# Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation

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## Summary

**Background** In November, 2015, an epidemic of microcephaly was reported in Brazil, which was later attributed to congenital Zika virus infection. 7830 suspected cases had been reported to the Brazilian Ministry of Health by June 4, 2016, but little is known about their characteristics. We aimed to describe these newborn babies in terms of clinical findings, anthropometry, and survival.

**Methods** We reviewed all 1501 liveborn infants for whom investigation by medical teams at State level had been completed as of Feb 27, 2016, and classified suspected cases into five categories based on neuroimaging and laboratory results for Zika virus and other relevant infections. Definite cases had laboratory evidence of Zika virus infection; highly probable cases presented specific neuroimaging findings, and negative laboratory results for other congenital infections; moderately probable cases had specific imaging findings but other infections could not be ruled out; somewhat probable cases had imaging findings, but these were not reported in detail by the local teams; all other newborn babies were classified as discarded cases. Head circumference by gestational age was assessed with InterGrowth standards. First week mortality and history of rash were provided by the State medical teams.

**Findings** Between Nov 19, 2015, and Feb 27, 2015, investigations were completed for 1501 suspected cases reported to the Brazilian Ministry of Health, of whom 899 were discarded. Of the remainder 602 cases, 76 were definite, 54 highly probable, 181 moderately probable, and 291 somewhat probable of congenital Zika virus syndrome. Clinical, anthropometric, and survival differences were small among the four groups. Compared with these four groups, the 899 discarded cases had larger head circumferences (mean *Z* scores –1·54 *vs* –3·13, difference 1·58 [95% CI 1·45–1·72]); lower first-week mortality (14 per 1000 *vs* 51 per 1000; rate ratio 0·28 [95% CI 0·14–0·56]); and were less likely to have a history of rash during pregnancy (20·7% *vs* 61·4%, ratio 0·34 [95% CI 0·27–0·42]). Rashes in the third trimester of pregnancy were associated with brain abnormalities despite normal sized heads. One in five definite or probable cases presented head circumferences in the normal range (above –2 SD below the median of the InterGrowth standard) and for one third of definite and probable cases there was no history of a rash during pregnancy. The peak of the epidemic occurred in late November, 2015.

**Interpretation** Zika virus congenital syndrome is a new teratogenic disease. Because many definite or probable cases present normal head circumference values and their mothers do not report having a rash, screening criteria must be revised in order to detect all affected newborn babies.

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## Introduction

Reports of a new exanthematic disease were issued in northeast Brazil in late 2014, and in early 2015, Zika virus outbreak was reported, following its probable introduction in 2013.[1–3] By September, 2015, reported microcephaly cases increased sharply in this region, and an association with Zika virus was suggested.[2,4] The causal association was acknowledged by WHO and by the US Centers for Disease Control and Prevention (CDC) in April, 2016.[5–7] With the steady increase in microcephaly, the Brazilian Ministry of Health (MOH) set up a surveillance system and as of June 4, 2016, 7830 suspected cases had been reported.[8]

Clinical characteristics of newborn babies with microcephaly[9–11] showed that they were different from those resulting from toxoplasmosis, others (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes (TORCH infections), with severe intracranial calcifications and other neurological abnormalities. In addition to calcifications, neuroimaging identified distinctive characteristics, including severe cortical malformations, ventriculomegaly, cerebellar hypoplasia, and abnormal hypodensity of the white matter.[9,10,12,13]

Published case series from Brazil included up to 104 children.[9–11] We reviewed the first 1501 suspected cases with complete investigation in the MOH database to identify those with laboratory results, clinical observations, and neuroimaging findings that were compatible with congenital Zika virus infection. We aimed to classify these newborn babies according to

## Research in context

### Evidence before this study

We searched the literature using PubMed and Web of Science for "Zika virus". Up to now, published case series of congenital Zika virus syndrome in Brazil were restricted to local studies with up to about 100 patients. These case series described clinical characteristics of affected newborn babies, but did not provide detailed information about anthropometry or prognosis and did not compare confirmed and discarded cases.

