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Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study

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Summary

Background The emergence of Zika virus in the Americas has coincided with increased reports of babies born with microcephaly. On Feb 1, 2016, WHO declared the suspected link between Zika virus and microcephaly to be a Public Health Emergency of International Concern. This association, however, has not been precisely quantified.

Methods We retrospectively analysed data from a Zika virus outbreak in French Polynesia, which was the largest documented outbreak before that in the Americas. We used serological and surveillance data to estimate the probability of infection with Zika virus for each week of the epidemic and searched medical records to identify all cases of microcephaly from September, 2013, to July, 2015. Simple models were used to assess periods of risk in pregnancy when Zika virus might increase the risk of microcephaly and estimate the associated risk.

Findings The Zika virus outbreak began in October, 2013, and ended in April, 2014, and 66% (95% CI 62–70) of the general population were infected. Of the eight microcephaly cases identified during the 23-month study period, seven (88%) occurred in the 4-month period March 1 to July 10, 2014. The timing of these cases was best explained by a period of risk in the first trimester of pregnancy. In this model, the baseline prevalence of microcephaly was two cases (95% CI 0–8) per 10 000 neonates, and the risk of microcephaly associated with Zika virus infection was 95 cases (34–191) per 10 000 women infected in the first trimester. We could not rule out an increased risk of microcephaly from infection in other trimesters, but models that excluded the first trimester were not supported by the data.

Interpretation Our findings provide a quantitative estimate of the risk of microcephaly in fetuses and neonates whose mothers are infected with Zika virus.

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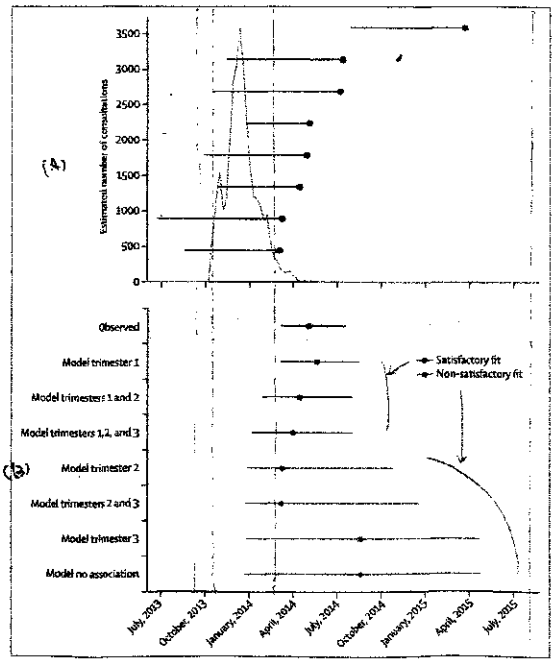

Figure 1: **Frequency of consultations and timing of microcephaly cases during the 2013–14 Zika virus outbreak in French Polynesia**
Outer dashed lines indicate the start and end of the study period (September, 2013, to July, 2015). Inner dashed lines show the time period when 95% of consultations for suspected Zika virus infection occurred (Oct 14, 2013, to Feb 17, 2014). (A) The solid purple line shows the estimated number of weekly consultations for suspected Zika virus infection. For each case of microcephaly, a black line indicates the duration of pregnancy and a black dot indicates the end of pregnancy due to delivery or medical abortion. (B) Timing of microcephaly cases predicted for different assumptions about the period of risk in pregnancy when infection of the mother with Zika virus would increase the risk of microcephaly for fetuses or neonates, compared with the observed timing. Dots indicate the median date and horizontal lines the 15th to 85th percentiles. Models are sorted by fit (best fitting at the top).

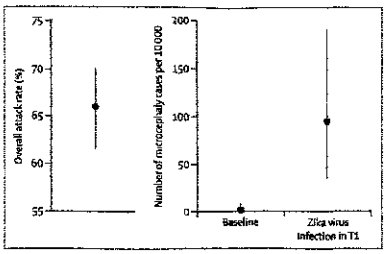

Figure 2: **Attack rate and strength of the association between infection with Zika virus and microcephaly in French Polynesia**
(A) Final attack rate (95% CI) based on seroprevalence after the end of the outbreak. (B) Baseline prevalence of microcephaly (number per 10 000 neonates) and risk of microcephaly associated with Zika virus infection in mothers (number per 10 000 women infected in the first trimester of pregnancy). T=trimester.

	Findings
Mother's age at beginning of pregnancy (years)	29·2 (24·3–34·1)
Sex of fetus or neonate	
Male	6 (75%)
Female	2 (25%)
Pregnancy outcome	
Medical termination	5 (62·5%)
Birth	3 (37·5%)
Gestational age at end of pregnancy (weeks)	
Medical termination	30·1 (26·1–31·4)
Birth	38·0 (37·2–39·5)

Data are median (IQR) or number (%).

Table 1: **Characteristics of mothers and of fetuses or neonates with microcephaly**

	Baseline prevalence of microcephaly per 10 000 neonates†	Number of microcephaly cases per 10 000 women infected in the period of risk	Risk ratio (95% CI)	p value*	AICc for model fit†
Trimester 1	2 (0–8)	95 (34–191)	53·4 (6·5–2061·2)	0·0007	0
Trimesters 1 and 2	2 (0–8)	50 (17–101)	26·4 (3·0–352·0)	0·0015	1·37
Trimesters 1, 2, and 3	2 (0–9)	42 (13–86)	20·8 (2·1–424·1)	0·0032	2·73
Trimester 2	4 (0–12)	84 (12–196)	23·2 (3·4–407·8)	0·02	5·76
Trimesters 2 and 3	4 (0–13)	53 (0–135)	11·9 (0·177·5)	0·05	7·67
Trimester 3	10 (3–18)	0 (0–251)	0 (0–49·3)	1·0	11·43
No association	10 (5–18)	–	–	–	7·15

Six scenarios were considered for the "period of risk" during pregnancy when infection of the mother with Zika virus might increase the risk of microcephaly. A last scenario assumed no association between infection and microcephaly. AICc=Akaike information criterion with a correction for small sample size. *Compared with no association. †Quality of fit increases with decreasing value, with differences in values ≥2 indicating substantial improvement in fit.*

Table 2: **Prevalence and risk of microcephaly associated with Zika virus infection for different periods of risk during pregnancy**

	Number of cases of microcephaly per 10 000 women infected in the period of risk (95% CI)			Change from baseline
	Trimester 1	Trimesters 1 and 2	Trimesters 1, 2, and 3	
Final attack rate				
50%	125 (45–251)	66 (22–133)	55 (17–123)	32%
60%	104 (38–209)	55 (19–111)	46 (14–94)	9%
66% (baseline)*	95 (34–191)	50 (17–101)	42 (13–86)	0
70%	90 (32–179)	47 (16–95)	40 (12–81)	−5%
80%	78 (28–157)	41 (14–83)	35 (11–71)	−18%
Weekly number of births				
60	127 (46–256)	67 (23–136)	56 (17–115)	33%
80·4 (baseline)†	95 (34–191)	50 (17–101)	42 (13–86)	0
100	76 (28–154)	40 (14–82)	34 (10–158)	−20%

*Based on a serological study done after the end of the epidemic.† †Based on official annual data.‡

Table 3: **Sensitivity analysis of the estimated risk of microcephaly associated with Zika virus infection to assumptions about final attack rates and birth rates**