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Estimating the risk for microcephaly after Zika virus infection in Brazil

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Objectives: Here we evaluate the variability of the risk estimates for microcephaly as the most severe congenital malformation by state in Brazil. For the state of Pernambuco, where figures are available stratified by different microcephaly definitions and per week during the year 2015, we compare these additional sources of variability in detail.

Methods: We assessed the absolute risk of notified and confirmed microcephaly cases by state in Brazil. For the denominator of the risk estimates we used the number of the live births in the time window. We varied the hypothetical proportion of the pregnant women exposed to ZIKV infection during pregnancy between 10%-50%. Relative risk estimates were calculated using the reported background frequency estimates of microcephaly.

Findings: The absolute risk of microcephaly varied largely between 0-5% and up to 30% over geography and depending on the definition used. With a background risk of microcephaly of around 2 per 10,000 live births in Brazil, the relative risk for Pernambuco state, one of the states hardest hit by the epidemic, can be estimated in the order of 20 to 200 (assuming 50% exposure) or 100-1000 (assuming 10% exposure), depending on the definition of microcephaly used.

Conclusions: The observed magnitude of the variability calls for the investigation of potential effect modifiers. Seroprevalence studies are needed to provide estimates of the proportion of the population that were exposed to ZIKV virus during the epidemics. In the absence of a robust estimate of the absolute and relative risk, cohort studies are urgently needed to determine the quantified risk estimate per gestational age in pregnant women - including, but not limited to microcephaly as endpoint.

Background

Zika virus (ZIKV) was first described in rhesus monkeys from Zika forest, Uganda in 1947(1). It was only in 2007 when the virus was reported for the first time outside Africa and Asia(2), causing an epidemic on Yap Island, Micronesia(3). In 2013-14, another epidemic occurred in French Polynesia(4). With its emergence in Brazil in 2015, ZIKV has entered new territory. In October 2015, an increase in microcephaly cases was first noticed in Recife, Northeast Brazil, continuing throughout the following months and reaching an unprecedented number of 1912 cases by 30 of April 2016 (5). In the absence of alternative explanations and due to the temporal clustering observed, a causal association with ZIKV infection during pregnancy had been hypothesised (6, 7). Based on the accumulating evidence, the Brazilian Government started to consider this association as early as November 2015(8), Interestingly, after the reports about the potential link between ZIKV and microcephaly had surfaced from Northeast Brazil, researchers in French Polynesia reanalysed their data and were able to detect this association as well(9, 10). The potential for perinatal transmission of ZIKV had already been documented in 2014(11). The hypothetical association between ZIKV infection and microcephaly was reported by CDC(7), ECDC(12), and WHO(13) in November and December 2015. On 1 February 2016, WHO declared the clusters of microcephaly and other neurological disorders a Public Health Emergency of International Concern (PHEIC)(14). ZIKV has been identified in the amniotic fluid of foetuses with microcephaly in Brazil(15) and isolated cases of congenital malformations associated with ZIKV infection have started to appear in other parts of the world, like Slovenia(16) and Hawaii(17), in individuals with a travel history to Brazil. To our knowledge, never before in the history of public health have countries advised their populations to postpone planned pregnancies, as for example in Brazil(18), Jamaica(19), El Salvador(20), or Colombia(21). The accumulating evidence was

considered to be strong enough to support an aetiological link between ZIKV infection and birth defects(22).

Still, the actual risk of microcephaly or other congenital malformations linked to ZIKV infection during pregnancy remains unknown and needs to be assessed thoroughly and rapidly. Taking into account the number of live births and the number of microcephaly cases reported in Brazil we present absolute risk estimates of microcephaly as the most severe congenital malformation by state in Brazil. For the state of Pernambuco, where figures are available stratified by different microcephaly definitions and per week during the year 2015, we compare the resulting relative risk estimates in detail.