### Added value of this study

We report on 1501 suspected cases of which 602 were deemed to be definitely or probably due to Zika virus. In addition to describing these cases in terms of sex, gestational age, imaging findings, and maternal history of rash, we present detailed analyses of anthropometry and survival, which were not previously addressed in the literature. We calculate the sensitivity of different screening criteria including anthropometry and report of a rash. We also show that the peak of microcephaly occurred among infants born in late November, 2015.

### Implications of all the available evidence

The Zika epidemic has been rapidly declining in recent weeks. Because a substantial proportion of definite or probable cases present head circumference values in the normal range, the initial focus on equating congenital Zika virus infection with microcephaly should be modified.

categories of diagnostic certainty, and to describe their clinical and anthropometric characteristics and prognosis.

## Methods

### Study population

On Nov 19, 2015, the MOH set up surveillance system for microcephaly and CNS malformations possibly associated with congenital infection. Suspected cases included live newborn babies with microcephaly defined as 33 cm or less for term boys and girls, which was reduced to 32 cm on Dec 12 (appendix p 4). Fetuses, miscarriages, and stillbirths with CNS alterations were also reported to the system, but were not included in the present analyses.

See Online for appendix

### Procedures

Newborn babies had their head circumference measured in the maternity hospital using a protocol provided by the MOH. Those babies who fulfilled these criteria were reported to the MOH while undergoing in-depth assessment in their home states through clinical examination followed, if needed, by neuroimaging and laboratory testing (figure 1). When the diagnostic work-up was completed, suspected cases were considered by the MOH to have been fully investigated, classified as "confirmed" or "discarded" and added to the national database,[14] which included the child's sex, head circumference, and state of residence. The amount of detail available on each suspected case varied. For example, a report might describe specific imaging signs such as calcifications, or simply inform that the examination was suggestive of congenital infection according to the MOH criteria (appendix p 6).[15] Likewise, investigation of other infectious causes of fetal brain abnormalities could have been incomplete or unavailable. Available results for all suspected cases were re-reviewed by a medical geneticist (LS-F), a paediatrician (FCB), and an obstetrician (MFS), and classified into five categories: (1) definite cases, defined as newborns with laboratory evidence of Zika virus infection during pregnancy through serology or PCR, independently of other findings. The other four categories included newborn babies without laboratory evidence of Zika virus infection: (2) highly probable cases, newborn babies with imaging reports mentioning specific findings that were highly suggestive of Zika virus infection, including brain calcifications, ventricular enlargement, or both, with negative laboratory results for syphilis, toxoplasmosis, and cytomegalovirus; (3) moderately probable cases, newborn babies with imaging findings as in category 2, but without results for one or more of the three infections (syphilis, toxoplasmosis, and cytomegalovirus); (4) somewhat probable cases, newborn babies with imaging reports lacking a detailed description of the findings, for which a state-level physician concluded that a congenital infection was likely involved, for whom laboratory results for syphilis, toxoplasmosis, or cytomegalovirus were negative or unavailable; (5) discarded cases, newborn babies that were not included in the above categories. All newborn babies with laboratory evidence of syphilis, toxoplasmosis, or cytomegalovirus were included in this category except those who were also positive for Zika virus.

Our main analyses were based on newborn babies investigated up to Feb 27, 2016. To derive epidemic curves by date of birth, we report on suspected cases as of April 30, 2016.

Newborn babies were linked individually to their birth records at the National Birth Registration System (SINASC; Brasilia, Brazil)[16] to obtain information about gestational age and birthweight. The linkage variables include mother's name, municipality, and date of birth.

### Statistical analysis

We used the InterGrowth standards to calculate percentiles and *Z* scores of head circumference by sex and gestational age;[17] scores were not calculated for 138 newborn babies (9%) because of missing values for head circumference or gestational age or because the latter was outside the reference range (24–42 weeks).

