8301 cases of microcephaly were reported in Brazil, mainly in the Northeast region. The number of newly reported cases is declining throughout the country, except in the Southeast region. The numbers of cases that remain under investigation still represent 37.7% of all reported cases in early July. Meanwhile, from January to June, 2016, 165,241 cases of Zika virus disease were reported in Brazil. The state of Rio de Janeiro (Southeast) experienced the third highest incidence, lagging behind only the states of Bahia (Northeast) and Mato Grosso (Midwest). In early June, the number of new Zika virus cases showed a marked decline in all of the regions, except the North. Although the Zika epidemic seems to be diminishing, continued monitoring and surveillance of reported microcephaly and neurological abnormality cases is essential, and investigation efforts need to be vastly improved, as some states still reported high incidences of Zika disease in the first half of 2016.

Abbreviations: MoH, Ministry of Health; RT-PCR, reverse transcriptase protein chain reaction; WHO, World Health Organization.

* Corresponding author.
E-mail addresses: mariaclaramb@globo.com (M.C. Magalhães-Barbosa), arnaldoprata@globo.com (A. Prata-Barbosa), jaque.robaina@gmail.com (J.R. Robaina), caducer@gmail.com (C.E. Raymundo), felimasetta@gmail.com (F. Lima-Setta), acunha@hucff.ufrj.br (A.J.L.A. Cunha).

http://dx.doi.org/10.1016/j.tmaid.2016.09.006
1477-8939/

In November 2015, the Brazilian Ministry of Health (MoH) implemented a monitoring and surveillance system for microcephaly when increased numbers of cases began to be reported following an outbreak of Zika virus disease in Northeastern Brazil [1]. Since then, weekly bulletins have been published that include the most recent information about reported cases of microcephaly and neurological abnormalities in the country and in its various regions [2]. Available evidence supports a causal relationship between Zika virus infection in pregnancy and microcephaly in newborns [3]. Recently, the risk of Zika virus transmission during the Olympics has been the subject of much debate and speculation in the press. The aim of the present study was to analyze publicly available data to promote an evidence-based discussion about the trends in cases of microcephaly and Zika virus disease throughout Brazil as well as specific regions within the country.

Data extracted from the epidemiological reports from the Secretary of Health Surveillance of the Brazilian MoH to monitor cases of microcephaly and neurological abnormalities associated with congenital infections from November 08, 2015 to July 2, 2016 [1,2] were analyzed. Reported cases of Zika virus disease in Brazil from January 3, 2015 to June 11, 2016 were also analyzed to look for any parallels between the disease and microcephaly cases. Beginning in January 2016, the total cumulative number of reported microcephaly cases were classified as being 1) under investigation, 2) confirmed (by neuroimaging and/or laboratory testing), or 3) excluded; and among confirmed cases, whether or not they were associated with Zika virus infection during pregnancy. It should be noted that the MoH microcephaly case definition changed over the study period, resulting in changes in the reported number of cases of microcephaly at different times [4,5]. For the present analysis, investigated cases were defined as those for which neuroimaging or laboratory testing was completed (i.e., confirmed and excluded cases). Newly reported cases *per* week (Zika virus disease) or *per* two-week periods (microcephaly and neurological abnormalities suggestive of congenital infection) were examined to assess trends.

During November 2015–July 2016, 8301 cases of microcephaly and/or other neurological abnormalities were reported, including 6079 (73.2%) in the Northeastern region of Brazil, where the Zika virus disease epidemic was first recognized (Table 1). Among reported cases, investigation was complete for 5171 (62.3%) cases, of which 1656 (32.0%) were confirmed and 3515 (68.0%) were excluded. Overall, 255 (15.4%) of the 1656 confirmed cases were found to be associated with Zika virus infection by specific positive tests (reverse transcription–polymerase chain reaction [RT-PCR] and/or serology) in samples from the newborn and/or the mother.

