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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Introduction

Zika virus is an arthropod-borne virus in the genus of *Flavivirus*.[1] Since identification of Zika virus infection in Brazil in May, 2015, the virus has spread throughout the Americas. Up to Feb 19, 2016, 28 countries of the region had reported cases.[2] Although infection with Zika virus often leads to mild disease, its emergence in the Americas has coincided with a steep increase in patients developing Guillain-Barré syndrome (an autoimmune disorder that causes acute or subacute flaccid paralysis) and the birth of babies with neurological complications, such as congenital microcephaly.[3–5]

Congenital microcephaly is a neurological abnormality that is present at birth and defined as head circumference at least 2 SD smaller than the mean for sex, age, and ethnicity,[6] with head circumference at least 3 SD smaller being deemed severe.[7] Microcephaly might occur alone or in combination with other abnormalities. The condition is associated with a reduction in brain volume and frequently with intellectual disabilities, motor disabilities, or both, including speech impairment,[8] poor neurocognitive outcome,[9] and behavioural issues.[10] Causes include genetic[11] or environmental factors[12] during pregnancy that affect fetal brain development.[13] Prenatal viral infections (eg, rubella or cytomegalovirus),[14] maternal alcohol use,[15] and hypertensive disorders[16] have been associated. Cases have also been reported after intrauterine infection with West Nile virus (another flavivirus)[17] and chikungunya virus.[18]

On Feb 1, 2016, WHO declared the suspected link between Zika virus and microcephaly to be a Public Health Emergency of International Concern.[19] To reduce the risk of microcephaly, women who were pregnant and of childbearing age were recommended to avoid travelling to affected countries, to use condoms with partners returning from affected countries, and to delay pregnancy.[20,21] The amount of monitoring that is required for pregnant women during Zika virus epidemics is being investigated. Ideally, clinical management, individuals' decisions regarding family planning, and the response of the broader public health community would be informed by precise calculations of the risk of microcephaly in fetuses and neonates whose mothers have been infected with Zika virus. However, although evidence of an association is growing,[22,23] this risk has not yet been clearly quantified.

Timely assessment of this association from data gathered in an ongoing epidemic, such as that in the Americas, poses potential difficulties. First, delays might occur between infection of mothers with Zika virus and the diagnosis of microcephaly in fetuses or neonates. Ascertainment of all potentially associated cases,

Research in context

Evidence before this study

Microcephaly is defined by head circumference at least 2 SD smaller than normal head circumference. Its incidence is estimated to be between 5·8 per 100 000 livebirths in the USA and 18·7 per 100 000 livebirths, stillbirths, and medical abortions in Europe. Long-term outcomes of this condition are heterogeneous, but it has been associated with several neurological disorders, such as epilepsy or intellectual deficiencies. Following the Zika virus epidemic in South America, microcephaly in neonates has been reported in several countries, leading WHO to declare a Public Health Emergency of International Concern. The association between Zika virus and microcephaly, however, remains to be quantified.

Added value of this study

We did a retrospective analysis of a large Zika virus outbreak in French Polynesia in 2013–14, based on four datasets that provided information on all cases of microcephaly, the weekly number of consultations for suspected infection with Zika virus, seroprevalence for Zika virus antibodies, and the number of births during the outbreak. Use of mathematical models enabled us to provide strong statistical support for the association between Zika virus infection and microcephaly and to establish that the period of risk in pregnancy when infection of mothers increases the risk of microcephaly in fetuses and neonates was likely to contain the first trimester of pregnancy (possibly also the second and third trimesters). We estimated that the number of microcephaly cases associated with Zika virus was 95 (95% CI 34–191) per 10 000 women infected in the first trimester.

Implications of all the available evidence

Our findings strongly support the previously suspected link between infection with Zika virus during pregnancy and microcephaly. They emphasise the need for health authorities of affected countries to organise fetal monitoring, promote vector control, and provide evidence-driven information for pregnant women.

therefore, could take some time. Second, surveillance systems detect only a small proportion of Zika virus infections[24] and, therefore, the true number of pregnant women who have been infected is unknown. The total number of infections can be estimated by serological cross-sectional surveys only once an epidemic is over. Thus, the numerator and denominator needed to calculate the risk of microcephaly per infected pregnant woman remain uncertain while outbreaks continue.