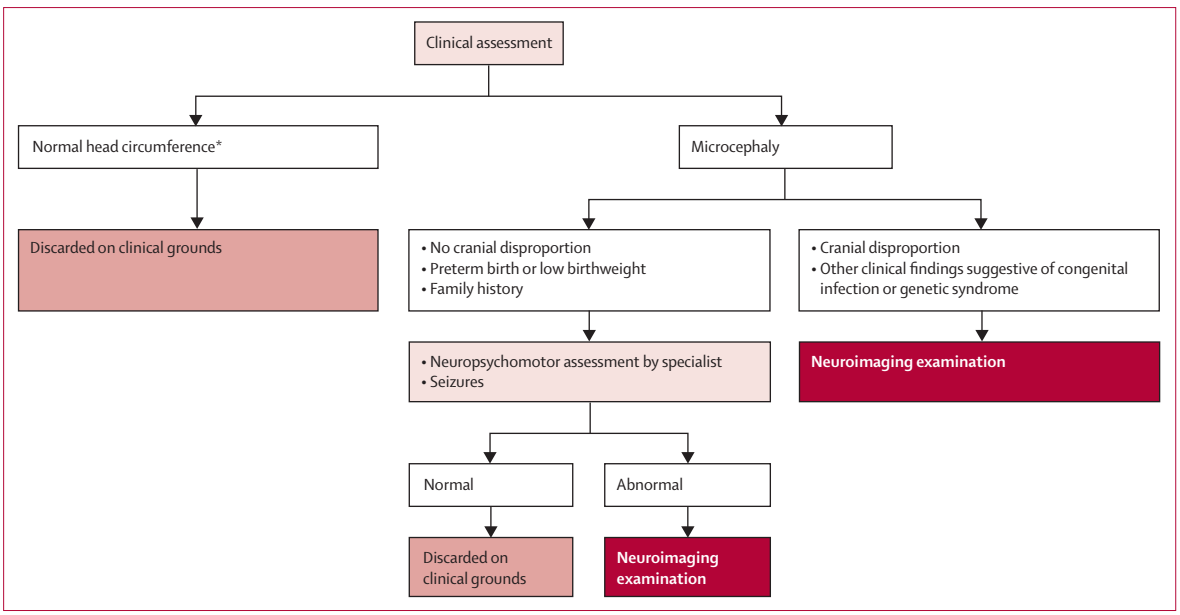


***Figure 1:*** **Flowchart for the clinical and imaging assessment of suspected cases at state and municipal level**
*Includes newborns who (when re-examined) had normal head circumferences either because the initial measurement was inaccurate or gestational age had been wrongly estimated; also includes infants who were included when the definition of microcephaly was ≤33 cm and who were re-examined after the cutoff was lowered to 32 cm.

For gestational ages expressed in full weeks, we added 3 days to reflect the midweek value.

We used $\chi^2$ tests to compare proportions, and analysis of variance to compare means. 95% CIs were obtained from the Stata command margins, from a multinomial logistic regression model, so that dependence of the categories of each variable was taken into account. A receiver operating characteristics (ROC) curve was calculated to show the predictive performance of head circumference in identifying definite or probable cases; specificity was estimated on the basis of the normal distribution of head circumference values (appendix p 12). Data were analysed with Stata 13 (StataCorp 2013, Stata Statistical Software: Release 13, College Station, TX, USA StataCorp LP).

Newborn babies reported to the national surveillance system were added to an anonymised dataset. There was no primary data collection and informed consent was not required. The protocol was approved by the Research Ethics Committee of the Catholic University of Pelotas (reference 55979716.7.0000.5339).

### Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and accept responsibility for the submission.

## Results

By Feb 27, 2016, 5909 suspected cases had been reported,[18] including 5554 (94%) liveborn infants. Of the latter, 1501 had complete investigations (27% of those reported; appendix p 7). The distribution of child ages at the time of reporting was skewed, with a median of 8 days (IQR 1–57) and a mean of 32 days (SD 46). Information about birthweight and gestational age was obtained for 1385 newborns whose records were linked to the national birth registration database.

