Microcephaly in Brazil: how to interpret reported numbers?

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Brazil is facing its first outbreak of Zika virus, particularly in the northeast region. Most cases of Zika virus infection are self-limited and without sequelae, but there have been clusters of cases of microcephaly in some areas of known Zika virus transmission. Although strongly suspected, the causal relation between in-utero exposure to Zika and microcephaly is yet to be established. The increased number of microcephaly cases in Brazil has led to a high level of concern among pregnant women throughout the country. On Feb 1, 2016, WHO's International Health Regulations Emergency Committee advised that the clusters of microcephaly and other neurological disorders and their possible association with Zika virus constitutes a Public Health Emergency of International Concern.[1]

Measurement of newborn head circumference is useful as a screening tool for detecting microcephaly, independently of its cause. Before 2015, the annual numbers of reported cases of microcephaly in Brazil were consistently below 200.[2] Between mid-2015 and Jan 30, 2016, 4783 suspected cases of microcephaly were reported, including newborn and fetal losses.[3] Of these, 1103 cases have completed clinical, laboratory, and imaging examinations, and 404 (36·2%) were classified as confirmed cases of microcephaly. Among the confirmed cases, brain abnormalities were detected by imaging in 387 babies and Zika virus was detected in 17 babies, including in two fetal losses.[3] The remaining 709 cases were discarded and 3670 suspected cases of microcephaly remain under investigation.[3] Although 36·2% seems to be a high rate of true positives, it has to be interpreted with caution because in the present situation newborn babies with visible cranial deformities are likely to be fast-tracked for in-depth examination. This temporal increase in suspected cases of microcephaly could also be distorted given both raised awareness, with more children than usual being measured and reported, and changing definitions of microcephaly over time. The possibility of over-reporting and misdiagnosis was recently raised by the Latin American Network of Congenital Malformations,[4] and their report led to speculation in the international scientific press on the magnitude of the increase in microcephaly cases.[5]

To help interpret these numbers, it is instructive to assess how head circumference criteria for defining suspected cases of microcephaly have evolved (table). Before Dec 8, 2015, Brazil's Ministry of Health[6] recommended a cutoff for head circumference of less than or equal to 33 cm for term newborn babies (both sexes and all gestational ages); for preterm babies, the cutoff was the 3rd centile of the Fenton[7] curves of head circumference by gestational age and sex. On Dec 8, 2015, the Ministry of Health in Brazil revised the case definition for suspected microcephaly in newborn babies and reduced the head circumference criterion in term newborn babies to less than or equal to 32 cm.[8] On Jan 21, 2016, the Pan American Health Organization

	Cutoffs	Specificity*	Sensitivity†	Estimated annual number of suspected cases (thousands)‡	
				Northeast Brazil	Brazil
Brazil's Ministry of Health[6] (up to Dec 8, 2015)	≤33 cm for term newborn babies of both sexes; <–2 SD of Fenton reference[7] by gestational age and sex for preterm babies	79·3%	92%	158	602
Brazil's Ministry of Health[8] (after Dec 8, 2015)	≤32 cm for term newborn babies of both sexes; <–2 SD of Fenton reference by gestational age and sex for preterm babies	93·8%	86%	46	178
Pan American Health Organization[9]	<3rd percentile (WHO child growth standards[10]) for term newborn babies (<31·6 cm for girls and 32·0 cm for boys) and of the Fenton or InterGrowth reference for preterm babies	96·1%	80%	29	114
Below –2 SD, InterGrowth standards[11]	<–2 SD (InterGrowth standards) for gestational age and sex, all newborns	97·8%	85%	18	63
Below –3 SD, InterGrowth standards[11]	<–3 SD (InterGrowth standards) for gestational age and sex, all newborns	99·9%	57%	0·8	3

*Based on applying the InterGrowth standards to the distribution of livebirths by gestational age in Brazil. †Preliminary results based on a case series of 31 newborn babies with radiological evidence of brain abnormalities. ‡Calculated on the basis of sensitivity and the gestational age distribution of Brazilian newborn babies.