We did a retrospective analysis of a large Zika virus outbreak that took place in French Polynesia in October, 2013, to April, 2014,[25] to assess and characterise the strength and nature of the association with microcephaly. In particular, we assessed the risk of microcephaly in fetuses or neonates whose mothers had been infected by Zika virus. The French Polynesian outbreak had various properties that support such an assessment. First, it was the largest documented Zika virus outbreak before that in the Americas. Second, French Polynesia has strong infrastructures for surveillance of infectious diseases and detection of complications during pregnancy. Third, sufficient time has elapsed since the end of the outbreak for all cases of microcephaly potentially associated with Zika virus infection to be detected. Finally, serological data, which are necessary to estimate the number of pregnant women who were infected during the epidemic, are available.[26,27]

See Online for appendix

Methods

Study design

We analysed four datasets that documented all cases of microcephaly in French Polynesia from Sept 1, 2013, to July 31, 2015, the weekly number of consultations for suspected infection with Zika virus, seroprevalence for Zika virus antibodies at the start and end of the epidemic, and the number of births in French Polynesia. We used serological data to establish the overall proportion of the population infected during the epidemic and used epidemic curves to establish the weeks when infections were likely to have occurred. From these datasets we estimated the probability of infection for each week of the epidemic. These probability values can be used to calculate the proportions of women who were infected with Zika virus during the first, second, or third trimesters of pregnancy among those who became pregnant in any given week. With this information, expected trends in microcephaly could be estimated and compared for different periods during pregnancy when infection with Zika virus might increase the risk of microcephaly for fetuses or neonates (appendix).

Microcephaly data

We retrospectively identified all fetuses or neonates whose head circumferences were at least 2 SD smaller than normal, adjusted for gestational age and sex. Head circumference is measured in the second trimester during standard monitoring of pregnancy (appendix). We did an exhaustive search of the medical records of patients who had been referred to the only prenatal diagnosis specialist centre of the territory. We searched in-hospital discharge data from neonatology wards for other cases. All suspected cases of microcephaly were reviewed by specialists (MB, PG-A, DE-G, VA, CG).

Surveillance data

Weekly numbers of patients who attended consultations for suspected infection with Zika virus were estimated from data provided by the local sentinel surveillance

system. Outside epidemic periods the system relies on 20 sentinel general practitioner sites. During epidemics capacity may be expanded. During the Zika virus outbreak of 2013–14, information was gathered weekly from an average of 50 sentinel sites, covering 30% of all general practitioner sites in the territory. From these data we extrapolated the total number of consultations. Patients with suspected infection were those who presented with rash, fever higher than 38·5°C, or both, and with at least two of conjunctivitis, joint pain with or without muscle pain, and limb oedema. Laboratory confirmation of infection was obtained for a small proportion of cases.

Serological data

We used data from three serological studies done in French Polynesia. One assessed serum samples from 593 people aged 18–79 years from Tahiti (the largest island in the territory), obtained between July, 2011, and October, 2013 (before the epidemic).[27] Another assessed samples from 196 people aged 7–86 years (median 41 years) from the general populations of five of the most inhabited islands, obtained between February and March, 2014 (second half of the epidemic).[26] The third assessed samples from 476 children from Tahiti aged 6–16 years (median 11 years), obtained between May and June, 2014 (after the end of the epidemic).[26] All serum samples were tested for evidence of historic exposure to Zika virus with indirect ELISA for IgG.[27]

Demographic data

The population of French Polynesia was 270 000 in December 2013. In the period 2013–14, an average of 4182 babies were born per year.[28]

Statistical analysis

We developed a simple mathematical and statistical model to characterise the association between Zika virus and microcephaly. We assumed that there is a period of risk during pregnancy when infection of the mother increases the risk of microcephaly in the fetus or neonate. Therefore, if the mother was infected with Zika virus during this period, the risk of microcephaly would be $\rho_0+\rho_Z$ and otherwise would be ρ_0 (baseline). We considered six possible periods of risk: trimester one; trimesters one and two; trimesters one, two, and three; trimester two; trimesters two and three; and trimester three. Additionally, we assessed a scenario with no association (ie, no period of risk).