Figure 1 shows the investigation flowchart recommended by the MOH. Of the 901 newborn babies who were discarded at State level, 547 (61%) did not require neuroimaging (appendix pp 8–11). After clinical and neuropsychomotor examination, these newborn babies were dismissed, most frequently because they had no obvious abnormalities such as craniofacial disproportion or neurological symptoms, or because they were proportionately small newborn babies (eg, with low birthweight). Detailed imaging reports were available for 686 suspected cases (ultrasonography results were available for 608, CT for 121, and MRI for 15 newborn babies); 563 did not have imaging examinations and for the remaining 252, results were mentioned but the type of exam was not specified (appendix p 9).

There were 76 definite, 54 highly probable, 181 moderately probable, and 291 somewhat probable cases (table 1). There was high agreement between the original MOH and our revised classifications: 40 (7%) of the originally confirmed cases were discarded after revision, and 42 originally discarded cases were considered as definite or probable cases.

Missing values for the variables under study are shown in the appendix (p 9), which also describes the availability of laboratory and imaging results.

583 (97%) of 602 definite or probable cases and 749 (83%) of 899 discarded cases were from the northeast region (table 1), where 28% of all births in Brazil occur.

All nine states in this region had definite, highly, or moderately probable cases. Discarded cases included a higher proportion of female and term births than did definite or probable cases (table 1).

Using the proportional distribution of newborn babies by category (table 1), we estimated the curves of microcephaly cases by epidemiological week of birth (figure 2), including all those reported up to April 30, 2016.

| | Definite cases | Highly probable cases | Moderately probable cases | Somewhat probable cases | Discarded cases | p value† | p value‡ |
|---|---|---|---|---|---|---|---|
| Number of cases | 76 | 54 | 181 | 291 | 899 | .. | .. |
| Classified by MOH as confirmed | 100·0% | 94·4% (88·3–100·0) | 91·72% (87·7–95·7) | 91·8% (88·6–94·9) | 4·4% (3·1–5·8) | <0·0001 | 0·07 |
| Northeast region* | 98·7% (96·1–100·0) | 96·3% (91·3–100·0) | 91·7% (94·8–99·6) | 96·2% (94·0–98·4) | 83·3% (80·9–85·8) | <0·0001 | 0·72 |
| Female sex* | 44·0% (32·8–55·2) | 53·7% (40·4–67·0) | 54·7% (47·4–61·9) | 54·5% (48·8–60·3) | 63·9% (60·7–67·0) | <0·0001 | 0·40 |
| Gestational age* | | | | | | | |
| <37 weeks | 16·7% (8·1–25·3) | 9·6% (1·6–17·6) | 12·5% (7·6–17·4) | 9·9% (6·4–13·4) | 6·3% (4·7–7·9) | 0·004 | 0·46 |
| 37–38 weeks | 29·2% (18·7–39·7) | 46·2% (32·6–59·7) | 36·9% (29·8–44·1) | 38·3% (32·6–44·0) | 34·9% (31·8–38·1) | .. | .. |
| ≥39 weeks | 54·2% (42·7–65·7) | 44·2% (30·7–57·7) | 50·6% (43·2–58·0) | 51·8% (45·9–57·6) | 58·8% (55·5–62·0) | .. | .. |
| Reported rash | 71·4% (38·0–100·0) | 75·0% (62·8–87·2) | 62·1% (53·8–70·4) | 55·0% (46·5–63·6) | 20·7% (16·4–24·9) | <0·0001 | 0·10 |
| Mortality per 1000 | 41·1 (4·4–86·6) | 60·0 (5·8–125·8) | 58·8 (21·5–96·1) | 48·1 (22·6–73·7) | 14·2 (5·5–22·9) | <0·0001 | 0·93 |

Data are % (95% CI). MOH=Ministry of Health. *Missing values: six for sex, 29 for gestational age, none for region, and 121 for type of birth. †$\chi^2$ test comparing the five categories. ‡$\chi^2$ test comparing the four categories of definite or probable cases.

