

These points of scepticism should not detract from the many things that are right and important about this analysis and about the GBD project as a whole. And it is also clear that the GBD investigators are aware of these challenges and continually seeking ways to improve their models and move, iteratively, towards a clearer view of the truth. Globally, progress is being made to reduce diarrhoeal disease. If the GBD data could be used to also identify areas where data are particularly thin or dated, and so reduce uncertainties in the case of individual countries, that also would be a huge advance. As child survival researchers, we are hugely encouraged by this report, even as it reminds us that there are roughly 1.3 million excellent reasons why our job remains incomplete.

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## Dengue infection during pregnancy and risk of preterm birth



Studies that investigate dengue among pregnant women are rare. Although there is a high incidence of dengue infection in women of childbearing age,<sup>1</sup> the effects of dengue infection during pregnancy on fetal outcomes are neither well understood nor well documented.<sup>2</sup> Since the first reported case of a pregnant woman with dengue fever in 1948, little evidence has been consolidated.<sup>2,3</sup> Now, with increased recognition of dengue cases among adults, including women of reproductive age, and the association of Zika virus with congenital malformations, establishment of reference data is necessary for future analysis of trends on birth outcomes.

As reported in *The Lancet Infectious Diseases*, Laura Nascimento and colleagues<sup>4</sup> used the extensive database of the Brazilian Ministry of Health to evaluate a retrospective cohort of 56 817 suspected cases of dengue infection in pregnant women from 2007 to 2013. The databases used were the national reportable disease

information system (SINAN), a consolidated system of passive registration for suspected dengue cases in Brazil since the 1990s, and the livebirth information system (SINASC), a database of birth registration. The authors referenced and briefly reviewed the information obtained from SINAN and SINASC in previously published studies.<sup>5,6</sup> In Brazil, which contributes to up to 7% of annual dengue cases worldwide, successive dengue epidemics have occurred since 1986 and all four serotypes of dengue virus are in circulation.<sup>7</sup>

From 56 817 reported cases of dengue in pregnant women, the authors analysed 3898 laboratory-confirmed cases and 3165 dengue-negative cases linked with livebirth data. Besides comparing maternal characteristics, the authors estimated relative risks (RRs) and odds ratios (ORs) between the groups with and without dengue infection and stratified by gestational age for different outcomes: malformation, preterm births, and low birthweight. Maternal



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dengue infection was associated with an increased incidence of preterm birth (adjusted analysis: OR 1.26, 95% CI 1.06–1.49,  $p=0.006$ ; unadjusted analysis: RR 0.81, 95% CI 0.70–0.93,  $p=0.004$ ). Notably, after adjusting for covariates, the direction of the effect changed, suggesting that both the risk of dengue acquisition and the quality of adequate prenatal care depend strongly on demographic and socioeconomic determinants. The authors found no association between dengue infection and low birthweight and congenital malformations, confirming previous findings of smaller studies.<sup>2</sup> This is the largest dengue population studied so far, which provides baseline data before the introduction of chikungunya and Zika viruses to the country.

Although secondary databases have inherent limitations related to under-reporting of passive surveillance systems and data quality, in this study the analyses included comparison groups and a large sample size, which strengthened the results. Similar to most studies of this topic, this one was restricted to pregnant women with symptomatic dengue infection, introducing a potential bias because of the absence of asymptomatic infections, which could account for almost 50% of all infections.<sup>2,5,8–11</sup> Additionally, dengue infection in pregnant women in the second and third trimester is more likely to be reported than in earlier periods of pregnancy and in women of reproductive age who might not know they are pregnant. The databases used did not permit adequate estimation of the role of dengue infection in miscarriages, especially those occurring during the first trimester of pregnancy.<sup>2</sup>

The association between preterm birth and dengue virus infection in pregnant woman is biologically plausible, because the intense inflammation reaction

triggered by maternal infection can indirectly stimulate uterine contractions leading to preterm delivery.<sup>2,3,5,11</sup> Since prematurity is among the main causes of neonatal and infant death,<sup>2</sup> we recommend close monitoring of pregnancies in areas with concurrent circulation of several arboviruses and where differentiating between dengue, Zika, and chikungunya virus infections is challenging.

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## Dengue and stillbirth

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Dengue, a viral disease mostly transmitted by *Aedes aegypti*, is widespread in tropical and subtropical regions of Africa, the Americas, Asia, and Oceania.<sup>1</sup> The incidence of dengue is increasing in many areas, with more than half of the world's population now vulnerable.<sup>2</sup> Many dengue infections are subclinical, but others present with symptoms including high fever, headache, weakness, muscle pain, and sometimes a rash that usually diminish after 6 days. At its worst, dengue

might cause dengue haemorrhagic fever or dengue shock syndrome, resulting in death. Generally, dengue infection is more harmful to vulnerable populations and is a leading cause of serious illness and death among children in some Asian and Latin American countries.<sup>3,4</sup>

Preterm birth and low birthweight are the most common adverse pregnancy outcomes associated with maternal dengue infection.<sup>3</sup> However, several case reports<sup>5–7</sup> have suggested that the dengue virus can be