We followed the cohort of women (n_s) whose pregnancies started in a given week (w_s). Assuming that the birth rate was constant during the study period, we defined it as 80·4 per week (n_s=4182/52). To calculate the probability that these women were infected by Zika virus

***Panel:* Modelling assumptions for estimation of risk of microcephaly associated with Zika virus infection**

- During pregnancy there is a period of risk when Zika virus infection of the mother increases the risk of microcephaly for the fetus or neonate
- All microcephaly cases in the study period have been identified
- The number of Zika virus infections in a given week is proportional to the number of consultations for suspected infection in the same week
- The proportion of women of childbearing age infected with Zika virus during the epidemic was similar to the proportion of seropositive children (estimated in a serological study)
- The birth rate is constant during the study period and can be estimated from official statistics

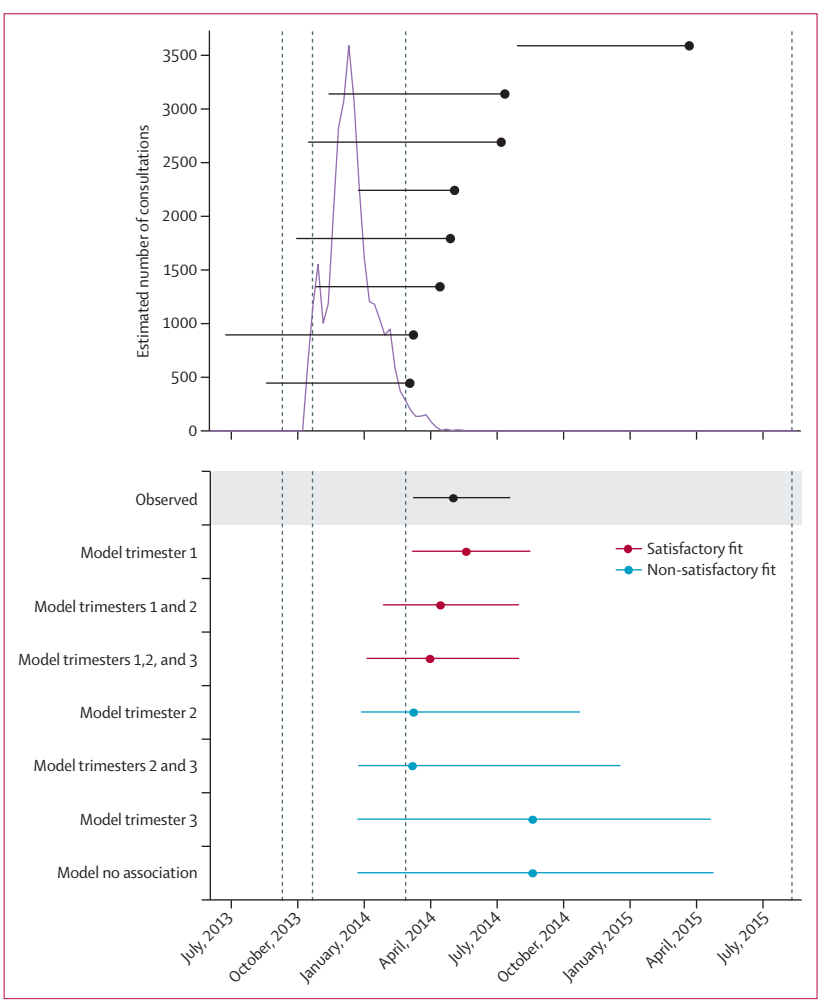

***Figure 1*: Frequency of consultations and timing of microcephaly cases during the 2013–14 Zika virus outbreak in French Polynesia**

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).