***Table 1:*** **Distribution of suspected cases by category, according to sex, gestational age, and residence, and concordance with original classification**

The peak of the microcephaly epidemic occurred in the last week of November, 2015, which is compatible with a peak of the Zika virus infection epidemic in late February and early March, 2015.

Information about the presence of a rash during pregnancy was available for 664 (44% of the total) women, of whom 266 (40%) reported a rash (table 1). Rashes were less frequent among discarded cases than among definite or probable cases (20·7% *vs* 61·4%, ratio 0·34 [95% CI 0·27–0·42]), but did not vary significantly (p=0·10) among the four categories of definite or probable cases. Among 183 definite or probable cases whose mothers provided information about the timing of the rash, 141 (77%) of 183 reported that it took place in the first trimester, 33 (18%) in the second trimester, and nine (5%) in the third trimester.

Information about survival at the median age of 8 days when reporting occurred was available for 1212 (81%) of 1501 newborns. Confidence intervals are large due to small numbers. Table 1 shows that discarded cases had lower mortality rates than did definite or probable cases (14 per 1000 *vs* 51 per 1000; rate ratio 0·28 [95% CI 0·14–0·56]). Among 523 suspected cases with information, mortality rates were 97 per 1000 when mothers reported a rash, and 23 per 1000 when there was no such report (p<0·0001).

Table 2 shows the anthropometric characteristics by sex. Missing values are described in the appendix (p 11). Variability, expressed by the standard deviation, was substantially larger for confirmed cases than for discarded cases. The discarded cases had significantly larger head circumferences, head circumference *Z* scores (mean *Z* scores –1·54 for discarded cases *vs* –3·13 for definite or probable cases, difference 1·58 [95% CI 1·45–1·72]), and birthweight than did definite or probable

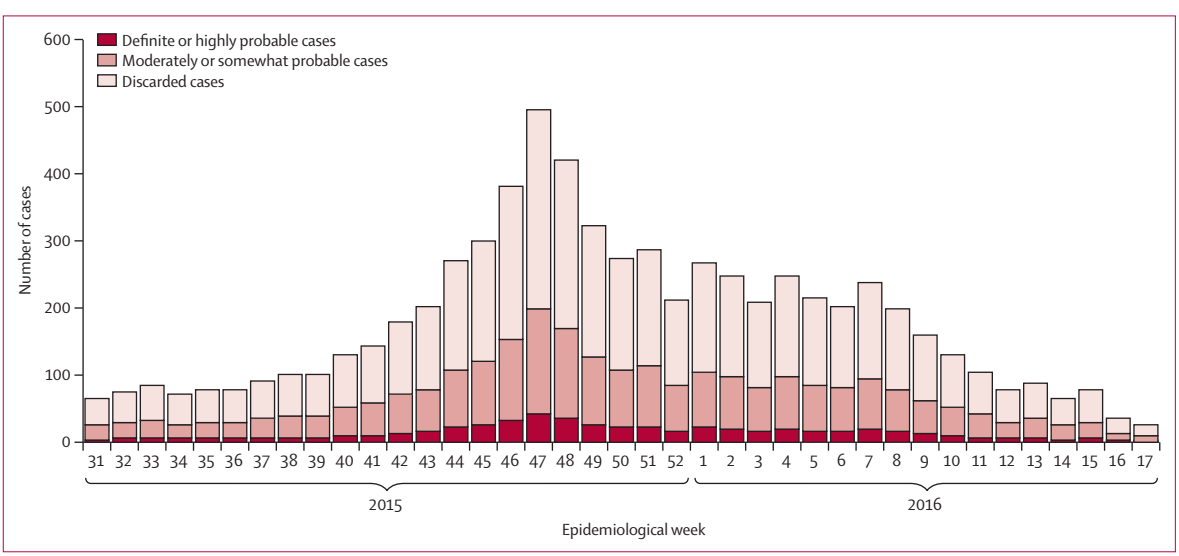


***Figure 2:*** **Actual number of suspected cases of microcephaly by epidemiological week of birth, showing the estimated numbers of definite or highly probable, moderately or somewhat probable, and discarded cases**

cases (table 2). After exclusion of discarded cases, no significant differences were noted among the four remaining categories in terms of head circumference *Z* scores or birthweight, but head circumference values in cm increased as diagnostic certainty decreased. The ratio of head circumference to birthweight did not vary significantly among the five categories (data not shown).