New reported cases of microcephaly have declined since the end of February 2016 in all regions except the Southeast (chi-square test for trend; $p = 0.103$) (Table 1, Fig. 1A–F). Marked fluctuations in the number of new reported cases coincided with changes in the definition criteria for microcephaly in early December and with the Carnaval Holiday in mid-February. Aside from the Carnaval period, the number of new reported cases has been decreasing since the end of January, mainly in the Northeast. Some of this decline in mid-March occurred after the last change in the definition criteria for microcephaly (Fig. 1A). The number of newly completed investigations (confirmed + excluded cases) in every two-week period from January to July, 2016, fluctuated and ranged from 139 (June 19–July 2) to 694 (March 27–April 9) (Table 1). Meanwhile, the cumulative number of cases under investigation continued to increase until the end of March, and then began to decline afterwards, with the exception of a slight increase that occurred in the last two-week period studied. By early July, the number of cases under investigation still accounted for 37.7% of all reported cases (3130/8301) (Table 1). From January 16 to July 2, the total of new confirmed cases *per* two-week period was 1452 for the entire country, with 1206 in the Northeast and 110 in the Southeast (Table 1). The calculated incidences of new confirmed cases were 9.7/10,000 live births in Brazil, 8.1/10,000 live births in the Northeast and 0.7/10,000 live births in the Southeast.

In regard to Zika virus disease, 165,932 cases were reported in Brazil during January 3-June 11, 2016 (Table 2). The mean number of new cases *per* week indicated a declining trend in the country as a whole (β −242.42; chi-square test for trend $p < 0.001$) in all the regions except the North (β +21.52; chi-square test for trend $p < 0.001$) (Fig. 1A–F). In early May, the mean number of new cases in the country seemed to be declining, but at the end of May it increased again, and was still as high as 12,336 *per* week in the country (Fig. 1A and Table 2). Since May 28, the mean number of new cases showed a marked decline across the country, in all regions except the Northern region (Fig. 1A–F). In the Northeast, new cases began to decline in the last week of April, increased again at the end of May and declined from May 28 onward (Fig. 1B). In mid-June, the region still contributed the highest number of new cases in the country (1042 *per* week) (Table 2). The Southeast had the highest mean number of new cases in early May (6776 new cases *per* week), but showed a dramatic fall from May 28 onward (246 new cases *per* week) (Table 2). From January to June, the Southeastern state of Rio de Janeiro had the third highest incidence of Zika virus disease cases (278.1/100,000), behind only Bahia in the Northeast region (305.5/100,000) and Mato Grosso in the Midwest region (612.0/100,000) (incidence data from states not showed in tables).

Beginning in early March, the number of newly reported cases of microcephaly declined in Brazil, especially in the Northeast region where the largest number of cases is concentrated. The second highest number of cases occurred in the Southeast, followed by the Midwest, the North and the South, all of them with numbers well below the Northeast. Meanwhile, newly reported cases of Zika virus disease in Brazil were still increasing by mid-May, mainly in some states of the Northeast, Southeast and Midwest, but fell dramatically from the end of May onward, in all of the regions except the North.

Some specific events might have contributed to the decline in the new reported cases of microcephaly. In November 2015, when the increase in microcephaly was recognized to be temporally associated with the Zika virus disease outbreak, the MoH implemented an overly-sensitive

Table 1 Cumulative cases and newly reported cases of microcephaly *per* two-week periods from January to July 2016 in Brazil and regionally.

