Tropical Medicine and International Health doi:10.1111/tmi.12240

VOLUME 19 NO 2 PP 153–158 FEBRUARY 2014

Dengue epidemics and adverse obstetrical outcomes in French Guiana: a semi-ecological study

Matthieu Hanf[1], Eleanor Friedman[2], Celia Basurko[1], Amaury Roger[1], Pascal Bruncher[3], Philippe Dussart[4], Claude Flamand[5], Gabriel Carles[6], Pierre Buekens[2], Gerard Breart[7], Bernard Carme[1] and Mathieu Nacher[1]

1 *Centre d'Investigation Clinique Epidemiologie Clinique Antilles Guyane, inserm CIE802, Centre Hospitalier de Cayenne, Cayenne, France*
2 *Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA, USA*
3 *Protection Maternelle et Infantile, Conseil Général de la Guyane, Cayenne, France*
4 *Centre National de Référence des Arboviroses, Institut Pasteur de la Guyane, Cayenne, France*
5 *Cellule de l'InVS en Région Antilles Guyane, Cayenne, France*
6 *Service de Gynécologie Obstétrique, Centre Hospitalier de l'Ouest Guyanais, Saint Laurent du Maroni, France*
7 *INSERM U953, Recherches Epidémiologiques en Santé Périnatale et Santé des Femmes, Hôpital Tenon, Paris, France*

Abstract

OBJECTIVE To determine whether dengue epidemics are associated with an increase in adverse obstetrical outcomes.

METHODS Semi-ecological study combining individual data on obstetrical events from the perinatal registry and aggregated exposure data from the epidemiologic surveillance of dengue in Cayenne, French Guiana between 2004 and 2007.

RESULTS After adjustment for individual risk factors, analysis showed that an epidemic level of dengue transmission during the first trimester was associated with an increased risk of post-partum haemorrhage and preterm birth. The associated risks seemed to depend on the epidemic level.

CONCLUSIONS Despite its limitations, this study suggests that dengue in the first trimester may be related to preterm birth and to post-partum bleeding, thus leading to specific hypotheses that should be tested in prospective studies.

keywords dengue fever, pregnancy, preterm birth, Post-partum haemorrhage, French Guiana

Introduction

Dengue is an increasing problem in the tropical world. Every year there are between 50 and 100 million cases of dengue fever and 500 000 cases of dengue haemorrhagic fever worldwide (Halstead 2007). Given the incidence during dengue epidemics, a significant number of pregnant women must also get infected with dengue. However, there are few studies on the obstetrical consequences of dengue during pregnancy. There have been reports of severe complications for both mother and foetus of symptomatic dengue in case series in French Guiana (Carles *et al.* 1999; Basurko *et al.* 2009), but a recent systematic review of the published studies was inconclusive on adverse pregnancy outcomes (Pouliot *et al.* 2010). Most of the studies are case reports or case series, with only few comparative studies. Given the lack of data on this question and its potential public health importance, we aimed to test the hypothesis that dengue has adverse consequences using a combination of two sources: aggregated exposure data from the epidemiologic surveillance of confirmed dengue from the Institut Pasteur, and individual obstetrical data from the Perinatal Registry in French Guiana, which contains exhaustive individual data on obstetrical events (Cardoso *et al.* 2003).

Materials and methods

Ethics statement

Adverse maternal outcomes in French Guiana are reported in the Perinatal Registry. This registry is completely anonymous, is approved by the Commission Nationale de l'Informatique et des Libertés (CNIL) and is managed by the maternal and child care department of the Conseil Général de la Guyane. Access to the data was based on special permissions given by the Conseil Général de la Guyane.

Individual obstetrical data

The Perinatal Registry includes all births (living and dead) in public and private hospitals in French Guiana.