The average head circumference *Z* scores varied (p<0·0001) according to presence of a rash: –2·0 (SD 0·1) when a rash was not reported, –3·0 (0·1) when a rash was present in the first trimester, –2·4 (0·2) in the second trimester, and –1·5 (0·5) in the third, and –2·3 (0·4) when a rash was reported but the mother did not recall when. Mortality rates were 25 per 1000 among newborns with head circumference less than –2 SD, and seven per 1000 for the remaining infants (p=0·02).

Table 2 and appendix (p 13) show that discarded cases were notably different from the other four categories in terms of head circumference *Z* scores (p<0·0001). Scores seemed to be smaller in newborn babies with stronger evidence of Zika virus infection, but after exclusion of discarded cases the difference was no longer significant (p=0·56). Even the definite category infection included nine (13%) of 68 newborn babies with head circumferences above –2 *Z* scores (table 2).

These data were used to draw a receiver operating characteristic curve (appendix p 12) showing the sensitivity (based on definite or probable cases) and specificity (based on the normal distribution of head circumferences among non-affected newborns) of different cutoffs for head circumference. The cutoff of –2 SD has a sensitivity of 83% and specificity of 98%.

Among 319 definite or probable cases with full information, 161 (50%) of 319 had both microcephaly (<–2 *Z* scores) and a history of a rash, and 277 (87%) of 319 had at least one of the two symptoms. For the 266 suspected cases with a report of a rash, 77 (29%) of 266 were discarded, indicating a positive predictive value of 71·1% (189/266).

| | Number* | Head circumference (cm) | Head circumference *Z* scores | Head circumference >–2 SD (%)† | Birthweight (g) |
|---|---|---|---|---|---|
| **Definite cases** | | | | | |
| Female | 32 | 28·3 (2·3) | –3·4 (1·2) | 13·2% | 2534 (694) |
| Male | 40 | 29·0 (2·5) | –3·4 (1·4) | .. | 2634 (489) |
| **Highly probable cases** | | | | | |
| Female | 24 | 29·0 (2·3) | –3·1 (2·2) | 14·3% | 2411 (585) |
| Male | 20 | 29·1 (2·0) | –3·6 (1·2) | .. | 2570 (533) |
| **Moderately probable cases** | | | | | |
| Female | 88 | 29·1 (2·4) | –3·0 (1·6) | 21·7% | 2657 (552) |
| Male | 76 | 29·8 (2·2) | –3·1 (1·5) | .. | 2653 (548) |
| **Somewhat probable cases** | | | | | |
| Female | 142 | 29·1 (2·4) | –3·2 (1·4) | 21·7% | 2620 (586) |
| Male | 117 | 30·2 (2·1) | –2·8 (1·4) | .. | 2669 (496) |
| **Discarded cases** | | | | | |
| Female | 544 | 31·8 (1·3) | –1·4 (1·1) | 69·7% | 2760 (418) |
| Male | 304 | 31·8 (1·2) | –1·7 (1·0) | .. | 2763 (494) |
| p value‡ | .. | <0·0001 | <0·0001 | <0·0001 | <0·0001 |
| p value§ | .. | 0·006 | 0·15 | 0·32 | 0·23 |

Data are mean (SD), unless otherwise shown. *Number of cases with available head circumference values. †These estimates were not stratified by sex. ‡Analysis of variance comparing discarded cases with definite or probable cases. §Analysis of variance comparing the four categories of definite or probable cases.