Methods

For notification purposes, microcephaly has been defined by the MOH Brazil (after 8 December 2015) as a head circumference of less than 32 cm in full-term babies and of -2 standard deviations below the mean head circumference for preterm babies, based on the Fenton scale(23). The sensitivity and the specificity of the definition used by the MOH in Brazil were reported as 86% and 93.8%, respectively(23). Imaging (and in some cases virological investigations) are being carried out to confirm the cases notified. In addition, cases have been reclassified based on more specific definitions (as for example the WHO InterGrowth standards) (24).

We assessed the risk estimates of notified and confirmed cases over geography in Brazil, comparing federal states from North to South. Not all of the notified cases have undergone testing for confirmation. We used the proportion of confirmed cases among those tested and extrapolated this figure to the total (predicted confirmed category).

For the denominator of the risk estimates we used the number of the live births [average of the latest available data from 2011-2013(25)] in the time window. We varied the hypothetical proportion of the pregnant women exposed to ZIKV infection during pregnancy between 10%-50%. Relative risk estimates were calculated using the background frequency of microcephaly, which was reported as 1.98 (95% CI 1.48-2.27) per 10,000 live births per year in Brazil (ECLAMC) (26), and 2.85 (95% CI 2.69-3.02) per 10,000 live births in Europe (EUROCAT). The number of microcephaly cases reported for Pernambuco state amounted to five in 2011, nine in 2012, 10 in 2013, and 12 in 2014 (6), which is considerably lower than the ECLAMC estimate we used for the relative risk estimates.

Results

Using the notified microcephaly cases based on the definition by the MOH Brazil by state(5) and 10% [50%] of the number of the live births in the time window in the denominator (for the proportion of pregnant women exposed), the absolute risk estimates for microcephaly between November 2015 and April 2016 ranged from 0.1% [0.02%] (Santa Catarina, Southern Brazil) to 31.0% [6.2%] (Paraiba), with 3.9% [0.8%] in Rio de Janeiro state and 18.5% [3.7%] in Pernambuco (**Figure 1A&B**).

The predicted absolute risk based on the proportion confirmed (proportion of confirmed extrapolated to those who have not undergone confirmatory testing) ranged from 0% (Acre) to 12.8% [2.6%] (Rio Grande du Norte), with 1.3% [0.3%] in Rio de Janeiro state and 5.0% [1.0%] in Pernambuco (**Figure 1A&B**).

In Pernambuco, 1912 microcephaly cases were notified as by 30 April, among them 803 qualifying for Microcephaly according to the WHO InterGrowth standards(24). These were further subdivided in those below -3 SD (N=316) and those between -2 and -3 SD (N=487).

The proportion confirmed was similar between those not qualifying for the InterGrowth definition (N=1054; 19.5% confirmed) and those fitting the InterGrowth definition with head circumference values between -2 and -3 SD; 21.2% confirmed); only the group with severe microcephaly fitting the InterGrowth standards below -3 SD exhibited a higher confirmation rate of 53.1%.

The 803 cases defined by the InterGrowth standards in Pernambuco are also available stratified per week over the course of the epidemic. Within the three peak months (Oct-Dec 2015), 574 cases were documented versus 229 cases before and after the peak period. The absolute risk based on the peak period only is 14.2% under the assumption of 10% exposure and 2.8% under the assumption of 50% exposure.

Depending on the definition used, the relative risk estimates for microcephaly in Pernambuco state vary between 123 and 933 (10% exposure) or 25 and 187 (50% exposure) (**Figure 2**).