© 2013 John Wiley & Sons Ltd

Data were available for a 4-year period (January 2004 to December 2007). Inclusion criteria for births are a gestational age >22 weeks or a weight >500 g. Each birth is registered by an obstetrician or a midwife. The anonymous data are gathered from the mother's interview, medical files and maternity follow-up booklets, which allowed us to compile 28 different items relating to the pregnancy and delivery of the infant. Various adverse obstetrical outcomes were studied: preterm birth, low birth weight, malformations, preeclampsia, post-partum haemorrhage and caesarean section.

Post-partum haemorrhage was defined as bleeding >500 ml for a vaginal delivery and >1000 ml for caesarean section. Preeclampsia was defined as blood pressure >160/90 mm Hg and proteinuria >0.5 g per 24 h after 20 weeks since last menstrual period. A range of malformations (cardiovascular, orthopaedic, neurological, multiple and unknown) were pooled into a single variable representing all malformations. Down syndrome was excluded from this list. All adverse obstetrical outcomes were determined independently of the mother's dengue fever status at delivery. The analysis was restricted to pregnancies for which pregnant women were living in the urban area of Cayenne, which consists of the city of Cayenne and its neighbouring communes (Matoury, Macouria and Rémire Montjoly). The analysis was restricted to this circumscribed area of Cayenne so that dengue cases occurred in the area where the women lived, thus genuinely reflecting an increased risk of getting dengue during the pregnancy. For each studied outcome, only pregnancies with no missing data on maternal age, gestational time, parity, gravidity and birth weight were used in the analysis.

Aggregated dengue surveillance data

For each pregnancy, aggregated data from the epidemiologic surveillance of dengue confirmed by the National Reference Center for arboviruses (the Institut Pasteur de la Guyane (IPG)) were used. A confirmed dengue diagnosis was defined (i) during the acute phase of the disease as positive virus isolation, and/or positive viral RNA detection by reverse transcriptase polymerase chain reaction (RT-PCR), and/or positive NS1 antigen detection, and/or positive DENV IgM detection; (ii) the diagnosis of early convalescent dengue cases was based on DENV IgM detection (Dussart *et al.* 2008). Weekly totals of confirmed cases are transmitted to the Cellule de l'InVS en Region Antilles Guyane (CIRE) for epidemiologic surveillance, alert and intervention. We used cases from a single reference laboratory, so the number of confirmed cases would not be artificially inflated by the increase in the number of laboratories able to perform tests for dengue during the time period of the study.

Statistical methods

Univariate and multivariate logistic regression models were used to test whether dengue epidemic levels during the three defined time periods were significant risk factors for various adverse maternal outcomes. To calculate the total monthly number of confirmed dengue fever cases, the month of delivery and the term at delivery (established using the last menstrual period) were used to determine the month of conception.

To investigate potential biological mechanisms of dengue fever on pregnancy outcomes, we constructed three periods of exposure for dengue, the first one beginning from the estimated month of conception and covering the next 2 months (first trimester). The second one included the 3 months following the first trimester (second trimester). The third one included the last 3 months before delivery, regardless of the trimester of pregnancy.

As preterm births have an incomplete or absent third trimester, the associated total number of dengue cases in the third trimester would be artificially low for preterm births compared with term births. The use of the last 3 months of pregnancy instead of the traditional third trimester was used to avoid an artificial protective association between dengue in the third trimester and adverse outcomes related to gestational duration. Therefore, the last 3 months of pregnancy cannot be interpreted in this study to represent the third trimester, as it may well be a combination of data from the second and third trimester.

The total numbers of dengue cases per period were categorized (<20, 20–60 and >60) and transformed into indicator variables. This categorization roughly corresponded to the levels of cases observed during a non-epidemic period, a moderate epidemic period or a high epidemic period in French Guiana during this time period.

To control for potential confounding, adjustment variables were also included. The adjustment variables were the woman's age, ethnic origin, gravidity, parity, twin pregnancy, having had a medical follow-up, the number of ultrasound scans and having had various pathologies during pregnancy, including chronic health conditions of the mother, as well as pregnancy specific medical conditions. Low birth weight (<2500 g) and preterm birth (gestation <37 weeks) were also included in the model depending on the outcome under investigation.