***Table 2:*** **Head circumference and birthweight according to sex and diagnostic categories**

## Discussion

Our series of 602 definite or probable cases is six times larger than earlier reports.[9–11] Our series includes all suspected cases in the country with complete investigations up to February, 2016, including those described in earlier series.[9–11] Unlike earlier reports, which entailed in-depth assessment of newborn babies by a research team, we used routinely reported information to classify suspected cases into five categories according to diagnostic certainty.

We show that definite or probable cases were substantially different from discarded cases. Among the discarded cases, girls were over-represented because single sex cutoffs were used and girls tend to have smaller heads than boys.[19] The higher prevalence of preterm birth among definite or probable cases than among discarded cases should be interpreted with caution. The fixed cutoffs used for term newborn babies led to many false positives who were later discarded;[19] this is supported by the 6·3% preterm prevalence among discarded cases, compared with 11% in the northeast.[20] The four-fold excess mortality is likely to be real. Early neonatal mortality in the northeast is around ten per 1000,[21] lower than the 14 per 1000 among discarded cases; these present lower mean birthweight than the general population, which is compatible with higher mortality. Although all suspected cases were selected on the basis of small head circumferences, definite or probable cases had substantially smaller means and greater SDs than discarded cases.

By contrast, the four categories of definite or probable cases were similar in terms of sex, gestational age, residence in the northeast region, head circumference *Z* scores, birthweight, and survival. There were only two significant differences between the four categories: diagnostic certainty was positively associated with reported rashes and with smaller head circumferences before taking gestational age into account.

Although rashes were more commonly reported in early pregnancy, these also occurred later in gestation. As expected, the earlier the rash occurred during pregnancy, the smaller was the mean head circumference at birth, suggesting a causal association. Rashes were reported for more than 70% of definite or highly probable cases, and 62% of moderately probable cases. These rates are in the range of those reported earlier.[9,10]

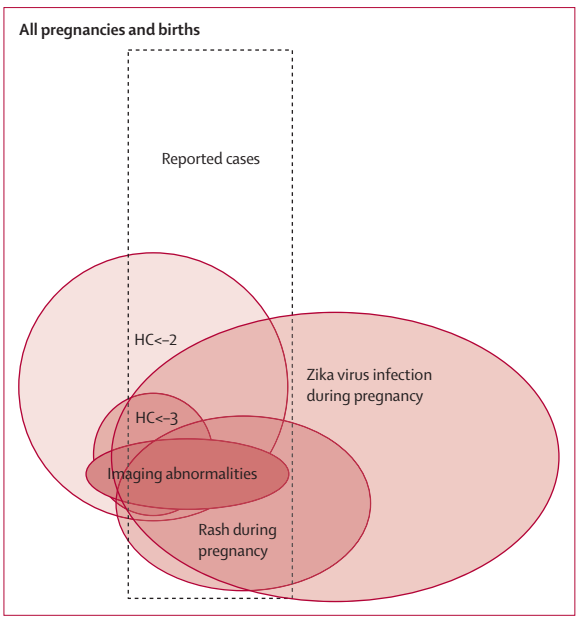


***Figure 3:*** **Proposed overlap between Zika virus infection, rash during pregnancy, neuroimaging findings, and head size**
Note: areas are not drawn to proportion and will vary according to Zika virus incidence in the population. HC=head circumference.

Malformations associated with late-pregnancy rashes confirm earlier reports from a prospective cohort[22] and are compatible with the strong neurotropic effect of Zika virus.[22,23] Such children would be born with normal sized heads as cranial growth largely takes place up to 30 weeks,[24] but yet present important brain damage. This finding also raises the possibility that Zika virus infection in newborn babies might lead to neurological damage.

