NEURODEVELOPMENTAL DISORDERS

Risks of Zika virus during the first trimester of pregnancy

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The ongoing Zika virus (ZIKV) epidemic in the Americas raises urgent questions about the risks of microcephaly in the children of ZIKV-infected mothers. New research into the 2013–2014 ZIKV outbreak in French Polynesia supports a link between maternal ZIKV infection during the first trimester of pregnancy and microcephaly.

Refers to Cauchemez, S. *et al.* Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. *Lancet* http://dx.doi.org/10.1016/S0140-6736(16)00651-6 (2016)

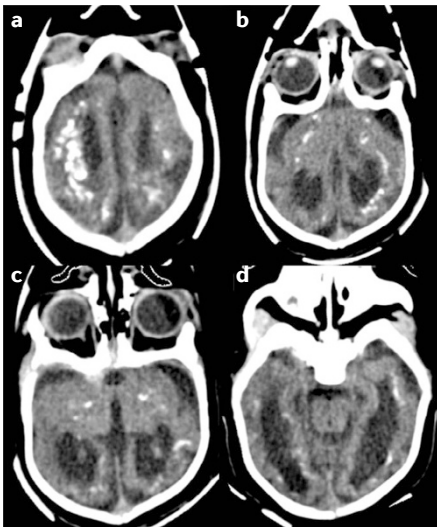

Figure 1 | **Intracranial calcifications.** Axial head CT images of an infant with congenital microcephaly related to intrauterine Zika virus infection. **a**,**b** | Band-like and larger calcifications. **c** | Isolated and punctate calcifications. **d** | Band-like and larger calcifications. Calcifications are observed at the level of the corticomedullary junction (part **a**) and periventricularly within the frontal, parietal and temporal lobes (parts **a**–**d**), as well as within the basal ganglia (parts **b**,**c**). In addition, global cortical hypogyration, moderate ventriculomegaly, and abnormal hypodensity of the supratentorial white matter are noted. Images from the Medical Research Council-funded Digital Imaging Platform project, courtesy of Andrea Poretti (Johns Hopkins Children's Center, Baltimore, Maryland, USA).

A recent apparent dramatic increase in the rate of microcephaly in Brazil has been linked to a new outbreak of Zika virus (ZIKV), a flavivirus transmitted by mosquitoes and through sexual intercourse[1–3]. The case for a causal link between ZIKV infection and microcephaly is based on epidemiological data and detection of the virus in relevant tissues. In addition, calcifications have been observed in the brains of microcephalic fetuses (FIG. 1) and newborns infected with ZIKV. In an important new study, published in *The Lancet*, Simon Cauchemez and colleagues have analysed data from a previous ZIKV outbreak in French Polynesia to explore the link between ZIKV and microcephaly in detail[4].

Congenital microcephaly is a clinical sign, defined by the international INTERGROWTH-21st Newborn Size Standards as a head circumference at least 2 SD smaller than the mean for sex and gestational age at birth. Although a subset of babies born with small heads will have normal neurological development, some have brain abnormalities that place them at risk of developmental delay and intellectual disability due to a range of genetic, environmental and infectious causes[5]. They may also develop convulsions and physical disabilities including hearing and visual impairment.

On 1st February 2016, WHO declared the suspected link between ZIKV and microcephaly to be a Public Health Emergency of International Concern. In light of the emerging ZIKV epidemic in the Americas, we need urgent answers to a number of questions. First, when in pregnancy is the fetus most susceptible to the effects of maternal ZIKV infection? Second, how great is the risk of microcephaly if the mother is infected with ZIKV during this period? Last, what is the likelihood that developmental delay and intellectual disability will result from brain abnormalities due to ZIKV infection?

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To address these questions, Cauchemez *et al.* developed a simple mathematical and statistical model to characterize the association between ZIKV and microcephaly[4]. The current epidemic in the Americas has not yet provided sufficient data to model this association, so Cauchemez *et al.* instead focused on the largest previously documented ZIKV outbreak, in French Polynesia in 2013–2014 (REF. 6). Their retrospective analysis was based on four data sets: all microcephaly cases (although neither the fetal nor the newborn head circumference charts used are specified), the weekly number of consultations for suspected infection with ZIKV, seroprevalence of ZIKV antibodies, and the number of births during the outbreak. In the period 2013–2014, an average of 4,182 babies were born per year to a population of 270,000 in French Polynesia; it is not clear, however, whether this figure includes stillbirths as well as liveborns. Before the ZIKV outbreak, the seroprevalence of this virus had been 0.8%. By the second half of the outbreak, seroprevalence was estimated to be 50%, and this figure had risen to 66% by the end of the outbreak.