Discussion

The variability of the risk estimates for microcephaly in Brazil is substantial. Important differences were observed with regard to (i) geography, (ii) the definition for microcephaly, and (iii) the assumptions about the proportion of pregnant women exposed during the time period. In the Yap Island 2007 and French Polynesia 2013-14 epidemics, the seroprevalence rates reflecting the proportion of the population exposed to ZIKV were 73%(3) and 50-66%(27), for outbreaks that lasted 4 months and 14 months, respectively. These data are not yet available for the 2015 Zika epidemics in Brazil. The high seroprevalence rates reported after the limited-duration epidemics in Micronesia and French Polynesia suggest that transmission is very effective, which in turn results in herd immunity building up quickly and blocking further transmission. Both in Micronesia and in French Polynesia, serological tests

were carried out for ZIKV antibodies as well as for related flaviviruses including dengue viruses – and the known potential for cross-reactivity was taken into account when interpreting the results (3, 27). Nevertheless, due to cross-reactivity, the high seroprevalence rates for ZIKV reported from Micronesia and French Polynesia might still be an overestimate of the true exposure. At the same time, the chance of stochastic die out of an epidemic is higher in isolated and smaller island populations(28), which could potentially translate to an underestimate of the true seroprevalence rate (assuming it reached an equilibrium).

As another source of variability, we observe large differences between the federal states in Brazil with the highest figures in the Northeast and lower figures further inland and in the South. Comparable to many states in Brazil with moderate risk estimates, the absolute risk for microcephaly linked to ZIKV infection in French Polynesia (in the first trimester) was also estimated in the range of 1% in a retrospective analysis (9). Some states might have experienced the epidemic later in the year 2015 (or not have experienced an epidemic, only imported cases) and therefore not report microcephaly cases. However, the epidemics in Pernambuco and Rio de Janeiro state peaked almost at the same time in the spring of 2015(24, 29). The reason why risk estimates in the Northeast of Brazil are substantially higher compared to Rio de Janeiro merits further attention. It is possible that co-factors or effect modifiers play a role, which needs to be evaluated by future studies.

Definitions for microcephaly in Brazil have changed and additional, more specific definitions like the WHO InterGrowth standards have been implemented. It is noteworthy that more specific definitions also come with the potential of decreased sensitivity(23). Current estimates of sensitivity and specificity of different definitions are based on relatively small samples(23) and need to be validated using larger studies.

Here we concentrate on the risk estimates for microcephaly – however, the full spectrum of congenital abnormalities and adverse pregnancy outcomes (including placenta pathology),

depending on gestational age at time of infection might be substantially larger than microcephaly alone. In an interim analysis from Rio de Janeiro, 29% of 42 pregnant women with a confirmed ZIKV infection during pregnancy had congenital abnormalities detected by ultrasound (including 1 case of microcephaly)(30).

Conclusions

We have analysed the currently available data from Brazil regarding the variability of the risk of microcephaly linked to ZIKV infection during pregnancy. One challenge we were facing is the fact that numbers are updated frequently and that changing or additional definitions for microcephaly were implemented over time, which translates into a substantial variability depending on the definition used. In addition, the risk estimates of microcephaly vary substantially between the federal states in Brazil with higher risk in the Northeast and lower risks in the South. Furthermore, an important determinant of the variability is the assumed proportion of the pregnant women exposed to ZIKV infection during the vulnerable period of the pregnancy. Community-based seroprevalence surveys in the age bracket of pregnant women are needed to better understand the force of infection and the proportion of the population exposed over the course of ZIKV epidemics.

With a background risk of microcephaly of around 2 per 10,000 live births in Brazil, the resulting relative risk for Pernambuco state, one of the states hardest hit by the epidemic, can be estimated in the order of 20 to 200 (assuming 50% exposure) or 100-1000 (assuming 10% exposure), depending on the definition of microcephaly used. In the absence of a robust estimate of the absolute and relative risk, cohort studies are urgently needed to determine the quantified risk estimate per gestational age in pregnant women - including, but not limited to microcephaly as endpoint. Because of the large variability of the current risk estimates, cohort studies also have to take into account the evaluation of co-factors or effect modifiers.

Preliminary estimates of the magnitude and the plausible ranges of the absolute and relative risk estimates (as provided here) are of high importance to inform scientists about the plausibility, the study design, and sample size of future cohort studies.