Statistical significance was set at $P < 0.05$. All statistical analyses were conducted using R 2.12.0 and the package 'epicalc' (Development Core Team 2011).

© 2013 John Wiley & Sons Ltd

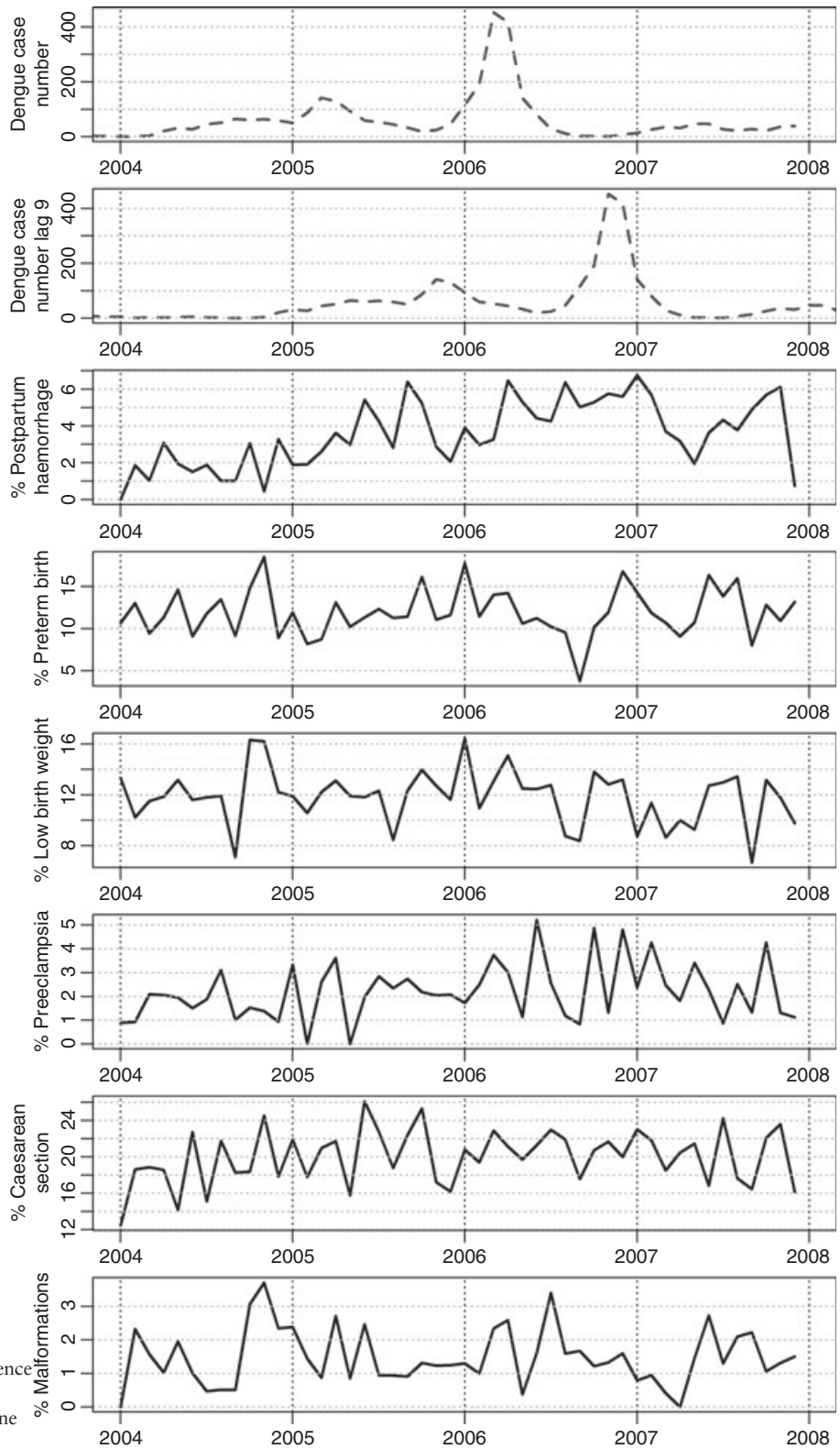

Figure 1 Monthly confirmed dengue cases (lag 0 and 9 months) and incidence of the six studied adverse obstetrical outcomes in the urban area of Cayenne between 2004 and 2007.