Case type	Site	Cumulative cases Nov 8–Jan 16	New cases Jan 17–30	New cases Jan 31 Feb 13	New cases Feb 14–27	New cases Feb 28 Mar 12	New cases Mar 13–26	New cases Mar 27 Apr 9	New cases Apr 10–23	New cases Apr 24 May 7	New cases May 8–21	New cases May 22–Jun 4	New cases Jun 5–18	New cases Jun 19–Jul 2	Cumulative cases Nov 8–Jul 2
Reported cases	Brazil	**3893**	**890**	**497**	**629**	**571**	**296**	**239**	**213**	**210**	**185**	**207**	**209**	**262**	**8301**
	Northeast	3402	545	392	439	371	166	134	109	148	106	80	90	97	6079
	Southeast	240	204	56	74	118	91	70	65	33	55	99	63	130	1298
	North	89	46	12	40	24	9	19	19	9	143	2	41	12	329
	Midwest	161	84	37	32	34	22	8	10	15	0	19	7	18	454
	South	1	11	0	44	24	8	8	10	5	10	7	8	5	141
Confirmed cases	Brazil	**224**	**180**	**104**	**133**	**222**	**81**	**169**	**85**	**128**	**108**	**117**	**85**	**40**	**1656**
	Northeast	223	178	93	131	208	62	132	71	92	83	100	37	19	1429
	Southeast	0	2	3	0	6	4	28	8	17	15	6	9	12	110
	North	0	0	1	2	1	1	4	6	11	6	3	14	1	50
	Midwest	0	0	7	0	7	13	3	0	6	0	8	5	7	56
	South	1	0	0	0	0	1	2	0	2	4	0	0	1	11
Excluded cases	Brazil	**282**	**427**	**128**	**209**	**303**	**192**	**525**	**254**	**359**	**253**	**330**	**154**	**99**	**3515**
	Northeast	214	337	114	163	204	112	431	214	308	165	161	79	58	2560
	Southeast	46	26	3	17	32	50	65	28	19	40	74	35	28	463
	North	12	5	0	3	2	1	13	8	11	15	54	14	3	141
	Midwest	10	49	11	19	35	20	8	4	21	16	34	21	6	254
	South	0	10	0	7	30	9	8	0	0	17	7	5	4	97
Investigated cases (confirmed + excluded)	Brazil	**506**	**607**	**232**	**342**	**525**	**273**	**694**	**339**	**487**	**361**	**447**	**239**	**139**	**5171**
Zika-associated CASES	Brazil	**6**	**11**	**NA**	**65**	**15**	**33**	**59**	**5**	**11**	**3**	**16**	**9**	**22**	**255**
Under investigation cases	Brazil	**3387**	**3670**	**3935**	**4222**	**4268**	**4291**	**3836**	**3710**	**3433**	**3257**	**3017**	**3007**	**3130**	**3130**

Note: cumulative cases — cases accumulated from November 8 to the respective column's date; NA — not available.
Numbers in bold refer to Brazil as a whole.