Table: **Preliminary estimates of the specificity, sensitivity, and number of suspected cases of microcephaly in Brazil according to different screening criteria**

(PAHO)[9] proposed the use of fixed cutoffs of 32·0 cm and 31·6 cm for term boys and girls, on the basis of the 3rd percentile for term newborn babies of any gestational age according to the WHO Growth Standards.[10] For preterm babies, PAHO[9] recommended use of the 3rd centile of either the Fenton[7] or InterGrowth[11] curves. Use of fixed cutoff head circumference measurements for all term infants is inappropriate since it does not account for the fact that 68·1% of term newborn babies in Brazil are below 40 weeks' gestational age, partly owing to the fact the country has the highest caesarean section rate in the world.[12]

The reasons for choosing the Fenton[7] reference are unclear. The Fenton chart is based on a meta-analysis of six pre-existing studies from high-income countries with non-standardised methods, as is the case for most neonatal anthropometric charts.[13] Instead, we applied the sex-specific and gestational-age specific InterGrowth standards[11] to the gestational age distribution of Brazilian infants in 2012[14] to estimate the specificity of evolving definitions of suspected cases of microcephaly (table). InterGrowth[11] is a prescriptive standard for fetal and newborn growth based on healthy gestations from eight countries. In this prospective, multicentre study, women had a reliable ultrasound estimate of gestational age using crown–rump length before 14 weeks of gestation or biparietal diameter if antenatal care started between 14 weeks and 24 weeks or less of gestation.[11] Newborn anthropometric measures were obtained by identically trained anthropometric teams using the same equipment at all sites, which included Brazil. The InterGrowth study was designed to be fully consistent with the WHO Growth Standards,[15] which are used throughout the world, thus providing a comparable standard for fetal growth and newborn size. Both standards are perfectly matched for term newborn babies. Because microcephaly cases were excluded from the InterGrowth samples, the distribution of head circumferences in the standard is appropriate for estimating specificity of a given cutoff.

The use of a cutoff of –3 SD below the mean value for newborn head circumference was proposed by a 2013 systematic review of microcephaly, on the basis of the finding that most newborn babies with head circumferences between –2 SD and –3 SD below the mean range do not have any evidence of malformation.[16] The –3 SD cutoff has been used traditionally by the Latin American Collaborative Study of Congenital Malformations.[4] A WHO manual on surveillance of birth defects defines microcephaly as a head circumference below –2 SD of sex-specific and gestational-age specific curves, but only if accompanied by structural abnormalities of the brain.[17] The WHO manual explicitly states that absence of such abnormalities rules out a diagnosis; it does not recommend diagnostic workouts for all children with small heads.[17]

We derived preliminary estimates of sensitivity from 31 cases of confirmed microcephaly from ten states in Brazil, including eight northeastern states.[18] The newborn babies had head circumferences below the Ministry of Health cutoff at the time of birth and had brain abnormalities confirmed by imaging that were compatible with congenital infection (mainly brain calcifications, lissencephaly, and ventriculomegaly). These are the first consecutive confirmed cases available to our coauthors who are involved in surveillance in the ten states. In these 31 babies with microcephaly there was no evidence of intrauterine exposure to other infectious diseases, such as syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpesvirus. The average head circumference was 28·4 cm (SD 2·3), with a mean InterGrowth Z score of –3·5 (SD 1·4). Only three newborn babies had head circumferences greater than or equal to 32 cm, all with mild radiological signs of brain abnormalities.

The table shows the sensitivity of the different diagnostic criteria for suspected microcephaly based on our case series. These preliminary results must be interpreted with caution given the small number of cases, the fact that most measurements were rounded to full cm instead of mm, and the possibility of notification bias. Although the specificity of the cutoffs used so far seem high, in a country with almost 2·9 million annual births there would still be many newborn babies classified as suspected cases who would require in-depth investigation. The table shows that the number of cases of suspected microcephaly range from more than 600 000 with the initial criterion from the Ministry of Health[6] to just over 3000 if –3 SD is used as the cutoff. The fact that 3670 of the 4783 suspected cases of microcephaly identified in the past months are still under investigation is not surprising given delays in obtaining access to advanced diagnostic facilities in Brazil's national health system.[19] This backlog of cases

under investigation may become worse as increasing numbers of suspected cases are reported and babies' head circumferences are measured more often than in the past. Another consideration is the emotional stress for parents whose healthy babies with small heads are incorrectly screened as positive.

There is a trade-off between specificity and sensitivity. Since there is no effective treatment for congenital microcephaly, there is a strong argument to prioritise specificity over sensitivity. Increasing specificity would reduce the iatrogenic potential of radiation during brain tomography, which is 100 times higher than that for a chest x-ray,[20] and would help alleviate the emotional effects on parents of healthy children who are given a false-positive result in the screening assessment. This approach would also reduce the burden and costs to an already overstretched health system. Although true cases of microcephaly that are missed by a less sensitive cutoff could benefit from early intellectual stimulation, there would still be opportunities to detect their condition later during infancy.