© 2013 John Wiley & Sons Ltd

Table 1 Univariate and multivariate† logistic regressions predicting the impact of dengue epidemics on six adverse obstetrical outcomes for 107776 pregnant women residing in the Cayenne area, French Guiana. 2004–2007

Outcomes	Pregnancy period	*N* confirmed dengue cases	*N* events (%)	Crude OR [95% CI]	Adj. OR [95% CI]	*P* (Wald's test)
Preterm birth	First trimester	<20	246 (10.5)	1	1	–
		20–60	112 (10.6)	1.00 [0.79, 1.27]	1.17 [0.89, 1.54]	0.268
		>60	926 (12.6)	1.22 [1.05, 1.41]	1.31 [1.06, 1.63]	0.014*
	Second trimester	<20	198 (11.0)	1	1	–
		20–60	133 (12.2)	1.12 [0.89, 1.42]	1.12 [0.84, 1.5]	0.423
		>60	953 (12.1)	1.11 [0.95, 1.31]	0.96 [0.71, 1.3]	0.796
	Last 3 months	<20	164 (12.1)	1	1	–
		20–60	122 (11.1)	0.90 [0.70, 1.16]	0.90 [0.69, 1.17]	0.442
		>60	998 (12.0)	0.99 [0.83, 1.18]	0.95 [0.75, 1.22]	0.702
Post-partum haemorrhage	First trimester	<20	45 (1.9)	1	1	
		20–60	36 (3.4)	1.78 [1.14, 2.78]	2.39 [1.46, 3.93]	<0.001*
		>60	312 (4.2)	2.25 [1.64, 3.08]	3.06 [2.04, 4.59]	<0.001*
	Second trimester	<20	58 (3.2)	1	1	
		20–60	37 (3.4)	1.05 [0.69, 1.60]	1.65 [1.01, 2.68]	0.044*
		>60	298 (3.8)	1.18 [0.89, 1.57]	0.91 [0.57, 1.46]	0.689
	Last 3 months	<20	46 (3.4)	1	1	–
		20–60	51 (4.6)	1.38 [0.92, 2.07]	1.47 [0.95, 2.28]	0.086
		>60	296 (3.6)	1.05 [0.76, 1.44]	0.97 [0.65, 1.45]	0.890
Low birth weight	First trimester	<20	243 (10.4)	1	1	–
		20–60	104 (9.8)	0.93 [0.73, 1.19]	1.02 [0.74, 1.39]	0.907
		>60	930 (12.6)	1.24 [1.07, 1.44]	1.19 [0.97, 1.47]	0.099
	Second trimester	<20	94 (12.6)	1	1	–
		20–60	76 (10.6)	0.82 [0.60, 1.13]	0.89 [0.59, 1.35]	0.596
		>60	1107 (11.9)	0.94 [0.75, 1.17]	0.84 [0.62, 1.14]	0.270
	Last 3 months	<20	170 (12.6)	1	1	–
		20–60	116 (10.5)	0.82 [0.64, 1.05]	0.84 [0.6, 1.17]	0.297
		>60	991 (11.9)	0.94 [0.79, 1.12]	0.9 [0.71, 1.14]	0.395
Preeclampsia	First trimester	<20	47 (2.0)	1	1	–
		20–60	14 (1.3)	0.65 [0.36, 1.18]	0.74 [0.39, 1.41]	0.367
		>60	179 (2.4)	1.21 [0.88, 1.68]	1.22 [0.83, 1.80]	0.304
	Second trimester	<20	22 (1.9)	1	1	–
		20–60	12 (1.7)	0.56 [0.28, 1.14]	0.57 [0.27, 1.22]	0.148
		>60	206 (2.2)	0.75 [0.48, 1.17]	0.79 [0.48, 1.29]	0.349
	Last 3 months	<20	35 (2.6)	1	1	–
		20–60	25 (2.3)	0.87 [0.52, 1.47]	1.06 [0.6, 1.86]	0.842
		>60	180 (2.2)	0.83 [0.58, 1.20]	0.80 [0.53, 1.20]	0.284
Caesarean section	First trimester	<20	431 (18.5)	1	1	–
		20–60	198 (18.6)	0.65 [0.36, 1.18]	0.74 [0.39, 1.41]	0.367
		>60	1525 (20.7)	1.21 [0.88, 1.68]	1.22 [0.83, 1.80]	0.304
	Second trimester	<20	159 (21.3)	1	1	–
		20–60	144 (20.1)	0.56 [0.28, 1.14]	0.57 [0.27, 1.22]	0.148
		>60	1851 (19.9)	0.75 [0.48, 1.17]	0.79 [0.48, 1.29]	0.349
	Last 3 months	<20	254 (18.8)	1	1	–
		20–60	211 (19.2)	0.87 [0.52, 1.47]	1.06 [0.60, 1.86]	0.842
		>60	1689 (20.3)	0.83 [0.58, 1.20]	0.80 [0.53, 1.20]	0.284
Malformations	First trimester	<20	24 (1.0)	1	1	–
		20–60	18 (1.6)	1.66 [0.90, 3.07]	1.66 [0.88, 3.15]	0.118
		>60	118 (1.7)	1.57 [1.01, 2.44]	1.42 [0.88, 2.28]	0.152
	Second trimester	<20	13 (1.7)	1	1	–
		20–60	14 (1.9)	1.12 [0.52, 2.40]	1.15 [0.52, 2.53]	0.729
		>60	133 (1.4)	0.82 [0.46, 1.45]	0.89 [0.49, 1.62]	0.701
	Last 3 months	<20	18 (1.3)	1	1	–
		20–60	14 (1.3)	0.95 [0.47, 1.93]	0.90 [0.43, 1.86]	0.767
		>60	128 (1.5)	1.16 [0.70, 1.90]	1.03 [0.61, 1.75]	0.900