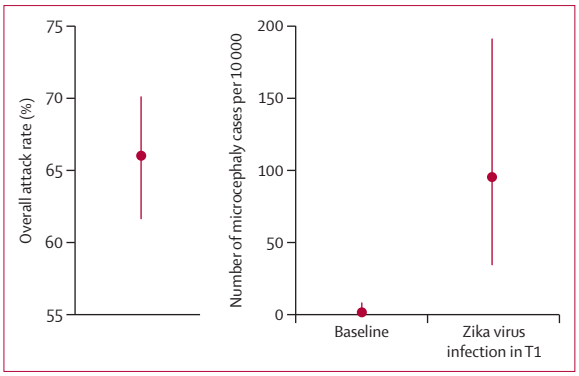

***Figure 2*: Attack rate and strength of the association between infection with Zika virus and microcephaly in French Polynesia**
(A) Final attack rate (95% CI) based on seroprevalence after the end of the outbreak. (B) Baseline prevalence of microcephaly (number per 10 000 neonates) and risk of microcephaly 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 (6·5–1061·2)	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 (1·4–407·8)	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 ≥4 indicating substantial improvement in fit.[31]

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

during the week in question, expressed as $p_i(w_i)$, we assumed that w_i was proportional to the number of consultations (I_{w_i}) for suspected infection with Zika virus in that week:

$$p_i(w_i) = \gamma \frac{I_{w_i}}{\sum_w I_w}$$

The parameter γ indicates the final attack rate. In our baseline scenario, γ was estimated from the serological study that was done after the end of the Zika virus outbreak.

Once the temporal trends of infection with Zika virus had been calculated, we used the model to predict trends in microcephaly under different assumptions about the period of risk in pregnancy. This process required modelling of the duration of pregnancy for microcephaly cases to take medical abortions into account (appendix).

For each model variant, we obtained maximum likelihood estimates of model parameters with a simulated annealing algorithm.[29] The likelihood ratio method[30] was used to compare the different period-of-risk models with the no association model and to derive 95% CIs. Otherwise, the Akaike information criterion with a correction for small sample size (AICc) was used.[31] The smallest AICc indicates the best-fitting model. Differences in AICc values of 4 or greater indicate substantial improvement in model fit.[31]

In a sensitivity analysis, we explored scenarios in which the final attack rate was 50%, 60%, 70%, or 80% and the weekly number of births was 60 or 100. We also fitted a saturated model in which the risk of microcephaly was estimated for each trimester of pregnancy (appendix).

Technical details are provided in the appendix and the key modelling assumptions are presented in the panel. All statistical analyses were done in R version 3.0.2.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
The outbreak began in October, 2013 (week 41), peaked in December, 2013, and ended in April, 2014 (figure 1). By the end of the outbreak, public health officials had recorded 8750 suspected infections with Zika virus, of which 383 (4·4%) were confirmed in the laboratory. More than 31 000 patients were estimated to have sought consultations for suspected Zika virus infection during this outbreak (figure 1).[32]

Before this outbreak, the seroprevalence of Zika virus had been 0·8%.[27] By the second half of the outbreak

prevalence was estimated to be 50% (95% CI 43–56; based on 97 of 196 samples),[26] and seroprevalence of 66% (62–70; 314 of 476) was reported after the end of the outbreak (figure 2).[26]

We identified eight cases of microcephaly during the study period (table 1). Five were seen in pregnancies that had been terminated through medical abortion and three in children who were born. Median gestational age of aborted fetuses was 30·1 weeks (IQR 26·1–31·4). Normal fetal karyotype was obtained from six fetuses or neonates and was unavailable for two.

The study period was 23 months, but seven (88%) of the eight cases of microcephaly were identified in a 4-month period from March 1 to July 10, 2014 (figure 1). Of the six periods of risk during pregnancy, four explained the timing of cases of microcephaly significantly better than the no association model (table 2). The two that did not perform significantly better than the no association model assumed the period of risk was restricted to trimester three or trimesters two and three.

