# Microcephaly and Zika virus infection

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Rarely have scientists engaged with a new research agenda with such a sense of urgency and from such a small knowledge base as in the current epidemic of microcephaly (6000 notified suspected cases in Brazil[1] and the first case detected in Colombia in March, 2016[2]) associated with the Zika virus outbreak across the Americas. Indeed, in 2015, in a review of infections that have neurological consequences, Zika virus was not even mentioned.[3] In only 5 months since the detection of the first excess cases of microcephaly in Brazil,[4] WHO has declared the clusters of microcephaly and other neurological disorders to be a Public Health Emergency of International Concern.[5] WHO had also stated that the causal relation of these disorders with Zika virus infection had not yet been scientifically proven.[5] The reluctance to accept the causal link stems from the rarity of isolation of Zika virus or detection of RNA in neonates with microcephaly.[1]

Before the outbreak of Zika virus in the Americas, the largest documented outbreak was in French Polynesia in 2013–14. An elegant piece of evidence supporting the theory that Zika is the cause of microcephaly comes from that outbreak. In the first investigation, no peak in the number of fetuses or neonates with microcephaly was detected.[6] The theory that mother-to-child Zika virus infection was a cause of the microcephaly epidemic in Brazil, however, required that there had been an increase in microcephaly associated with the Zika outbreak in French Polynesia. Further investigation identified 17 cases of severe neurological malformations, including microcephaly, and showed that a peak had been missed because most women had terminations.[7]

In *The Lancet*, Simon Cauchemez and colleagues[8] present a reanalysis of the data on Zika and microcephaly from the French Polynesian outbreak to estimate the magnitude of risk in women infected with Zika virus during pregnancy. They used serological data to estimate the total number of infections during the outbreak and data from surveillance on consultations for suspected Zika virus disease to attribute these infections to the weeks of the outbreak. They did an exhaustive search of medical records to identify all cases of microcephaly during the period Sept 1, 2013, to July 31, 2015. Eight cases of microcephaly were identified, seven of which occurred in a 4-month period around the end of the Zika virus outbreak. The baseline prevalence of microcephaly was two (95% CI 0–8) per 10 000 neonates. The researchers developed a mathematical model with six periods of assumed increased risk of microcephaly given Zika infection to investigate when the risk of infection and the magnitude of the risk were greatest. The period of risk with the best fit was infection in the first trimester of pregnancy. The risk of microcephaly associated with Zika virus infection was 95 (34–191) per 10 000 women infected in the first trimester: essentially a risk of microcephaly for infection in the first trimester of around 1% (0·3–1·9)

The finding that the highest risk of microcephaly was associated with infection in the first trimester of pregnancy is biologically plausible, given the timing of brain development and the type and severity of the neurological abnormalities.[9] However, the absolute risk of 1% estimated by Cauchemez and colleagues is perhaps lower than expected. In the state of Pernambuco, Brazil, where the risk was highest, during the 4 months of the epidemic 2% of all neonates were notified as suspected cases of microcephaly, not only those born to women known to have been infected.[4] Half of the suspected cases were confirmed by the presence of calcifications, other brain abnormalities, or both.[4] How to interpret the data has been the subject of some debate.[10]

After the paper by Cauchemez and colleagues[8] was written, Brasil and colleagues[11] reported preliminary results for 72 pregnant women with symptomatic,

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laboratory-confirmed Zika virus infections, recruited in Rio de Janeiro before fetal outcomes were known. Ultrasound images were available for 42 women, of which 12 (29%) showed abnormalities over the range of gestational ages at infection.[11] Nine women had rash and viraemia in the first trimester, and microcephaly was detected by ultrasonography in two of these, which corresponds to 22% risk of microcephaly after symptomatic Zika infection in the first trimester.[11]

These three different approaches addressed different questions: the risk in all neonates during the epidemic in Pernambuco[4] and the risk in neonates from women infected with Zika virus in the first trimester of pregnancy in the other two studies (with clinical symptoms in Rio de Janeiro[11] and independently of clinical symptoms in French Polynesia[8]). As expected the estimates are different, but are they consistent with a single underlying risk or, alternatively, will risk be dependent on other factors, such as the presence of clinical symptoms or previous dengue infection? Further data will soon be available from Pernambuco, Colombia, Rio de Janeiro, and maybe other sites that will gradually answer these questions. The fast production of knowledge during this epidemic is an opportunity to observe science in the making: from formulation of new hypotheses and production of new results that will provide confirmations and contradictions to the refinement of methods and the gradual building of consensus. I expect we will teach our students about the production of science using examples from this Public Health Emergency of International Concern for many years to come.

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I declare no competing interests.

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