Arguments for prioritising sensitivity include the fact that we are in the early stages of a new epidemic about which little is known. It is also conceivable that babies with microcephaly who would profit most from early intellectual stimulation could be exactly those whose head circumference is closer to the normal range.

On the basis of our results (table), we recommend use of a consistent set of diagnostic criteria for suspected microcephaly that take into account gestational age for term and preterm newborn babies; such criteria are provided by the InterGrowth standards.[11] These are preliminary recommendations that can be revised once a larger case series is accrued. The sensitivity of a cutoff for head circumference of –3 SD seems to be too low, particularly during what seems to be a new epidemic of microcephaly, when one does not want to miss many cases. We favour a cutoff of –2 SD, which has similar sensitivity to the current Ministry of Health[8] and PAHO[9] recommendations, with the advantage of greatly reducing the number of newborn babies who will need investigation. Although –2 SD and the 3rd percentile seem to be close, the latter cutoff would classify an additional 0·7% of the population as suspected cases, or about 20 000 Brazilian newborn babies per year. The recent availability of a computer and mobile-phone based application for the estimation of head circumference Z scores by gestational age and sex will contribute to the field implementation of the InterGrowth standards;[21] Portuguese and Spanish versions have also been made available.

Although there is evidence of an increased number of cases of microcephaly in Brazil, we show that the number of suspected cases relied on a screening test that had very low specificity and therefore overestimated the actual number of cases by including mostly normal children with small heads. We recommend that national and international agencies should refrain from reporting suspected cases and speed up investigation to report on confirmed cases with laboratory or radiological evidence. It is also important that health workers measure head circumference in all newborn babies using standardised anthropometric techniques, and report results in mm. The present situation in Brazil is certainly a severe public health challenge. Better measurement and use of the appropriate growth standards are essential for the continued surveillance of microcephaly cases that are potentially associated with the Zika virus infection.

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CGV and FCB were part of the team of researchers that created the InterGrowth standards; the standards are in public domain and the researchers involved in their creation do not receive any financial benefits from their use.

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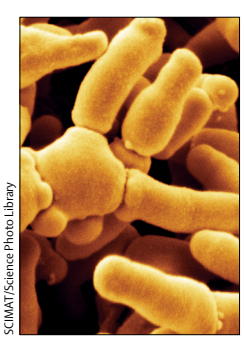
Not all probiotic strains prevent necrotising enterocolitis in premature infants



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Bifidobacterium breve

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In *The Lancet*, Kate Costeloe and colleagues[1] report the outcome of the highly awaited PiPS trial, assessing the potential preventive effect of the probiotic bacterium *Bifidobacterium breve* BBG-001 on necrotising enterocolitis, late-onset sepsis, and mortality in premature infants.[1] Necrotising enterocolitis remains among the most devastating diseases encountered in premature infants. The cause of necrotising enterocolitis is an excessive inflammatory process in the intestinal mucosa that presents clinically with feeding intolerance, abdominal distension, and bloody stools.[2] Mortality in affected babies is as high as 15–30%. Moreover, the systemic proinflammatory response and severe circulatory imbalance caused by necrotising enterocolitis also affects distal organs, such as the brain, leading to an increased risk of long-term neurodevelopmental impairment in survivors. Thus, there is a compelling case for implementation of prophylactic measures that are both safe and effective in this vulnerable patient population.

Meta-analyses of prospective randomised placebo controlled trials assessing probiotics as a measure to prevent necrotising enterocolitis in very low birthweight infants (<1500 g) have provided very encouraging results. In these meta-analyses, the incidence of necrotising enterocolitis in the neonatal period is reduced from 6% in the placebo group to 2% in the probiotic group.[3] Subsequently, there has been an animated debate about whether there is sufficient evidence to recommend probiotics to premature infants. The Cochrane collaboration has argued that there is already evidence to warrant a change in clinical practice,[3,4] while others have raised concerns about the methodological rigour of many of the published trials and the appropriateness of combining them in meta-analyses.[5]

In this context, Costeloe and colleagues' study[1] is important, because it is the largest trial published so far and also, without doubt, has a study design with a very high quality. The multicentre randomised placebo controlled trial included 1315 premature infants born from gestational week 23–30 in neonatal intensive care units in southeast England. The study product (*B breve* BBG-001) was manufactured and regulated as a pharmaceutical drug, contrary to most other probiotics on the market, and granted clinical trial authorisation from the Medicines and Healthcare Products Regulatory Agency (UK). 654 infants were allocated to the probiotic group and 661 infants were allocated to the placebo group. In view of the size of the trial, it had sufficient power to detect relevant effects on necrotising enterocolitis and sepsis. Importantly, by contrast with most of the previous probiotic prevention