Three models showed satisfactory fit (figure 1, table 2), all of which included the first trimester in the period of risk. The best-fitting model was that which included only the first trimester. In this model, the baseline prevalence was two cases (0–8) per 10 000 neonates. The risk of microcephaly was 95 cases (95 CI 34–191) per 10 000 women infected in the first trimester of pregnancy, corresponding to a risk ratio of 53·4 (95% CI 6·5–1061·2). The next two best-fitting models (50 cases, 95% CI 17–101, per 10 000 women infected in trimesters one or two and 42 cases, 13–86, per 10 000 women infected in trimesters one, two, or three), could not be ruled out (table 2, figure 2). No models that excluded the first trimester from the period of risk were supported by the data (figure 1, table 2).

In the sensitivity analysis, the relative changes in estimates ranged from –20% to 33% (table 3). For the best-fitting model (period of risk restricted to trimester one), the risk of microcephaly remained between 76 and 127 cases per 10 000 women infected in the first trimester of pregnancy. Analysis of the saturated model further supported best fit for this model (appendix).

	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 (17–113)	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.[26] †Based on official annual data.[28]

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

Discussion

The large outbreak of Zika virus infections in French Polynesia in 2013–14 enabled us to quantify and characterise the association between Zika virus infection in pregnancy and microcephaly. Of eight cases of microcephaly reported, seven occurred in a 4-month period around the end of the Zika virus outbreak. Such temporal clustering strongly supports the proposed association. Our mathematical model designed to predict temporal trends yielded three important conclusions. First, assumed periods of increased risk of microcephaly in fetuses or neonates of mothers infected with Zika virus explained the observed patterns significantly better than the no association model. Second, the best-fitting models of period of risk all included the first trimester of pregnancy, with that including only the first trimester having the best fit. Third, the availability of serological data allowed the risk of microcephaly per infected pregnant woman to be calculated.

With infection of the mother with Zika virus during the first trimester of pregnancy, we estimated that the risk of microcephaly was about 1%. This risk seems low compared with that for other viral infections associated to birth defects. For example, 13% of primary cytomegalovirus infections in pregnancy result in symptomatic congenital disease in neonates,[33] the risk of congenital rubella syndrome ranges from 38% to 100% if mothers are infected in the first trimester of pregnancy,[34] and global adverse fetal outcomes are seen in 10% of pregnant women infected by parvovirus B19. However, an important difference is that the incidence of Zika virus in the general population can be very high during outbreaks (eg, 66% in French Polynesia[26] and 73% on the island of Yap[24]), meaning that the risk to pregnant women is also high. By contrast, 1–4% of pregnant women are infected with cytomegalovirus,[35] fewer than ten cases of rubella are seen in pregnant women per year in France,[36] and 0·61–1·24% of women of childbearing age are infected with parvovirus B19.[37] Thus, although infection with Zika virus is associated with a low fetal risk, it is an important public health issue. No treatment is available for Zika virus and development of a vaccine will take time. Our findings highlight the need to inform pregnant women and women trying to become pregnant to protect themselves from mosquitos bites and avoid travel to affected countries as far as possible.

Our analysis strongly supports the hypothesis that infection in the first trimester of pregnancy is associated with an increased risk of microcephaly. Similar patterns

of risk are seen for other intrauterine viral infections that increase the risk of fetal brain damage, such as rubella or cytomegalovirus.[38] Large datasets are needed to investigate whether infection at other times in pregnancy and the severity of clinical symptoms in the infected mother also increase the risk of microcephaly. The baseline prevalence estimated with this model was consistent with previous estimates from Europe (1·9 per 10 000 neonates)[39] and Brazil (2·0 per 10 000 neonates).[40]

