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Further Pieces of Evidence on the Zika and Microcephaly Puzzle

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Two years after the "cluster of microcephaly cases" was detected in Brazil, we are still answering basic epidemiological questions.1 The immediate concern at the time of the epidemic was identifying the underlying cause of the neurological abnormalities. Prior to 2015, microcephaly was a rare but well-known condition.2 However, the upsurge in diagnoses in the Americas was different, and a range of potential causes were proposed. Under consideration was congenital Zika, but also alternative risk factors, including exposure to pesticides, receipt of vaccines during pregnancy, and an "epidemic" of over-diagnosis. Today, evidence from in vitro, animal model, and epidemiological investigations has established a clear, causal link between Zika virus (ZIKV) infection in pregnancy and microcephaly, and our motivating questions have shifted their focus from etiology to that of disease burden and biological mechanisms.3

In *The Lancet Child & Adolescent Health*, J. Erin Staples and colleagues4 advance our understanding by estimating that between 35 to 87% of the microcephaly cases observed in Paraíba, Brazil, between August 2015 and January 2016 were attributable to ZIKV exposure. This confirms ZIKV as a cause of microcephaly generally and of this epidemic specifically. The key caveat to the authors' estimate is that the percentage of cases attributable to ZIKV cannot be generalized to other times or places. Indeed, the attributable risk could be influenced by aspects of transmission (e.g., force of infection, epidemic versus sporadic incidence, epidemic stage/population immunity, seasonality, population density, competent vectors, and vector control measures), the frequency of terminations, and the baseline prevalence of non-Zika microcephaly. It is also likely that the fraction attributable could be higher with less restrictive diagnostic criteria and better laboratory tests.

While the rapid response of the investigative team to the ZIKV outbreak in Paraíba state took advantage of a unique opportunity and their efforts are to be lauded, the urgency with which this research was undertaken inevitably introduced limitations. Of note, this was a "retrospective" rather than "concurrent" case-control study: participants were recruited not at birth, but at 1 to 7 months of age. Cases were identified from the state's registry of microcephaly notifications, and only the 26% of notified infants (N=43/146) who had head circumferences (HC) ≤ the 3rd percentile and HC to length ratios of ≤ 0.65 upon re-examination were included in the final analyses. Although this high level of specificity may

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be justifiable due to concerns related to over-notification in early surveillance efforts,5 the choice of recruiting from past notified cases instead of at birth increased the study's vulnerability to recall biases in maternal reporting of Zika-like symptoms and relied on significant assumptions in terms of infant growth patterns, antibody persistence, and the timing of infections during pregnancy. It remains plausible that some of the mothers and children may have experienced ZIKV after birth. In addition, there will be value in the evaluation of the 103 infants diagnosed with microcephaly at birth who were excluded from these analyses. Did they differ in terms of their serology and brain imaging? Did they have any other clinical features consistent with Congenital Zika Syndrome as in similar notified but then excluded cases?5 These analyses could inform the debate surrounding the issue of whether Small for Gestational Age neonates with HCs below the microcephaly threshold but in proportion to their bodies should be included in the microcephaly case definition.

Nevertheless, using this unconventional definition of microcephaly, the authors found that the cases had 22-fold higher odds of having serum neutralizing activity to ZIKV at the follow-up visit and 6-fold higher odds of being born to a mother reporting ZIKV-like symptoms during the first trimester of pregnancy than geographically matched controls. Consistent with earlier studies,6–8 this investigation ruled out a number of alternative risk factors for microcephaly related to sociodemographic indicators and maternal exposures during pregnancy (of particular interest, pesticide use9) and also showed that a significant proportion of microcephaly cases were born to women who did not report symptoms in pregnancy. Unfortunately, due to its limited sample size, the current study was not able to address one of the most intriguing current questions: Does previous maternal dengue experience increase risks of developing microcephaly upon ZIVK infection in pregnancy? Evidence from non-human primate models suggests that pre-existing immunity to ZIKV may enhance dengue-2 viremia upon subsequent infection.10 Whether prior dengue experience can facilitate antibody dependent enhancement of ZIKV infection with potential consequences for fetal neurodevelopment remains an urgent question.

Looking to the future, the epidemiological research agenda should, first, prioritize determining the frequency, and full spectrum, of Congenital Zika Syndrome in neonates of women with symptomatic (and, also importantly, asymptomatic) ZIKV in pregnancy and identifying potential effect modifiers (e.g., pre-existing immunity to dengue). The joint analysis of a series of cohort studies funded by the Medical Research Council, the Wellcome Trust, the UK Department for International Development, the EU's Horizon 2020 platform, and the US National Institutes of Health will answer those questions. Second, population-based surveys that investigate immunity to ZIKV in Latin America as well as other regions, will be critical for the planning of vaccine trials. Finally, although diagnoses have slowed, public health challenges related to ZIKV and its adverse outcomes remain. It is essential that we continue to track the development of the children growing up with Congenital Zika Syndrome and consider the impacts for families as well as providing the support they require.

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