

# Study refutes suspicion that dengue increases risk of microcephaly associated with Zika

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Researchers compared data for pregnant women in Rio de Janeiro and Manaus who were infected by zika virus in 2015-16. Factors that influenced the risk of fetal malformation were the high zika attack rate in the area and being infected in the first trimester of pregnancy. Credit: TV Brasil

A pregnant woman infected by Zika virus does not face a greater risk of giving birth to a baby with microcephaly if she has previously been exposed to dengue virus, according to a Brazilian study that compared data for pregnant women in Rio de Janeiro and Manaus.

A Zika epidemic broke out in Brazil in 2015-16 in areas where [dengue](#) is endemic. Both viruses are transmitted by the mosquito *Aedes aegypti*.

Some of the states affected by the Zika epidemic reported a rise in cases of [microcephaly](#), a rare neurological disorder in which the baby's brain fails to develop completely. Others saw no such rise.

According to this new study by Brazilian researchers, two factors explain the rise in microcephaly in only some areas: The high Zika attack rate, and the mother's having contracted the virus in the first trimester of pregnancy. The term attack rate in epidemiology refers to the number of cases divided by the total population.

The study was supported by FAPESP via two projects (16/15021-1 and 13/21719-3), and was conducted under the aegis of the Network for Research on Zika Virus in São Paulo (Rede Zika). The results are described in an article in *Viruses*, a peer-reviewed open-access journal published by the Multidisciplinary Digital Publishing Institute (MDPI). The article appeared in late April in a special issue on Zika and pregnancy.

"The discrepancies between regions in terms of the numbers of reported cases of microcephaly during the Zika epidemic were puzzling. One of the hypotheses was that prior exposure to dengue might make Zika more severe, but in the state of São Paulo there weren't many adverse effects of Zika even though the region is highly endemic for dengue, so we decided to try to find out what could explain the differences," said virologist Maurício Lacerda Nogueira, a professor at the São José do Rio Preto Medical School (FAMERP) in São Paulo, and co-principal investigator for the study alongside Patrícia Brasil, a researcher at Oswaldo Cruz Foundation (FIOCRUZ) in Rio de Janeiro.

According to Nogueira, their attention was drawn to the attack rate when they analyzed the data for the two state capitals. In Rio de Janeiro, where many cases of microcephaly were reported, the number of people infected by Zika virus corresponded to 10 per 10,000 inhabitants, while

in Manaus, where relatively few babies were born with microcephaly, the attack rate was 0.6 per 10,000.

"Microcephaly caused by Zika is a rare phenomenon, but when there are many cases of Zika in an area it becomes more apparent. It had been suggested earlier that contracting Zika in the first trimester of pregnancy might be relevant, and now we've proved that it was," Nogueira said.

## **Methodology**

The researchers set out to understand the differences in the adverse outcomes of pregnancy and in the babies of the two populations by studying 114 pregnant women infected by Zika virus between September 2015 and June 2016. Infection was confirmed by RT-qPCR testing of blood and/or urine samples. The subjects were recruited at Heitor Vieira Dourado Tropical Medicine Foundation (FMT-HVD), an infectious disease hospital in Manaus, and FIOCRUZ's acute febrile illness clinic in Rio de Janeiro.

Prior exposure to dengue was assessed by serological tests to detect neutralizing antibodies, among others. The goal was to explore potential associations between pregnancy outcomes and the Zika attack rate, defined as the number of cases officially reported during the study period divided by the population of each city.

Overall, 31 women had adverse outcomes (27 in Rio and 4 in Manaus). In this group, four babies died before birth and 27 were born with brain anomalies. "Only Zika attack rates and infection in the first trimester of pregnancy were associated with adverse pregnancy and infant outcomes. Pre-existing immunity to dengue was not associated with outcomes (normal or abnormal) in patients with Zika during pregnancy," the authors of the article state in the Abstract.

And they conclude, "The strengths of our study include a careful classification of infant outcomes, made possible through detailed assessments at birth by a multidisciplinary team. [...] In addition, the use of a highly sensitive and specific [plaque reduction neutralizing antibody] assay to characterize pre-existing dengue immunity and the use of sera collected during the acute phase of RT-PCR-confirmed Zika infection lend credibility to our results. [...] Our main limitations are the modest sample size and convenience sample selection."

An earlier study led by Nogueira in 2017 showed that patients infected by Zika after exposure to dengue did not become more severely ill than other people. It was the first scientific study to show this in humans. [Prior research involving cells and rodents](#) had suggested the opposite.

## **Background**

Microcephaly is a rare neurological condition in which an infant's head and brain are significantly smaller than normal as a result of alterations in the formation of the nervous system during development in the womb. Children with microcephaly usually suffer from retarded or blocked mental, physical and motor development.

The causes of microcephaly include genetic factors and exposure to chemicals, bacteria and viruses. Scientists have recently shown that Zika contracted during pregnancy can impair fetal development.

During the epidemic in Brazil, Zika affected people of all ages and was associated with the occurrence of a large number of cases of microcephaly. In November 2015, Brazil declared a public health emergency because of the rising number of cases. The World Health Organization (WHO) then issued an epidemiological alert, stressing the possibility of congenital neurological malformations in babies born to women infected by Zika.

In 2015 alone, more than 2,400 cases of microcephaly were reported in Brazil. They occurred in about 540 municipalities in 20 states. In the period 2010-14, the total number of reported cases was 781.

In 2016 there were some 214,000 probable cases of Zika. The number fell to 17,000 in 2017 and 8,000 in 2018. In the first three months of this year, it was 448, according to the Ministry of Health's epidemiological bulletin.

The symptoms of Zika are similar to those of dengue. In most infected people, it causes fever, headache, red eyes, joint pain and rash. On average, the symptoms disappear in ten days.

The researchers are proceeding with their analysis of the interactions between Zika and dengue, particularly to see if Zika modulates infection by [dengue virus](#). Nogueira also participates in an international group that is working on models to predict epidemics of Zika, dengue and yellow fever.

**More information:** L. Damasceno et al. Why Did ZIKV Perinatal Outcomes Differ in Distinct Regions of Brazil? An Exploratory Study of Two Cohorts, *Viruses* (2021). [DOI: 10.3390/v13050736](https://doi.org/10.3390/v13050736)

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