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

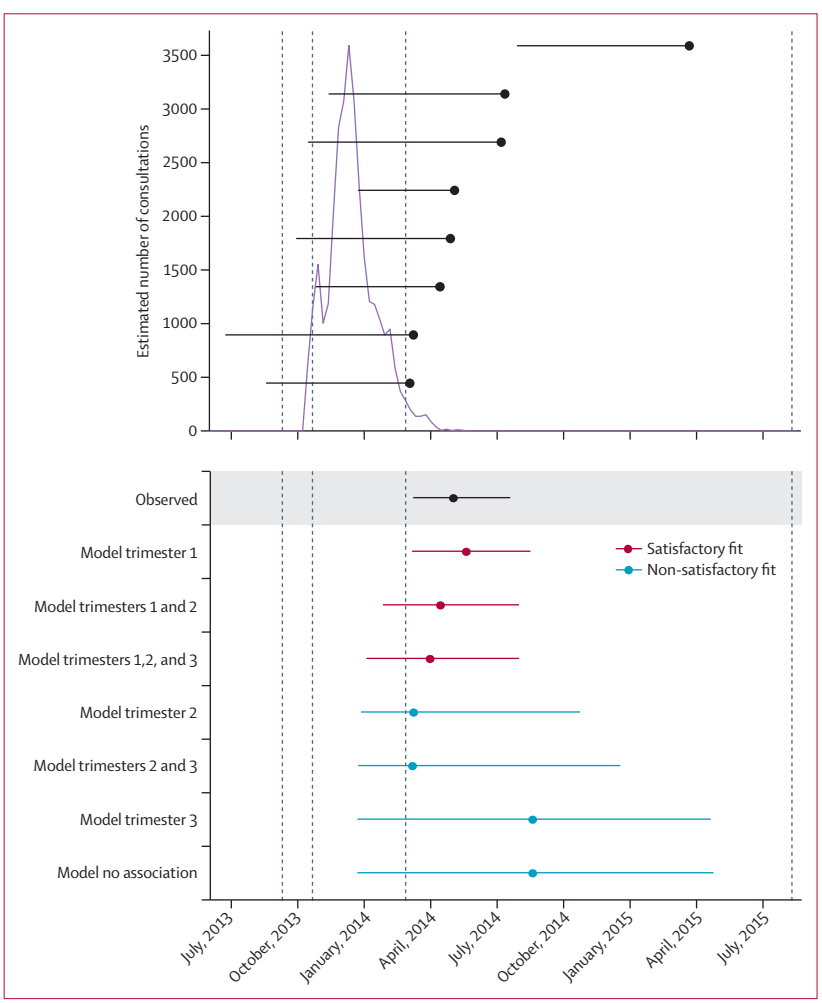

***Figure 1*: Frequency of consultations and timing of microcephaly cases during the 2013–14 Zika virus outbreak in French Polynesia**

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).

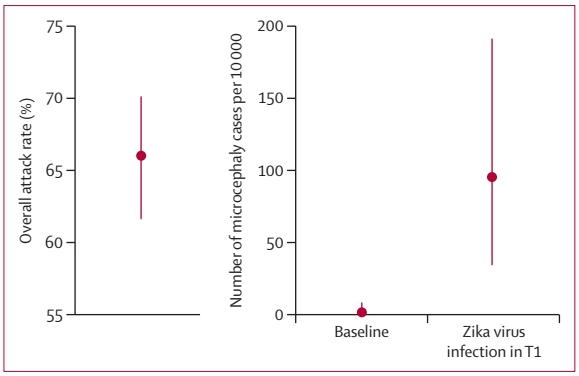

***Figure 2*: Attack rate and strength of the association between infection with Zika virus and microcephaly in French Polynesia**
(A) Final attack rate (95% CI) based on seroprevalence after the end of the outbreak. (B) Baseline prevalence of microcephaly (number per 10 000 neonates) and risk of microcephaly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