Up to 2014, fewer than 15 newborns with microcephaly were reported monthly in Brazil, a number that increased by 100-fold from November, 2015, to February 2016. This substantial increase is partly due to biases, including increased awareness and changes in cutoff points.[19] Nevertheless, about 40% of suspected cases are being confirmed by the MOH after investigation, a number that is consistent with our results. Additionally, neuroimaging suggests a substantially different phenotype from previously described microcephaly cases.[9,10]

Our time series shows that the first wave of the microcephaly epidemic is almost over, which is compatible with the seasonal pattern of infections transmitted by *Aedes aegypti* such as dengue, which occur in the first half of the year. Whether there will be a second wave in late 2016, either in the northeast or in other areas of the country from which Zika virus infections were recently reported remains to be seen.

Our study has several limitations, including the incomplete documentation inherent to routine surveillance systems. The MOH issued detailed definitions of laboratory and neuroimaging findings compatible with Zika virus-related microcephaly (appendix p 6), but it is not possible to ascertain compliance with these norms. Additionally, the comparison group used in our analyses was restricted to newborn babies with small head sizes. Although this restriction contributes to reducing selection bias (because comparisons originated from the same surveillance system), these children are hardly representative of the Brazilian population as a whole. There was strong digit preference for head circumferences, and gestational ages were expressed in full weeks for most cases. Further, women with severely affected infants might be more likely to recall a rash during pregnancy.

Another limitation is the scarce information about other infectious causes of microcephaly (appendix p 5). Because congenital rubella has been eradicated in the country, we prioritised ruling out of syphilis, toxoplasmosis, and cytomegalovirus in our classification of highly probable cases.

Despite the absence of full information for moderately and somewhat probable categories of cases, there are strong reasons to suppose that most of such newborn babies were affected by Zika virus congenital disease due to their similarity with the definite and highly probable categories, and because of the substantial increase in microcephaly in the northeast region.

The high cutoffs for head circumference adopted early in the epidemic made an unexpected contribution to the understanding of Zika virus congenital syndrome. About one in five definite or probable cases had head circumferences in the normal range, and would not have been enrolled had more specific cutoffs been used. The finding of several newborn babies with neuroimaging abnormalities despite normal sized heads suggests that the initial focus on microcephaly was too narrow.

Figure 3 shows our current understanding of the Zika virus congenital syndrome. Because reporting is not complete, some newborn babies with Zika virus congenital syndrome are not included in the series. In view of the huge interest in the epidemic, we believe that under-reporting of microcephaly cases is rare, but newborn babies affected late in pregnancy might fail to be reported as their heads will be in the normal range. Among all women with Zika virus infection during pregnancy, a proportion—estimated to be one in five[25]—will present a rash. Rashes might also be reported by some women without Zika virus. Among Zika virus-affected pregnancies, some fetuses will have brain abnormalities and microcephaly, others will have abnormalities with normal head sizes, and presumably others will not be affected.

The sensitivity of microcephaly alone to detect definite or probable cases was 83% (95% CI 79–86), and this increased slightly to 87% (84–90) when history of a rash was also considered. Recent guidelines define suspected cases on the basis of microcephaly or other brain malformations; probable cases are further defined in terms of imaging findings or the report of a rash during

pregnancy.[26] Our positive predictive value of a rash among suspected cases was only 71·1%, suggesting that these guidelines might have to be revisited.

Knowledge about Zika virus congenital syndrome is quickly evolving. At present, the relative sizes of the areas in figure 3 cannot be determined with certainty. Additionally, sizes will vary according to the intensity of Zika virus exposure in the birth cohort. There is no question, however, that just as our review shows that most suspected cases ended up being normal newborn babies with small heads, focusing on microcephaly alone will underestimate the true magnitude of this major epidemic.

#### Contributors

GVAF and CGV conceived the study design, led the data analyses, and drafted the report. LS-F, FCB, and MFS reviewed the suspected cases. GVAF, WKO, CMPH, EHC, VDP, and MLN organised the surveillance system and prepared the databases. MCC, FCB, EHC, and SS did the literature review and provided critical inputs to the report. All authors revised and approved the final version.

#### Declaration of interests

We declare no competing interests.

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