*P-value < 0.05.

†The adjustment variables in the multivariate models were the woman's age, ethnic origin, gravidity, parity, twin pregnancy, having had a medical follow-up, the number of ultrasound scans and having had various pathologies during pregnancy, including chronic health conditions of the mother, as well as pregnancy specific medical conditions. Low birth weight (<2500 g) and preterm birth (gestation <37 weeks) were also used depending the outcome under investigation.

© 2013 John Wiley & Sons Ltd

Results

During the 2004–2007 period, 24 624 pregnancies occurred throughout French Guiana of which 11 004 (44.7%) were among women living in the urban area of Cayenne. 97.9% of these pregnancies had no missing data for maternal age, gestational time, parity, gravidity and birth weight. Preterm birth, low birth weight, malformations, preeclampsia, post-partum haemorrhage, and caesarean section were observed in 1284 (11.9%), 1277 (11.9%), 160 (1.4%), 240 (2.2%), 393 (3.6%) and 2154 (20.0%) pregnancies, respectively. A vast majority of the preterm births that occurred during the study period were born between 34 and 36 weeks of gestation (63.6%). Only 4.1% were classified as extreme preterm births (gestation <25 weeks). Figure 1 shows the monthly numbers of confirmed dengue cases and the monthly incidences of studied outcomes in the Cayenne area during 2004–2007.

