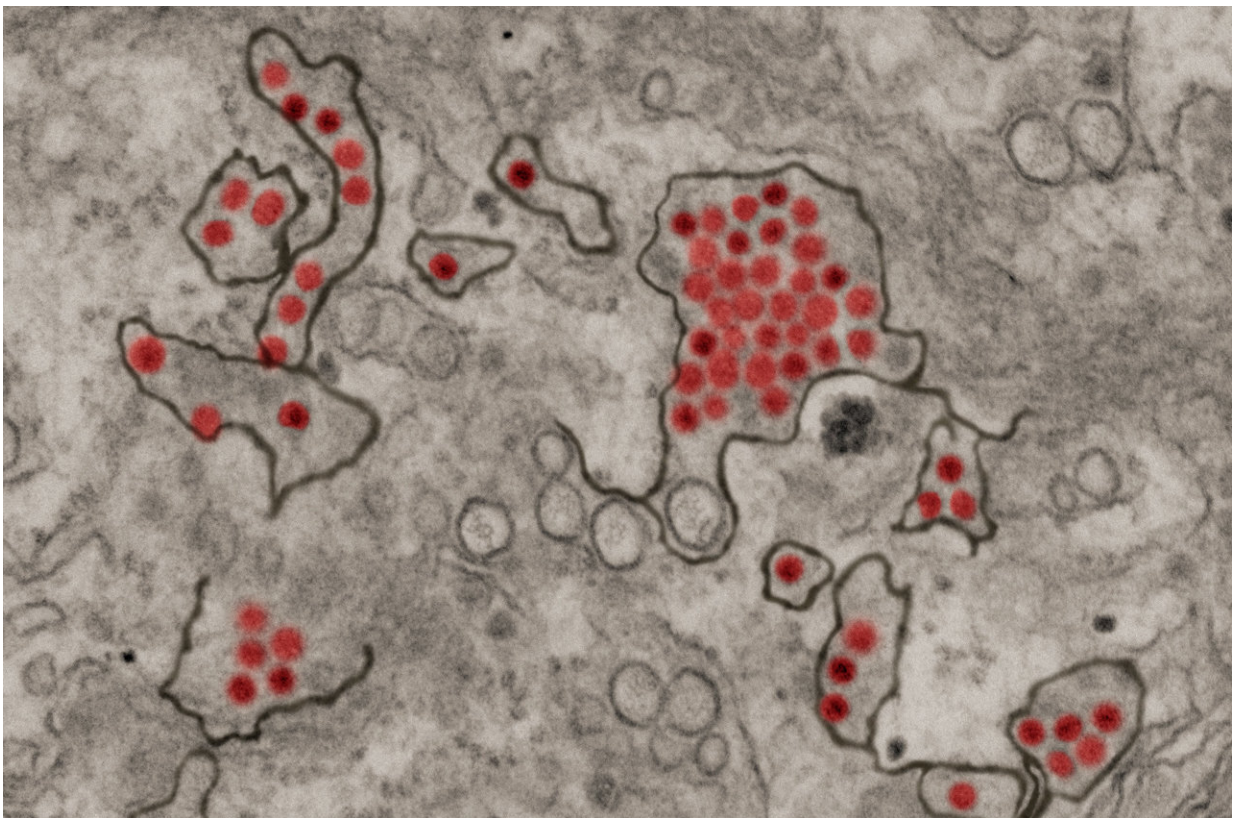


Prior Zika infection increases risk of subsequent severe dengue and hospitalization, study concludes

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Zika virus particles (red) shown in African green monkey kidney cells. Credit: NIAID

A study led by Brazilian researchers shows that people who have had the

Zika virus run a higher risk of subsequently having severe dengue and being hospitalized. The finding is highly relevant to the development of a Zika vaccine.

According to the scientific literature, a second infection by any of the four known dengue serotypes is known to be typically more severe than the first, but until now no correlation between this fact and the occurrence of other diseases had been investigated.

The study is [published](#) in the journal *PLOS Neglected Tropical Diseases*.

The mechanism that exacerbates dengue infection following a case of Zika differs from that of two consecutive infections by the dengue virus, the authors conclude. The viral load is higher in the second dengue episode, with high levels of inflammatory cytokines not seen in Zika.

Detection of other markers suggested that the increase in severity may be due to activation of T cells, key parts of the immune system that help produce antibodies, in a pathogenic immune response that has been termed the "original antigenic sin."

The process involves so-called T-cell memory, a response in which T cells produced during a previous infection stimulate the production of more T cells to combat a new infection. Because these new cells are not specific to the virus, they trigger an excessive release of inflammatory cytokines, which attack the organism's proteins and tissues, potentially leading to hemorrhage.