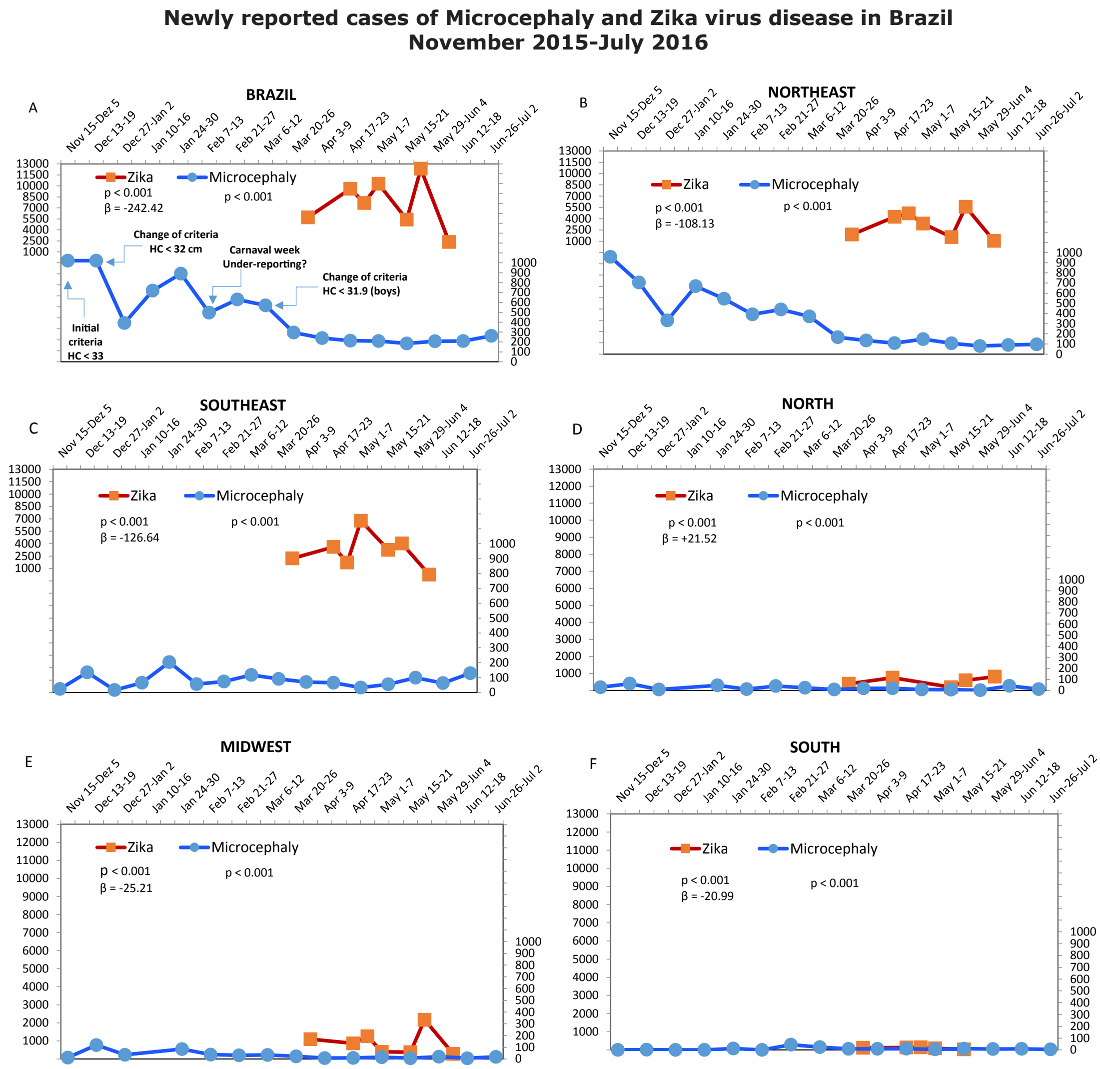

Figure 1 Newly reported cases of microcephaly and Zika virus disease in Brazil and its various regions from November 2015 to July 2016: 1A — Brazil; 1B — Northeast; 1C — Southeast; 1D — North; 1E — Midwest; and 1F — South. Note: p-value refers to chi-square test for trend applied to the number of Zika cases per week and to the number of microcephaly cases per two-week period; β coefficient refers to linear regression applied to the number of Zika cases per week.

case definition for microcephaly, which included all full term infants (37—42 weeks gestational age) with a head circumference ≤33 cm [6]. As the outbreak progressed and a large number of false positive cases were identified, the criteria were changed twice, in December 2015 (full term infants with head circumference ≤32 cm) and March 2016 (head circumference ≤31.9 cm for boys and ≤31.5 cm for girls) [4,5]. This might explain the first marked decline observed in the timeline of the new reported cases in the weeks following the first change, and part of the decline observed in mid-March after the second change. The other important decline in notified cases occurred in mid-February during Carnaval, which is the longest and most important holiday in Brazil, suggesting that cases during this period were likely being underreported. Aside from these factors, a true decline appears to have occurred from the end of January 2015 to early July 2016 in most of the regions except the Southeast.

This decline in reported cases of microcephaly might suggest that the end of the hotter summer season, which is the most favorable period for Zika dissemination by its most common vector in Brazil (*Aedes aegypti*), has resulted in a reduction of the epidemic of Zika virus and its commensurate outbreak of microcephaly. This is true for some states of the Northeast region, such as Pernambuco, Paraíba and Rio Grande do Norte, where the Zika virus epidemic began in April 2015, and most of the microcephaly cases peaked in December. The most recent MoH report of Zika virus disease cases from January 3 to June 11 [7] shows that the Southeast region has reported more suspected cases (65,820) than the Northeast (61,829) and the incidence rate in the Midwest region (163,6/100,000 inhabitants) is higher than in other regions (109.3/100,000 in the Northeast and 76.8/100,000 in the Southeast). It is possible that microcephaly cases will still increase in some states with the highest incidences of Zika virus cases in the studied period, such as Rio de Janeiro, Bahia and Mato Grosso. Therefore, despite the marked decline of Zika virus cases from the end of May to mid-June it is essential to continue monitoring the outbreak, particularly in these regions.