Table 1 shows that after adjusting for potential confounders, dengue epidemic levels were statistically significant risk factors during the first trimester of pregnancy for both post-partum haemorrhage and preterm birth. For post-partum haemorrhage, a number of confirmed cases of dengue ≥20 during the first trimester of pregnancy corresponded to an increased adjusted odds ratio ranging from 2.39 [1.46, 3.93] to 3.06 [2.04, 4.59], depending on the level of the dengue epidemic. Similarly, confirmed dengue cases >60 during the first trimester were significantly associated with preterm birth, adjusted odds ratio of 1.31 [1.06, 1.63]. Furthermore, for post-partum haemorrhage, a number of confirmed cases of dengue between 20 and 60 during the second trimester of pregnancy were also significantly associated with an increased adjusted odds ratio, adjusted odds ratio of 1.65 [1.01, 2.68], but not with a number of confirmed cases of dengue >60, adjusted odds ratio of 0.91 [0.57, 1.46]. No statistically significant association of dengue epidemic levels was found for the other studied adverse obstetrical outcomes (low birth weight, malformations, preeclampsia and caesarean section).

Discussion

Despite its limitations, this study is the first to examine the relation between the magnitude of dengue epidemics and a range of obstetrical outcomes using a combination of individual and ecological data. After adjusting for potential confounders, there was a statistically significant association between dengue epidemics and post-partum haemorrhage, and between dengue epidemics and preterm birth. The measure of association seemed to be in proportion with the level of the epidemic.

It is important to note that the pregnancy registry data and the confirmed dengue totals were calculated per month. Not having exact dates for either dengue cases or delivery information results in an imperfect fit between the variables we used to represent the first and second trimesters and the last 3 months of pregnancy and real associated pregnancy periods. Using the total number of confirmed cases in Cayenne for 3 months as a reflection of an individual woman's risk of getting dengue is a very coarse reflection of actual dengue cases in pregnant women. It rests on the plausible assumption that the number of pregnant women having dengue will be proportional to the overall magnitude of the dengue epidemic in the population. As there were many deliveries (n = 11 004), during these 4 years, we feel we have adequate statistical power to detect associations. Although it is possible that the observed associations could have resulted from an information bias in the perinatal records, local experience has indicated that there is an under-reporting of adverse outcomes in the Perinatal Registry in French Guiana due to the priority given to care relative to data collection. For the purpose of this study, we assumed that this under-reporting was fairly constant during the study period and did not affect the results. It could also be argued that a possible synchronous seasonal pattern of both dengue epidemics and studied adverse outcomes could also explain the observed relations (Strand *et al.* 2011). However, including in the final model, a variable representing the month of birth did not affect results. Another explanation to the observed associations could also be that being exposed to a dengue epidemic implies having a greater probability of exposure to vector control pesticides. Thus, the 'toxic' environment during a dengue epidemic is also a potential hypothesis for the observed associations. Furthermore, underlying trends in the data, such as the unexpected decrease of preterm births which was observed in 2007, followed by an increase in preterm births, as well as the increased frequency of post-partum haemorrhages during most of our study period, make the interpretation of the significant associations more complicated.

Using aggregated data leads to potential ecological biases. However, except for the 'toxic' hypothesis, we were not able to identify any other potential explanation that could account for the association between dengue epidemics and post-partum haemorrhage and preterm birth. In addition, adjustment for a range of potential confounders available in the individual registry data did not affect the results. It was counter-intuitive to observe that dengue during the first trimester, and less clearly during the second trimester, was linked to post-partum haemorrhage and preterm birth. Direct placental damage

© 2013 John Wiley & Sons Ltd

in the first trimester could lead to placental anatomical and functional abnormalities leading to subsequent complications. This could suggest that the pathophysiology of post-partum bleeding and preterm birth are not solely linked to acute thrombopenia or endothelial dysfunction during dengue, but also to other mechanisms that have effects after the acute episode. It has been shown that dengue infection leads to the synthesis of antiplatelet antibodies (Sun *et al.* 2007; Hung *et al.* 2008) and antiendothelial cell antibodies (Hung *et al.* 2008), which can persist months after the initial dengue episode (Lin *et al.* 2001). It has been speculated that these autoantibodies are linked to shared epitopes between NS1, platelet and endothelium surface molecules (Hung *et al.* 2008). It is possible that these autoantibodies are also associated with post-partum haemorrhage and preterm birth.