We used four datasets that provided information on different aspects of the Zika virus outbreak in French Polynesia. The first dataset was derived from an exhaustive search of all microcephaly cases during the study period. We used a strict case definition of microcephaly (rather than, for example, microcephaly and other neurological complications) for two reasons. First, the WHO decision to make the link between Zika virus and microcephaly a Public Health Emergency of International Concern focused on microcephaly and, therefore, we felt this link should be addressed first. Second, not using a standardised case definition for microcephaly has been an important source of confusion during the epidemic in the Americas,[41,42] possibly leading to overestimation of the number of microcephaly cases in South America.[43] To ensure the accuracy of the diagnosis, five specialists reviewed all potential cases. Although our analysis was restricted to the link between Zika virus and microcephaly, it will be important to ascertain whether Zika virus is associated with other fetal or neonatal neurological complications. Other types of complications were reported in French Polynesia, although links to Zika virus are not established.[4]

The second dataset was based on sentinel surveillance, which is subject to several limitations, such as detection of only a small proportion of infections. This issue, however, is unlikely to affect our analysis because we only used these data to establish the timing not the size of the epidemic. We assumed that the number of infections occurring in a given week was proportional to the number of consultations for suspected infection with Zika virus in the same week. This assumption might be undermined if propensity to consult for Zika virus symptoms or reporting practices changed substantially during the epidemic, as was seen, for example, in the influenza A H1N1 pandemic in 2009.[43]

For the third dataset, we used three seroprevalence studies to establish the final attack rate of Zika virus. These studies were done in different populations with different age structures, but there is little reason to expect a large difference in risk between children and adults. The risk of exposure to Zika virus in an outbreak on Yap Island was similar across age groups.[24] Additionally, the three estimates of seropositivity were consistent with that expected over the course of an outbreak in a previously naive population. Finally, our 66% estimate for the final attack rate is similar to that of 73% (95% CI 68–77) on Yap Island.[24] Our estimates for the risk of microcephaly remained relatively robust to large changes in the assumed attack rate (table 3). Since less than 1% of individuals tested positive for Zika virus before the start of the outbreak, despite high dengue seropositivity,[27] cross-reaction in serological assays is unlikely to be important.

Our analysis also relied on the total number of documented annual births. The quality of population statistics in French Polynesia is similar to that in mainland France. Birth counts were annual and, therefore, we assumed a constant birth rate during the study period. In practice small variations in weekly number of births would be expected but our estimates were altered little by such variations (table 3). Because we were interested in assessing the risk of microcephaly associated with Zika virus in fetuses that could have been expected to be liveborn in the absence of infection, it was more appropriate to use statistics on livebirths than on livebirths and medical abortions, even though medical abortion was performed for a substantial proportion of fetuses with microcephaly in this study.

Extrapolation of our findings to other settings should be approached with caution. First, the spread of an arbovirus such as Zika virus is affected by entomological, environmental, and climatic factors and, therefore, attack rates might differ between outbreaks. Second, there is a possibility that the risk of microcephaly associated with Zika virus infection will differ in other populations because of genetic factors.

Much more epidemiological and experimental research needs to be done to understand the role of infection with Zika virus in the development of congenital abnormalities such as microcephaly and to clarify the causal links. Experimental studies investigating transmission from mothers to fetuses should be prioritised. Countries affected by and at risk of outbreaks should test and follow up cohorts of pregnant women throughout pregnancy.[44] Studies should be standardised, at least to some degree, as the number of countries affected by the current outbreak in the Americas continues to grow. Our study was retrospective, and prospective studies to assess links between Zika virus and microcephaly are urgently needed. Groups such as the International Severe Acute Respiratory and Emerging Infection Consortium and the Consortium for the Standardization of Influenza Seroepidemiology are working with affected countries, WHO, the Centers for Disease Control and Prevention, and others to generate protocols.

This study provides strong statistical support for the suspected association between infection with Zika virus and microcephaly. We estimated that the risk of microcephaly increases to about 1% when mothers are infected with Zika virus during the first trimester of pregnancy. Our findings support the need for a strong and prompt response to protect, inform, and monitor

For the **International Severe Acute Respiratory and Emerging Infection Consortium** see https://isaric.tghn.org/

For the **Consortium for the Standardization of Influenza Seroepidemiology** see https://consise.tghn.org/

pregnant women and to provide strong research agendas to clarify the causal link between Zika virus and microcephaly and develop effective treatments and vaccines.