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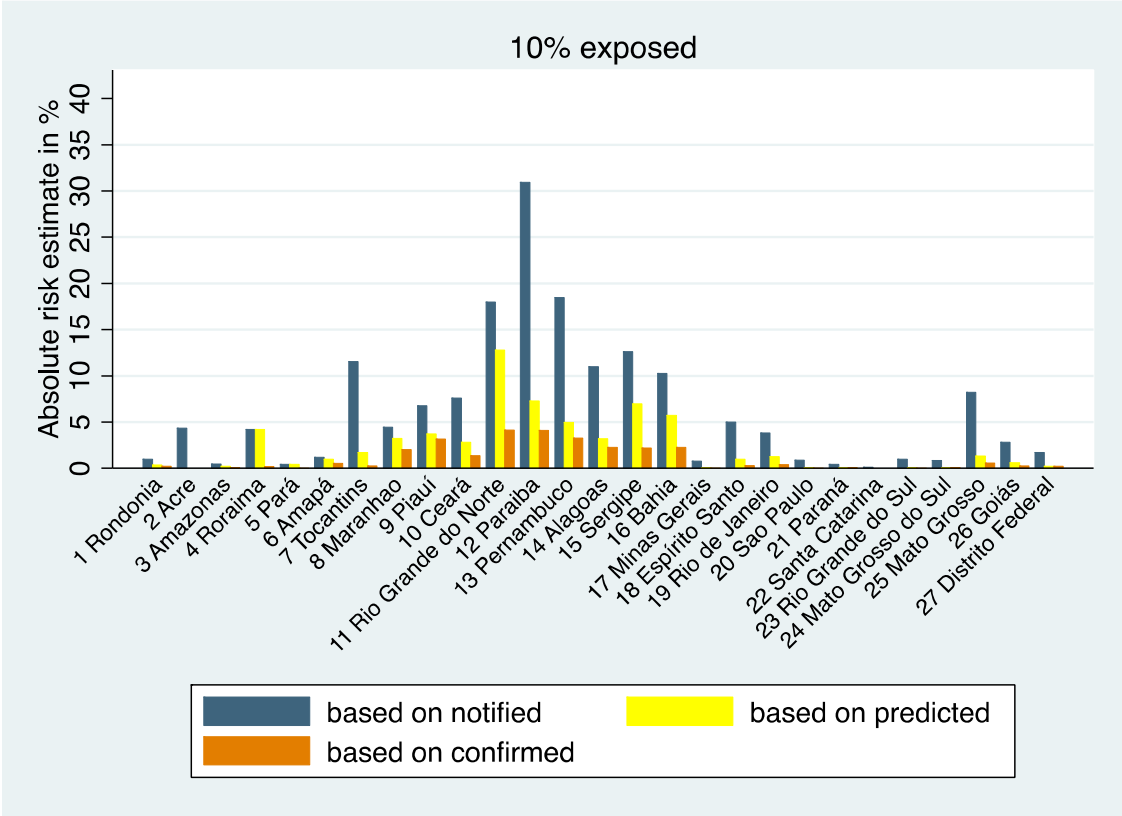
Conflict of Interest: The authors declare no conflict of interest.

Figure 1: absolute risk of microcephaly (%) by state in Brazil. A – under the assumption of 10% exposure; B – under the assumption of 50% exposure to ZIKV infection



