Zika virus and microcephaly: where do we go from here?

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In November 2015, the Brazilian Ministry of Health declared a public health emergency because of an unexpected and dramatic increase of reported microcephaly among newborn infants in northeast Brazil.[1] An intense international public health response rapidly identified a causal link between Zika virus infection and birth defects.[2] Although initial patients were diagnosed by the presence of microcephaly, it soon became apparent that Zika virus caused a congenital syndrome with a spectrum of phenotypes that extended beyond microcephaly.[3-6] Yet, despite early fears that this mosquito-borne pathogen would cause a widespread, devastating epidemic of birth defects, the occurrence of microcephaly after the second wave of transmission in 2016, when Zika virus spread from northeast Brazil across the country, was substantially lower than that following the first wave of transmission in early 2015.[1] Although the use of sensitive yet non-specific case criteria for microcephaly, among other factors, could have contributed to initial overestimation of the risk, the progression of the microcephaly epidemic remains puzzling.

The Article[7] by Thalia Velho Barreto de Araújo and colleagues in the *Lancet Infectious Diseases* presents the final report of a case-control study in Recife in northeast Brazil, and provides an important early snapshot of the microcephaly epidemic. This investigation, which follows on from a preliminary report,[8] enrolled additional participants to perform a comprehensive analysis of potential risk factors. The final report confirmed the strong association between Zika virus infection and microcephaly (matched odds ratio 73·1; 95% CI 13·0–∞). Furthermore, 99 (57%) of the 173 mothers of control infants tested positive for Zika virus-neutralising antibodies, suggesting that a high prevalence of infection with Zika virus in northeast Brazil in early 2015 could have contributed to the large subsequent burden of microcephaly.[7]

Importantly, this Article provides the first evidence that exposure to the insecticide pyriproxyfen and vaccines administered during pregnancy were not associated with an increased risk of microcephaly. Despite weak biological plausibility, insecticides and vaccines had been speculated to be potential risk factors at the height of the epidemic.[9] Notably, female neonates in this study had a significantly increased risk of microcephaly (67% of cases were female *vs* 49% of control infants); if not the result of selection bias, this finding could have important biological implications. Speculated implications include the possibility of an increased risk of developing congenital defects among female fetuses that are exposed to Zika virus or an increased risk in male fetuses of spontaneous abortion in utero. Although the matched design limited the ability to detect associations with socioeconomic status, as acknowledged by the authors, most cases were from low socioeconomic classes. Higher Zika virus seroprevalence has previously been observed in communities of lower socioeconomic classes than in higher socioeconomic classes.[10] Together, these findings suggest that the poor had a disproportionately higher burden of congenital Zika syndrome during the epidemic.

The Article also serves to highlight the challenges facing screening and care for infants with congenital Zika syndrome. First, 35% of the cases with microcephaly had detectable Zika virus by Zika-specific capture-IgM or qRT-PCR at birth. Among cases who tested negative for Zika virus, 20% had cerebral abnormalities, as detected by cranial CT scan, illustrating the potential limitations of current diagnostics in screening newborn infants. Second, the clinical spectrum of congenital Zika syndrome varied among infants with microcephaly. The preliminary report[8] found a high association (odds ratio 24·7; 95% CI 2·9–∞) between Zika virus infection and the risk of microcephaly in the absence of cerebral abnormalities. Additionally, 69 (83%) of the 91 cases in this Article were small for gestational age, suggesting a role for intra-uterine growth restriction, as was observed in a study[3] in Rio de Janeiro. Finally, although the prevalence of infection in Brazil and the Americas might not have reached the levels observed in this study, there is an enormous task at hand to screen the large number of infants who could have acquired congenital Zika syndrome during the Zika virus pandemic and are now reaching age 2 years.

An unanswered question is whether, in addition to infection rates among pregnant women, the risk of developing congenital Zika syndrome after infection was also high in northeast Brazil, given the large first wave of microcephaly cases in 2015. Reports[3,11,12] regarding the prevalence of microcephaly and adverse birth outcomes

found that these ranged from 3–4% in Rio de Janeiro and 5–42% in the USA. A 2017 study[13] in São Paulo, Brazil, found adverse outcomes in 15 (28%) of 54 infants (95% CI 17–41) of pregnant women infected with Zika virus, but these outcomes appeared to be substantially milder than those observed in the Rio de Janeiro study,[3] causing speculation of possible variation in risk across regions. However, case-control, prospective cohort, and enhanced surveillance investigations have not yet yielded insights on why a small fraction of fetuses of infected mothers develop microcephaly and severe sequelae. Elucidation of the role of pre-existing immunity to dengue and other potential factors might need to await completion of large prospective studies of pregnant women, such as Zika in Infants and Pregnancy, ZikaPLAN, ZIKAlliance, ZIKAction, and those being conducted by the US Centers for Disease Control and Prevention. Nevertheless, the authors should be commended for implementing this well designed case-control investigation and providing crucial evidence in the early stages of outbreak response and in this final report.

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