Contributors

SC, MB, TD, AF, and H-PM conceived and designed the study. MB, PB, and H-PM designed the case report forms and collected the epidemiological data. MB, PG-A, DE-G, VA, and CG provided care to mothers and children, collected the clinical data, and reviewed all clinical files of congenital malformation cases to decide whether they met the microcephaly case definition. SC and HS developed and ran the mathematical model. SC, TD, HS, MDVK, AF, and H-PM interpreted the model results. SC, MB, TD, MDVK, AF, and H-PM wrote the first version of the report and all authors critically reviewed and approved the final version.

Declaration of interests

We declare no competing interests.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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

Supplementary Material

Association between zika virus and microcephaly in French Polynesia, 2013-2015: a retrospective study

Contents

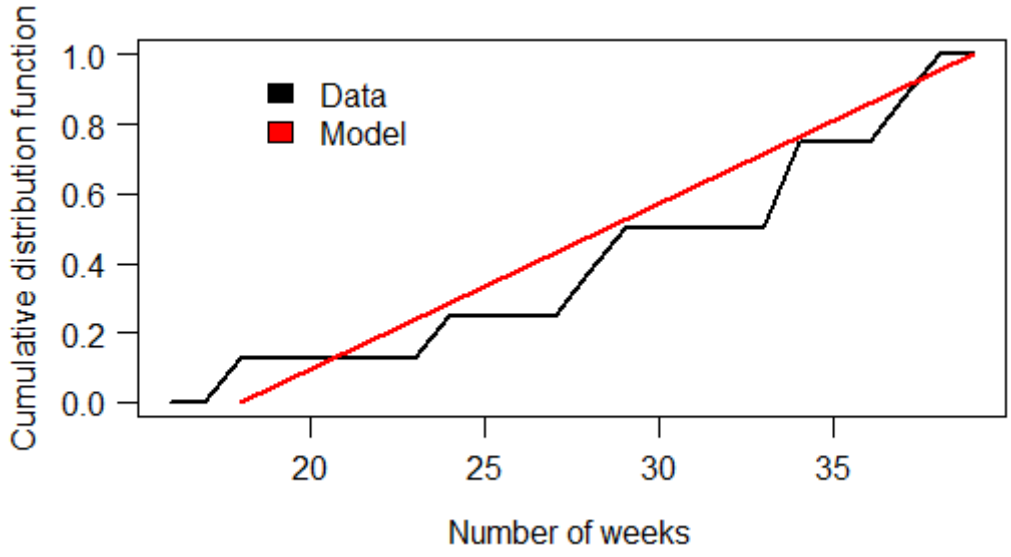
1 Standard follow-up of pregnancy in French territories

In French territories, standard follow up of pregnancy includes three sonograms. The first trimester ultrasound is to be performed between the eleventh and thirteenth weeks of gestation[1], in order for the physician to be able to measure nuchal translucency, a potential sign of Down syndrome. At this time, following the recommendations of the Comité National Technique de Dépistage Prénatal[2], head circumference is not among the measured parameters. It is only when the second trimester sonogram (between weeks 20 and 25) is done that foetal head circumference is assessed, allowing diagnosis of microcephaly, which explains the late occurrence of medical terminations.

2 Duration of pregnancy

Because medical abortion occurred in 5 of the 8 microcephaly cases, the average duration of pregnancy (where the end of pregnancy is defined as the date of delivery or of medical abortion) was shorter than what is observed in a normal pregnancy. In our dataset, the duration of pregnancy ranged from 18 to 38 weeks. We found that the distribution of duration of pregnancy was well approximated by a Uniform distribution on the range 18 to 39 weeks (Figure S1).