The researchers analyzed samples from 1,043 laboratory-confirmed dengue patients, identifying those with prior Zika and dengue infections. The cases occurred in 2019 in São José do Rio Preto, a large city in São Paulo state, Brazil, considered hyperendemic for dengue since more than 70% of the population has had the disease. Its climate and geography

favor the circulation of arboviruses throughout the year. Dengue epidemics occurred there in 2010, 2013, 2015, 2016 and 2019, with a record number of cases involving serotype 2.

"We concluded that a prior dengue infection was not a risk factor for severity, probably because the patients were already into their third or fourth infection. Prior Zika infection, however, was important and an aggravating factor in a second dengue episode. This led us to suggest novel mechanisms and renew our knowledge of the natural history of the disease," Cássia Fernanda Estofolete, an infectious disease specialist at the São José do Rio Preto Medical School (FAMERP) and first author of the article, told Agência FAPESP.

"Our findings confirmed the results of a [previous study](#) involving children who had Zika in Nicaragua. Later, when they had dengue, the risk of severity increased. We showed the same thing [risk of severe dengue increased by prior Zika or dengue] for adults in Brazil. We also showed that ADE [antibody-dependent enhancement, in which—instead of providing protection—antibodies enhance viral entry into host cells and can exacerbate the disease] is non-classical," said corresponding author Maurício Lacerda Nogueira.

"This raises questions about the type of Zika vaccine that should be used and the optimal timing: should it be administered with a dengue vaccine in order to avoid this problem of one following the other, for example? There are various possibilities, which need to be understood to ensure correct prescription. In Brazil, it's still more important to give the dengue vaccine first because of the number of cases," added Nogueira.

Case numbers

In November 2023, the number of dengue cases in Brazil surpassed the number notified in the 12 months of 2022, reaching 1,372,000, of which

1 million were confirmed between January and July (when the latest bulletin available was issued). The states of São Paulo and Minas Gerais had the most cases, according to the Health Ministry.

With regard to Zika, the latest numbers for 2023 are 4,773 probable cases, of which 1,725 were confirmed. Bahia and Rio Grande do Norte had the most cases. Arboviral diseases are usually under-reported, epidemiologists note, because they are hard to diagnose and because many people have mild symptoms and do not seek health services for treatment.

In 2016, when there were outbreaks of Zika in many parts of the world, Brazil had more than 1.5 million of the 2.38 confirmed cases in the Americas. In 2019, South America had a dengue epidemic, with more than 3.13 million notified cases, four years after Zika first appeared on the continent.

In March 2023, a dengue vaccine produced by a Japanese company won approval from ANVISA, Brazil's health surveillance agency, and this vaccine is now available from private clinics. Butantan Institute is developing an entirely indigenous dengue vaccine for distribution to public clinics. Development of a Zika vaccine is ongoing but at an earlier stage.

Dengue and Zika are both flaviviruses, are transmitted by the same mosquito (*Aedes aegypti*), and have similar symptoms, often making diagnosis difficult. Dengue is more serious because in addition to fever, headache, muscle and joint pain, rash and nausea, it can cause bleeding and even death.

The symptoms of Zika are milder, but the virus can cause severe problems in [pregnant women](#) and in babies, such as microcephaly and possibly Guillain-Barré syndrome, a neurological disorder that leads to

paralysis.

Specialists have been warning that Aedes mosquitoes and the diseases they transmit are appearing in temperate regions owing to global warming and climate change. Deforestation also contributes to the rise in case numbers, as the mosquitoes have more predators in biodiversity hotspots.

Analysis of samples

The study was conducted using samples from patients with suspected dengue, confirmed by RT-PCR. The samples were evaluated for past history of dengue and Zika infection using an enzyme-linked [immunosorbent assay](#) (ELISA) developed by the FAMERP group in partnership with Lee Gehrke's laboratory at the Massachusetts Institute of Technology (MIT) in the United States. The assay was specifically developed to eliminate the high cross-reactivity between flaviviruses observed in the commercial kits available on the market.

The analysis showed that patients with a history of Zika infection had a 2.34 times higher risk of developing severe dengue and a 3.39 times higher risk of hospitalization compared to the controls (subjects with no dengue and no Zika history). Relatively advanced age (over 59) was also a higher risk factor for severe forms of dengue and hospitalization.

With years of research behind them, Nogueira and his group published a 2021 study showing that a prior [dengue infection](#) in pregnant women infected by Zika virus does not increase the risk of giving birth to a baby with microcephaly.

Estofolete has now embarked on a new stage of the research, extending the study period to cover dengue cases notified in 2022 and changing the serotype.

"The goal is not just to answer questions about severity, but also to know whether the mechanism we detected is the same for all dengue serotypes because this influences other factors and mechanisms. We don't have a great deal of accumulated knowledge about Zika vaccines," he said.

More information: Cassia F. Estofolete et al, Influence of previous Zika virus infection on acute dengue episode, *PLOS Neglected Tropical Diseases* (2023). [DOI: 10.1371/journal.pntd.0011710](https://doi.org/10.1371/journal.pntd.0011710)

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