In a recent retrospective analysis of data from a Zika virus outbreak in French Polynesia during 2013–2015 [8], eight cases of microcephaly were reported in the four months following the Zika outbreak, corresponding to a prevalence of 2/10,000 live births. In Brazil, from late October 2015 to early March 2016, the prevalence of cases confirmed by neuroimaging and/or laboratory methods was 6.18/10,000 live births, higher than that found in the French Polynesia study, although more than half of the reported cases in Brazil remained under investigation [9]. Based on the results of the present analysis, the current incidence of new confirmed cases in Brazil from January to July 2016 is 9.7/10,000 live births. The true incidence is probably higher, as fully one-third of reported cases remain under investigation. Moreover, a great discrepancy is still observed between the Northeast and the Southeast, despite the similar number of reported Zika virus cases in both regions in the same period.

Important questions remain, particularly in regard to identifying effective preventive and management strategies for pregnant women and newborn infants. Why did the Northeast present so many more cases of microcephaly than the Southeast region? What is the sensitivity of RT-PCR for Zika virus in the neurologically compromised newborn whose mother had an undiagnosed rash illness early in pregnancy? Does Zika virus infection induce long-lasting or permanent immunity, as is the case following some other flavivirus infections? Monitoring and surveillance need to continue, and improvements in the confirmation system are critical. The WHO Zika strategic response framework [10] emphasizes the need to increase the diagnostic capacity in countries affected by Zika virus. The currently recommended RT-PCR test for Zika virus is unavailable in many places and may be only useful in the early acute phase (first five to seven days) of the disease.

The findings in this report are subject to at least three limitations. First, inaccuracy in measurement of head circumference, as well as changes in the case definition could have resulted in under- or over-reporting of cases. Second, the large number of cases remaining under investigation reduces our ability to quantify the true number of microcephaly cases. Third, the limited availability of specific tests for Zika virus prevents the evaluation of the virus as a cause of the neurological abnormalities in some cases, although compelling data supports a causal relationship.

In conclusion, since June 2016, the Zika virus epidemic appears to be waning in most regions of the country. The outbreak of microcephaly and neurological abnormalities associated with the Zika virus during pregnancy also seems to be declining, at least in the Northeast, the most heavily affected region of the country. However, microcephaly cases may still increase in the following months in those states with the highest incidences of Zika virus cases during the first months of 2016. Therefore, ongoing monitoring and surveillance are essential. Understanding the long-term immune response to Zika virus disease is important.

Table 2 Cumulative cases, mean of newly reported cases *per* week and incidence *per* 100,000 inhabitants of Zika virus disease in Brazil and regionally from January to June, 2016.

Epidemio. week	13		16		17		18		20		21		23		—
	Cumulative cases from Jan 3–Apr 2	Mean new cases *per* week from Jan 3–Apr 2	Cumulative cases from Jan 3–Apr 23	Mean new cases *per* week from Apr 3–23	Cumulative cases from Jan 3–Apr 30	Mean new cases *per* week from Apr 24–30	Cumulative cases from Jan 3–May 7	Mean new cases *per* week from May 1–7	Cumulative cases from Jan 3–May 21	Mean new cases *per* week from May 8–21	Cumulative cases from Jan 3–May 28	Mean new cases *per* week from May 22–28	Cumulative cases from Jan 3–Jun 11	Mean new cases *per* week from May 29–Jun 11	Incidence *per* 100,000 Jan3–Jun 11
Brazil	**91,387**	**5712**	**120,161**	**9591**	**127,822**	**7661**	**138,108**	**10,286**	**148,905**	**5399**	**161,241**	**12,336**	**165,932**	**2346**	**81,2**
Northeast	30,286	1893	43,000	4238	47,709	4709	51,065	3356	54,165	1550	59,745	5580	61,829	1042	109,3
Southeast	35,505	2219	46,318	3604	48,027	1709	54,803	6776	61,309	3253	65,328	4019	65,820	246	76.8
North	6295	393	8545	750	8379	NA	8053	NA	8432	190	9022	590	10,645	812	60,9
Midwest	17,504	1094	20,101	866	21,364	1263	21,756	392	22,508	376	24,683	2175	25,246	282	163,6
South	1797	112	2197	133	2343	146	2431	88	2491	30	2463	NA	2392	NA	8.2

Note: cumulative cases — cases accumulated from Jan 3 to the respective column's date; NA — not available.
Numbers in bold refer to Brazil as a whole.