Figure S1: Cumulative distribution function of the duration of pregnancy in the dataset (black line) and in our model (red line). In the model, we assume that the duration of pregnancy is Uniformly distributed between 18 and 39 weeks.



3 Expected number of microcephaly cases for a given week

The model is presented in the Methods section. Here, we explain how the model can be used to compute the expected number of microcephaly cases in a given week.

The 'period of risk' (when infection of the mother by ZIKV increases the risk of microcephaly by an additive term ρ_Z) is defined by the weeks of pregnancy when the period starts (T_S)

and when it ends (T_E). For example, if the period of risk is restricted to the first trimester, $T_S = 0$ and $T_E = 13$. We denote $g_{\text{risk}}(t)$ the function that indicates if week *t* of pregnancy is in the period of risk:

$$g_{\text{risk}}(t) = \begin{cases} 1 & \text{if } \mathrm{T}_S \le t < T_E \\ 0 & \text{otherwise} \end{cases}$$

Consider now the cohort of n_S women whose pregnancy started on week w_S. The number of these women expected to have a foetus/neonate suffering from microcephaly with pregnancy ending on week w_E is

$$MC_{w_S}(w_E \mid \theta) = n_S . \left(\rho_0 + \rho_Z \sum_{w_S \le w_I < w_E} p_I(w_I)\, g_{risk}(w_I - w_S)\, f(w_E - w_I) \right)$$

where θ gives the parameters of the model.

We can then obtain the expected number of microcephaly cases for a given week by summing up over all the different cohorts of pregnant women:

$$MC(w_E \mid \theta) = \sum_{w_S < w_E} MC_{w_S}(w_E \mid \theta)$$

4 Likelihood

The study period started on week T_S (starting on 2 September 2013) and finished on week T_F (finishing on 2 August 2015). The number of microcephaly cases from pregnancies that ended on week w_E is denoted $I(w_E)$.

Assuming that the weekly number of microcephaly cases is Poisson distributed, the likelihood of the parameters is

$$L(\theta) = P_{\text{Bin}}(n_{\text{pos}} \mid n_{\text{tested}}, \theta) \prod_{T_S \le w_E \le T_F} P_{Pois}(I(w_E) \mid MC(w_E \mid \theta))$$

where the first term corresponds to the Binomial density of the number of individuals who seroconverted among those tested in the serological study and the second term corresponds to the Poisson density of the weekly number of microcephaly cases.

5 Inference

We developed a simulated annealing algorithm to find the set of parameters that maximized the likelihood[3]. For the first 999 iterations (*i*=1,…, 999), the temperature was modelled as $T = (1 - i/1000)^2$ after which point the temperature was equal to $T = 10^{-6}$ for a further 6,000 iterations. To assess convergence to the global maximum, the algorithm was started

from 10 different initial conditions and we check that all the runs reached the same maximum.

6 Model estimating the risk of microcephaly per trimester

In our baseline analysis, we assume that there was 1 'period of risk' during pregnancy which may be affected by an increased risk of microcephaly and we consider different possible periods of risk. Here, we fit an alternative model where we estimate one level of risk per trimester. Estimates are presented in Table S1. They are consistent with the best fitting model presented in the paper where the 'period of risk' is restricted to trimester 1. In terms fitting performance, this model has a poor fit because it is over-parametrised (dAICc=15) and is therefore outperformed by the best fitting models presented in the paper.

Table S1: Risk of microcephaly associated with ZIKV infection in the different trimesters of pregnancy. This is estimated from a model that assumes the risk of microcephaly varies by trimester of pregnancy.

	Number of microcephaly cases
Baseline prevalence	2 (0,8) per 10,000 neonates
ZIKV infection in trimester 1	95 (13,191) per 10,000 women infected in trimester 1
ZIKV infection in trimester 2	0 (0, 110) per 10,000 women infected in trimester 2
ZIKV infection in trimester 3	0 (0, 135) per 10,000 women infected in trimester 3

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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, 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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Late maternal deaths: a neglected responsibility

Uros Ravbar/Getty Images

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 Mortality[4] 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 period[8] 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