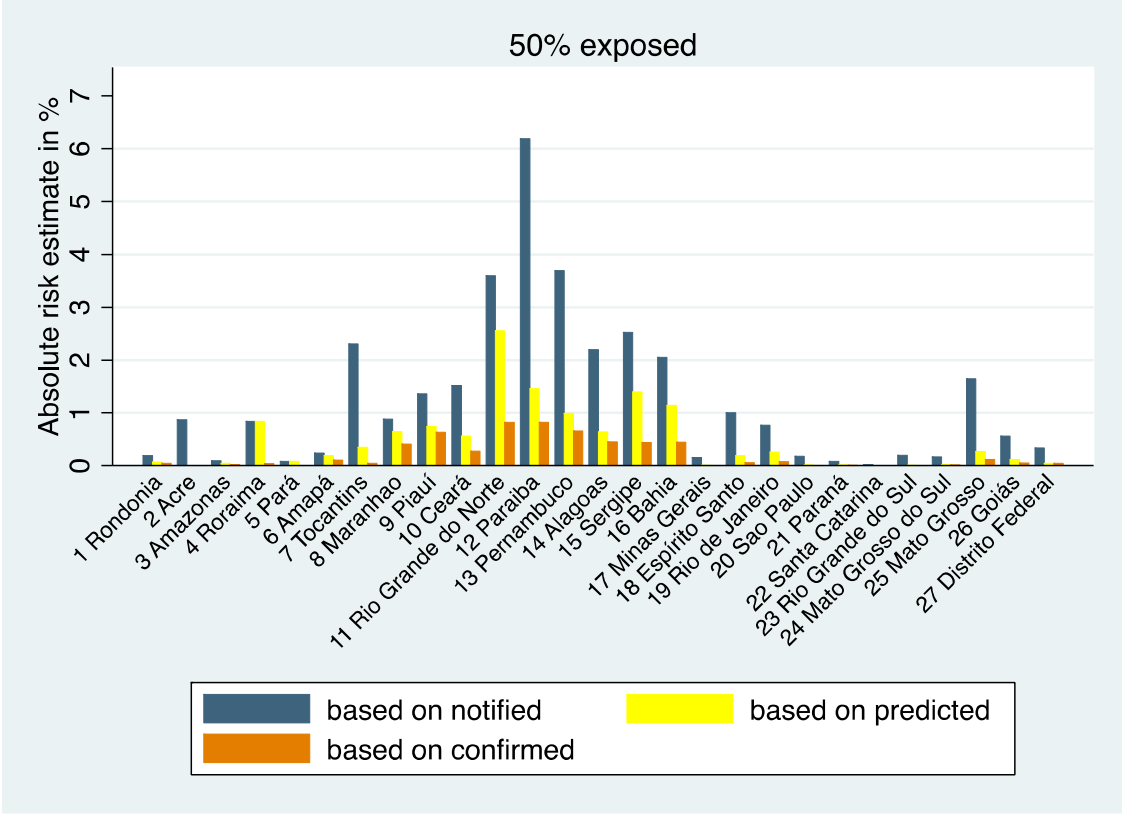


Table 1: Absolute risk estimates (%) for microcephaly, MOH Brazil definition, selected states in Brazil, November 2015 - April 2016