Sufficient resources for investigation of all reported cases are urgently needed.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Contributors

All of the authors participated in the conception, design and conducting of the study, as well as the management, analyses and interpretation of data. MCMB drafted the manuscript, and all of the authors contributed substantially to its revision. All of the authors approved the final version to be submitted.

Conflict of interest

None.

References

[1] Brasil. Ministério da Saúde. Centro de Operações de Emergências em Saúde Pública sobre Microcefalias. Monitoramento de Casos de Microcefalia no Brasil. *Informe epidemiológico n° 01/2015*. Semana epidemiológica (se) 46/2015 (15 a 21/11/2015). Brasília: Ministério da Saúde; 2016 (in Portuguese). [Monitoring Cases of Microcephaly in Brazil]. Available at: http://portalsaude.saude.gov.br/images/pdf/2015/novembro/24/COES-Microcefalias—-Informe-Epidemiol—gico—-SE-46—-24nov2015.pdf [Accessed 6 September 2016].

[2] Brasil. Ministério da Saúde. Centro de Operações de Emergências em Saúde Pública sobre Microcefalias. Monitoramento de Casos de Microcefalia no Brasil. *Informe epidemiológico n° 33/2016*. Semana epidemiológica (se) 26/2016 (26/06 a 02/07/2016). Brasília: Ministério da Saúde; 2016 (in Portuguese). [Monitoring Cases of Microcephaly in Brazil]. Available at: http://combateaedes.saude.gov.br/images/pdf/informe_microcefalia_epidemiologico33.pdf [Accessed 6 September 2016].

[3] Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects—reviewing the evidence for causality. N Engl J Med 2016; May 19;374(20):1981—7. http://dx.doi.org/10.1056/NEJMsr1604338.

[4] Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Protocolo de vigilância e resposta à ocorrência de microcefalia relacionada à infecção pelo vírus Zika. Brasília: Ministério da Saúde, Versão 1; 2016 (in Portuguese). [Protocol for healthcare and response to the occurrence of microcephaly related to Zika virus infection]. Available at: www.saude.gov.br/svs [Accessed 28 December 2015].

[5] Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Protocolo de vigilância e resposta à ocorrência de microcefalia relacionada à infecção pelo vírus Zika. Brasília: Ministério da Saúde, Versão 2; 2016 (in Portuguese). [Protocol for healthcare and response to the occurrence of microcephaly related to Zika virus infection]. Available at: http://combateaedes.saude.gov.br/images/sala-de-situacao/Microcefalia-Protocolo-de-vigilancia-e-resposta-10mar2016-18h.pdf [Accessed 6 September 2016].

[6] Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Centro de Operações de Emergências em Saúde Pública sobre Microcefalias. Nota Informativa N° 01/2015 — COES Microceflia (in Portuguese). Available at: http://www.saude.rs.gov.br/upload/1448404998_microcefalia_nota_informativa_17nov2015_MINISTERIO%20DA%20SAUDE.pdf; [Accessed 6 September 2016].

[7] Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Boletim Epidemiológico 28/2016 - Monitoramento dos casos de dengue e febre de chikungunya até a semana epidemiológica (SE) 23 (03/01/2016 a 11/06/2016) (in Portuguese). [Monitoring cases of dengue, chikungunya fever and Zika virus fever until Epidemiological Week 23/2016 (Jan 3 to June 11 2016)]. Available at: http://combateaedes.saude.gov.br/images/boletins-epidemiologicos/2016-Dengue_Zika_Chikungunya-SE23.pdf; [Accessed 6 September 2016].

[8] Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, et al. Association between Zika virus and microcephaly in French Polynesia, 2013-15: a retrospective study. Lancet 2016 May 21;387(10033):2125—32. http://dx.doi.org/10.1016/S0140-6736(16)00651-6.

[9] Cunha AJLA, Magalhães-Barbosa MC, Lima-Setta F, Prata-Barbosa A. Evolution of cases of microcephaly and neurological abnormalities suggestive of congenital infection in Brazil: 2015—2016. [Submitted]. Bull World Health Organ E-pub Mar 2016;16. http://dx.doi.org/10.2471/BLT.16.173583.

[10] WHO. Zika strategic response framework and joint operations plan. January—June 2016. Available at: http://www.who.int/emergencies/zika-virus/strategic-response-framework.pdf [Accessed 6 September 2016].