In this study, no significant association ($P < 0.05$) was seen between dengue epidemic levels and other adverse obstetrical outcomes. Previous studies have shown an association between dengue infection and low birth weight (Pouliot *et al.* 2010). We have found a trend for an association between dengue during the first semester and low birth weight, but not during the second trimester and the last 3 months of pregnancy (Table 1). However, the ecological design may have not been optimal here to detect a significant difference. Similarly, although no significant association was seen, a trend during the first trimester seemed to suggest a possible association between dengue epidemic levels and malformations. There again, the ecological design combined with the limited number of events for this adverse outcome may have not been able to detect a significant association.

Overall, this study identified a possible relation between potential exposure to dengue epidemics in the first trimester of pregnancy and preterm birth and post-partum haemorrhage. Prospective studies on the obstetrical consequences of dengue and their pathophysiology are needed to confirm these results and improve our insufficient knowledge of this potentially important public health problem.

Acknowledgements

This work was supported by INSERM (Institut National de la Santé et de la Recherche Médicale) and the Cayenne General Hospital. Funders had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

Basurko C, Carles G, Youssef M & Guindi WEL (2009) Maternal and fetal consequences of dengue fever during pregnancy. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **147**, 29–32. doi:10.1016/j.ejogrb.2009.06.028.

Cardoso T, Carles G, Patient G, Clayette P, Tescher G, Carme B (2003) Perinatal care and mortality in French Guiana. From 1992–1999. *Journal of Gynecology Obstetrics Biology Reproductive (Paris)* **32**, 345–355.

Carles G, Peiffer H & Talarmin A (1999) Effects of dengue fever during pregnancy in French Guiana. *Clinical Infectious Diseases* **28**, 637–640. doi:10.1086/515144.

Development Core Team R (2011). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria.

Dussart P, Petit L, Labeau B *et al.* (2008) Evaluation of two new commercial tests for the diagnosis of acute dengue virus infection using NS1 antigen detection in human serum. *PLoS Neglected Tropical Diseases* **2**, e280. doi:10.1371/journal.pntd.0000280.

Halstead SB (2007) Dengue. *Lancet* **370**, 1644–1652. doi:10.1016/S0140-6736(07)61687-0.

Hung NT, Lan NT, Lin Y-S *et al.* (2008) Anti-platelet and anti-endothelial cell autoantibodies in Vietnamese infants and children with dengue hemorrhagic fever. *American Journal of Infectious Diseases* **4**, 41–49. doi:10.3844/ajidsp.2008.41.49.

Lin CF, Lei HY, Liu CC *et al.* (2001) Generation of IgM anti-platelet autoantibody in dengue patients. *Journal of Medical Virology* **63**, 143–149.

Pouliot SH, Xiong X, Harville E *et al.* (2010) Maternal dengue and pregnancy outcomes: a systematic review. *Obstetrical & Gynecological Survey* **65**, 107–118. doi:10.1097/OGX.0b013e3181cb8fbc.

Strand LB, Barnett AG & Tong S (2011) The influence of season and ambient temperature on birth outcomes: a review of the epidemiological literature. *Environmental Research* **111**, 451–462. doi:10.1016/j.envres.2011.01.023.

Sun D-S, King C-C, Huang H-S *et al.* (2007) Antiplatelet autoantibodies elicited by dengue virus non-structural protein 1 cause thrombocytopenia and mortality in mice. *Journal of Thrombosis and Haemostasis* **5**, 2291–2299. doi:10.1111/j.1538-7836.2007.02754.x.

Corresponding Author **Matthieu Hanf**, Centre d'Investigation Clinique Epidémiologie Clinique Antilles Guyane CIC-EC INSERM CIE 802, Cayenne General Hospital, EHPAD, Avenue des Flamboyants, BP 6006 97300 Cayenne, French Guiana, France.
E-mail matthieu@hanf.fr

© 2013 John Wiley & Sons Ltd