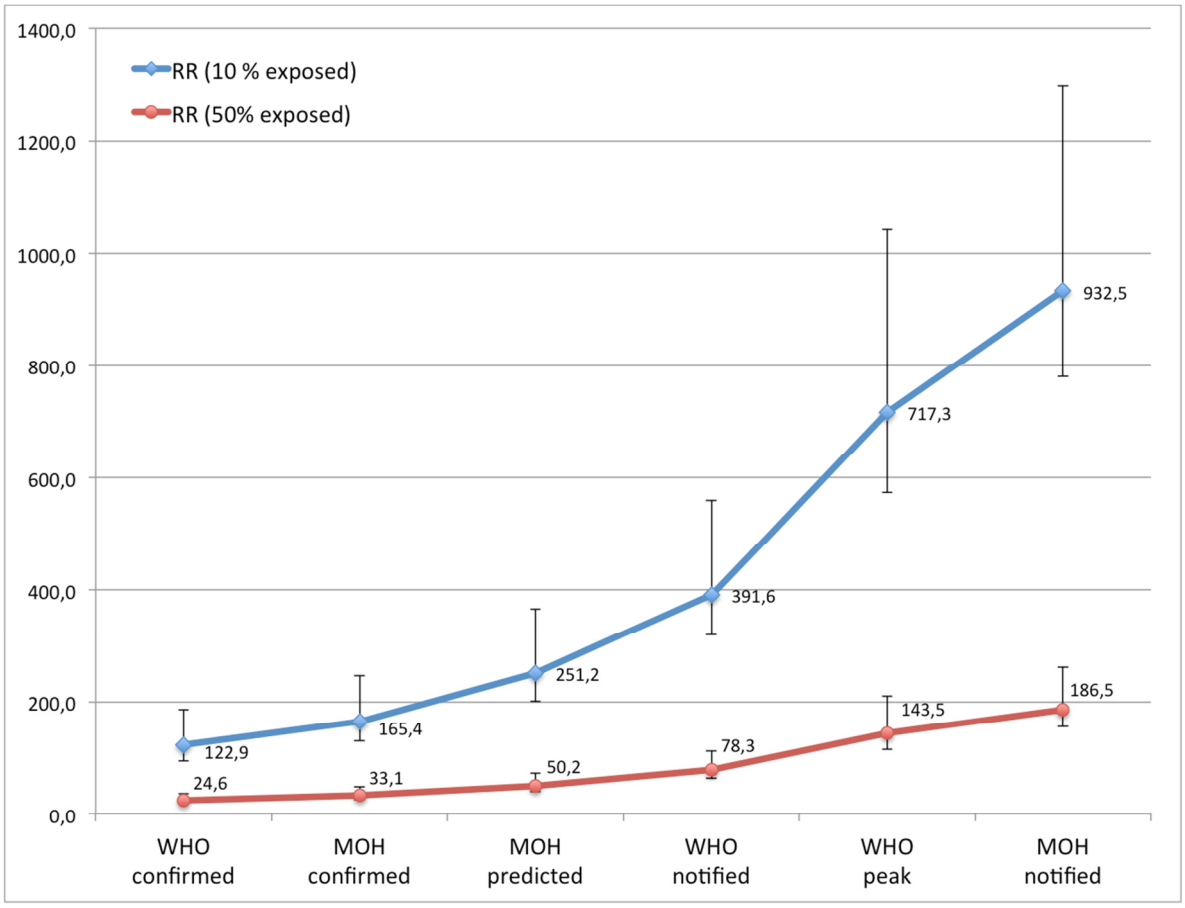
Location	N live births	10% exposure to ZIKV infection			50% exposure to ZIKV infection		
		Notified	Confirmed	Predicted confirmed	Notified	Confirmed	Predicted confirmed
Rio de Janeiro state	111,778	3.84	0.39	1.28	0.77	0.08	0.26
Pernambuco*	103,551	18.46	3.27	4.97	3.69	0.65	0.99
Paraiba	28,054	30.94	4.10	7.28	6.19	0.82	1.46
Rio Grande do Norte	23,245	17.98	4.13	12.79	3.60	0.83	2.56

* Time window for Pernambuco August 2015-April 2016

Table 2: Absolute risk estimates (%) for microcephaly in Pernambuco state, MOH Brazil definition vs. WHO Intergrowth definition

Location	Aug 15 – April 16										Peak Oct-Dec 2015	
	MOH Brazil definition						WHO InterGrowth				WHO InterGrowth	
	10% exposure			50% exposure			10% exposure		50% exposure		10% exposure	50% exposure
	Notified	Confirmed	Predicted confirmed	Notified	Confirmed	Predicted confirmed	Notified	Confirmed	Notified	Confirmed	Notified	Notified
Pernambuco	18.46	3.27	4.97	3.69	0.65	0.99	7.76	2.43	1.55	0.49	14.20	2.84

Figure 2: Relative risk estimates (95% confidence intervals) for microcephaly in Pernambuco – different microcephaly definitions, for 10% and 50% exposure



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