Cauchemez *et al.* analysed the prevalence and risk of microcephaly associated with ZIKV infection for different periods during pregnancy[4]. The study revealed eight cases of microcephaly: five in pregnancies that were terminated, and three in liveborn children. The study period was 23 months, but seven of the eight cases of microcephaly

were identified in a 4-month period from 1st March to 10th July 2014. Such temporal clustering and the results of mathematical modelling strongly support an association with ZIKV, although other causes of microcephaly were not excluded. Interestingly, the models that provided the best fit to the available data all included the first trimester of pregnancy, indicating that maternal ZIKV infection poses a greater risk during this period.

The study estimated the risk of microcephaly to be 1% if maternal ZIKV infection occurred during the first trimester of pregnancy. This risk seems low compared with that for other viral infections associated with birth defects (13% for primary cytomegalovirus (CMV), 38–100% for congenital rubella syndrome if mothers are infected in the first trimester of pregnancy, and 10% for parvovirus B19). However, the prevalence of ZIKV in the general population can be very high during outbreaks (66% in French Polynesia); by contrast, only 1–4% of pregnant women are infected with CMV, fewer than 10 cases of rubella are seen in pregnant women per year in France, and only 0.6–1.2% of women of childbearing age are infected with parvovirus B19. Thus, although ZIKV is associated with a low risk to the fetus, the high incidence of infection and its mode of transmission make it an important and urgent public health issue.

The ZIKV currently spreading in the Americas is closely related to the one detected in French Polynesia in 2013 (REF. 6), but extrapolation of the Cauchemez *et al.* findings to the Americas should be approached with caution. The attack rates might differ between outbreaks, as spread of ZIKV is affected by entomological, environmental and climatic factors. Also, the risk of microcephaly associated with ZIKV infection may differ in other populations owing to genetic factors.

Microcephaly is a very crude indicator of brain abnormalities, which are not reported by Cauchemez *et al.* WHO advises "additional clinical assessment and subsequent regular follow-up during infancy including: rate of head growth; pregnancy history and maternal and family history; developmental assessment; and physical and neurological examinations including hearing and ocular assessments for associated problems." Hence, studies with long-term follow-up are required; ultrasound, CT and MRI scans of affected infants should be shared among the scientific community, as initiated by the ZIKV Digital Imaging Platform Consortium; and the relationship between neurodevelopmental disorders and microcephaly severity needs to be quantified.

> "We do not understand the mechanisms through which ZIKV impairs brain development"

We do not understand the mechanisms through which ZIKV impairs brain development. During the first trimester, various progenitors generate waves of neuronal cohorts with precise temporal and special choreography, as these cells migrate to their final position[7]. Even subtle alteration of these neurogenic or migration programmes can lead to cognitive disorders in the long term[8]. More-detailed imaging and histopathological analyses are needed to detect abnormalities in the ZIKV-infected developing brain. Some of the damage can only be assessed later in life when cognitive functions fail to develop. The non-neuronal congenital abnormalities associated with maternal ZIKV infection, and their corresponding sensitivity periods, should also be documented in more detail. To aid this effort, a consistent set of diagnostic criteria, such as those provided by the INTERGROWTH-21st Standards, is needed[9].

Numerous mechanistic questions remain to be answered, including how maternofetal transmission occurs. Basic researchers are starting to address the cellular, genetic and molecular mechanisms underlying the damage caused by ZIKV in human neurospheres and brain organoid cultures[10], and animal models are being established and examined.

The Cauchemez *et al.* study[4] could have important implications for the understanding and management of the current ZIKV epidemic in the Americas. The findings clearly strengthen the association between the virus and microcephaly, and provide an important quantitative estimate of the risk of microcephaly in ZIKV-infected fetuses. The study emphasizes the need for health authorities in affected countries to promote vector control, organize fetal monitoring and newborn screening using standardized methods, and provide evidence-driven information for women of reproductive age.

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Competing interests statement
The authors declare no competing interests.

FURTHER INFORMATION
INTERGROWTH-21st Newborn Size Standards:
https://intergrowth21.tghn.org/
ZIKV Digital Imaging Platform Consortium:
http://www.obs-gyn.ox.ac.uk/news/uk-trebles-funding-to-tackle-zika-virus

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