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KFW declares no competing interests. JGT reports lecture fees and travel expenses from Ferring Pharmaceuticals.

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Microcephaly and Zika virus infection

Published Online

March 15, 2015

[http://dx.doi.org/10.1016/S0140-6736\(16\)00742-X](http://dx.doi.org/10.1016/S0140-6736(16)00742-X)

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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 Brazil¹ and the first case detected in Colombia in March, 2016²) 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 colleagues⁸ 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 colleagues⁸ was written, Brasil and colleagues¹¹ reported preliminary results for 72 pregnant women with symptomatic, 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 Pernambuco⁴ 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 Janeiro¹¹ and independently of clinical symptoms in French Polynesia⁸). 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



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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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Late maternal deaths: a neglected responsibility



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Maternal mortality, no matter when and where it occurs, results in sequelae that extend beyond the loss of the life of a single woman. The death of a mother adversely affects the ability of her family to survive and thrive, especially under conditions of socioeconomic deprivation.¹ Documentation of data on maternal mortality has helped identify areas of socioeconomic inequity and serves as a barometer of a society's health system.

Avoidable deaths from pregnancy complications occur on a global scale, with the greatest burden of mortality among women in low-to-middle-income countries.² Most countries record maternal death only up to 42 days post partum because of the assumption that avoidable death in pregnant women occurs during pregnancy or shortly thereafter. Although limited, the available data suggest otherwise. Globally, there are more post-partum and late maternal deaths from direct and indirect obstetric causes than maternal deaths during pregnancy.² Post-partum and late maternal deaths have not declined in the past decade, whereas deaths during pregnancy and the puerperium have.^{2,3} Estimates of post-partum and late maternal deaths are likely to be underestimated because late mortality has been variably specified and either counted or discounted in reporting systems used in the recent past. This problem was highlighted in reports by WHO and the US Centers for Disease Control and Prevention on maternal mortality surveillance.^{4,5} Interestingly, the introduction of a check box indicating pregnancy in the past year before death on national death certificates in some US states led to an increase in reported late maternal deaths in those states.⁵

Currently, physicians can be unclear about what counts as a late maternal death. The WHO Working Group on Maternal Mortality⁴ has suggested International Classification of Diseases (ICD) coding principles that define maternal death up to a year after delivery from causes directly related to pregnancy or indirectly precipitated by the effects of pregnancy on underlying

diseases; coincidental deaths are not included. The ICD10 code makes it obligatory to document the occurrence of pregnancy within a year of the death of any woman.⁶ These principles and the system of reporting have been tested against existing databases and reviewed by professional bodies, including the International Federation of Gynecology and Obstetrics, the American College of Obstetricians and Gynecologists, and the UK's Royal College of Obstetricians and Gynaecologists.⁴ However, the use of ICD10 coding of late maternal death is generally not applied globally, and so far there is no large data series outlining the specific causes leading to late maternal death on a global scale. What is known is that late maternal deaths fall into four main categories: cardiovascular causes, thromboembolism, cancer, and suicide.⁷

Pregnancy can trigger cardiovascular disease (eg, hypertensive disorders leading to heart failure), aggravate underlying disease (eg, rheumatic heart disease, congenital heart disease, or pulmonary arterial hypertension), or cause specific diseases, such as peripartum cardiomyopathy (PPCM). The latter disease typically presents only 1–3 months post-partum, with mortality rates of about 10–25% within 6 months after diagnosis.^{8,9} PPCM is the largest contributor to cardiovascular maternal death in South Africa,¹⁰ but because it often occurs outside the 42-day post-partum period⁸ women who die from PPCM are not usually reported as late maternal deaths in South Africa and elsewhere. Thus, epidemiological estimates of the burden of disease causing maternal mortality are skewed by the exclusion of deaths caused by PPCM. This situation is of concern because no matter how late these deaths occur, they are related to pregnancy.

Maternal deaths related to mental disorders have recently been assessed as part of the Confidential Enquiry into Maternal Deaths in the UK and Ireland.¹¹ Almost a quarter of maternal deaths that occurred between 6 weeks and 1 year after pregnancy in 2011–13 in the UK and Ireland were due to psychiatric