Title

Increased risk of malaria during the first year of life in small-birth-weight-for-gestational age infants: a longitudinal study in Benin

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Running title

Higher risk of malaria in SGA infants

Brief summary

Using a logistic mixed regression model we assessed the effect of SGA on the risk of malaria morbidity from 0-12months. SGA was associated with a 2-times higher risk of both malaria infection and clinical malaria after 6 months of age.

Word count

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Abstract

Background: According to the DOHaD paradigm, the foetal period is one of the most vulnerable periods that may have profound effects on health later in life. Few studies have assessed the effect of small-birth-weight-for-gestational age (SGA), a proxy for foetal growth impairment, on the risk of malaria during infancy in Africa.

Methods: We used data from a cohort of 398 mother-child pairs, followed from early pregnancy to age one in Benin. Infant's malaria was actively and passively screened using thick blood smear. A logistic mixed regression model was performed to assess the effect of SGA on the risk of both malaria infection and clinical malaria from birth to age one, after stratifying on the infant's age.

Results: After adjustment for potential confounding factors, as well as the infant's level of exposure to mosquitoes, SGA was associated with a 2-times higher risk of both malaria infection (aOR= 2.16, 95%CI: 1.04–4.51, p=0.039) and clinical malaria (aOR= 2.33, 95%CI: 1.09–4.98, p=0.030) after 6 months of age.

Conclusion: Our results suggest a higher risk of malaria during the second semester of life in SGA infants. They argue for a better follow-up of these infants after birth as currently done for preterm babies.

Key words: DOHaD, Small-birth-weight-for-gestational-age, malaria, infancy, epidemiology, cohort

Introduction

The foetal origins hypothesis, referred to as the Developmental Origins of Health and Diseases (DOHaD) paradigm, states that the environment during the peri-conception, gestation and early post-natal periods shapes developing individuals, leading to a predisposition to child and adult onset diseases in the case of a deleterious environment. In particular, intrauterine growth restriction (IUGR) has profound influences on subsequent health during childhood and adulthood [1]. Indeed, growth restricted newborns have a higher mortality and morbidity during the neonatal period and during infancy than appropriate-for-gestational age newborns [2]. Growth and neurocognitive impairments in childhood [3,4], as well as an increased risk of cardiometabolic disorders during adulthood have also been reported in these children [5].

Most of the DOHaD research has been conducted in high-income countries (HICs). Less evidence comes from low- and middle-income countries (LMICs), where IUGR rates are two to three-times higher than in HICs [2]. Small-birth weight-for-Gestational Age (SGA) is commonly used as a proxy for IUGR [6,7]. SGA is estimated to have affected 32.4 million newborns in LMICs over the last decade, with sub-Saharan Africa (SSA) accounting for 20% of this total burden [8].

While SGA has been associated with a higher risk of diarrhoea and respiratory tract infections during infancy in HICs [9,10], very few studies have assessed the effect of SGA on infectious diseases later in life in LMICs. Malaria is one of the most prevalent and lethal diseases during infancy in these areas. We aimed to assess the effect of SGA on malaria morbidity in the infant during his first year of life using data from a prospective longitudinal cohort study in Benin.

Methods

Study site, population and design

Between January 2010 and June 2011 in Allada, south Benin, 1182 pregnant women were followed part of a multi-country randomized clinical trial for the prevention of malaria in pregnancy (MiPPAD trial, NCT00811421) [11]. Among them, a sub-sample of 400 mothers and their infant were then included in the ancillary APEC study "Anaemia in Pregnancy: Etiology and Consequences" [12,13].

Women's and infant's follow-up

Pregnant women's follow-up has been described elsewhere [12,13]. Briefly, women were recruited at their 1st antenatal care (ANC) visit at a gestational age (GA) ≤ 28 weeks and followed-up throughout the pregnancy. Socio-demographic, anthropometric, clinical and biological data (thick blood smear (TBS) [14], haemoglobin (Hb) and C-reactive protein (CRP) levels) were collected twice during pregnancy and at delivery (Figure 1). At delivery, a TBS was also made from placental blood.

GA at birth was assessed by specifically trained midwives using the Ballard method [15]. Newborn's sex and characteristics (weight, length, and head circumference) were recorded. Weight was measured within 24 hours after birth using an electronic scale.

During the first year of life (APEC study), infant had three scheduled visits at the health center (Sékou or Attogon) at 6, 9 and 12 months of age (Figure 1). On these occasions, clinical (history of fever within the previous 24 hours, use of insecticide treated mosquito nets (ITN), temperature, breastfeeding practices), anthropometric (weight and length) and biological (TBS, Hb and CRP levels) data were collected. In addition, women were invited to attend the health center any time their infants had any symptoms. A rapid diagnosis test for malaria was performed for immediate diagnosis and treatment; the diagnostic was then confirmed by TBS. *Plasmodium* parasitaemia was quantified by the Lambaréné method [14].

Entomological and environmental data

Exposure to mosquitoes was estimated using a predictive model, which was developed by combining both entomological (number of mosquitoes caught in the infant's home at the nearest date of each scheduled visit), geographical, climatic and rainfall data [16]. This allowed assigning a quantitative risk of exposure to malaria vector at each infant's visit from birth to one year of age. The higher was this variable, the higher was the infant's exposure to mosquitoes [16].

Statistical analysis

The effect of SGA on the risk of malaria infection (first analysis) and clinical malaria (second analysis) during the first year of life was assessed using a longitudinal approach. To take into account the hierarchical two-level structure of the data, where malaria screenings (level 1) were clustered within infants (level 2) [17], we used a hierarchical logistic mixed model with random intercept to model dependence of malaria outcomes in the same infant. The analysis was stratified on two periods according to the infant's age: from birth to 6 months and after 6 months of age. This allowed us to take into account the variation in malaria susceptibility with the infant age [18,19].

Malaria infection was defined as a positive TBS (i.e., presence of at least one asexual *Plasmodium* parasite). Clinical malaria was defined as the combination of a positive TBS and fever (temperature ≥ 37.5°C) or history of fever in the last 24 hours. Therefore, the analysis related to "malaria infection" included both asymptomatic and febrile malarial infections. Second, if an infant had two distinct malarial episodes (one asymptomatic and one symptomatic) within the same period of time (0-6 or 6-12 mo), he was accounted forin both proportions and was included in both risk analyses. Infants were considered not to be at risk of malaria for 14 days after receiving treatment with an anti-malarial drug. Placental malaria

infection was defined as the presence of *Plasmodium* parasite in placental smear. Maternal malaria infection at delivery was defined by either placental or peripheral malaria.

Low birth weight (LBW) was defined as a birth weight < 2500 g. GA at birth was calculated according to the following formula: GA = [((2 x Ballard score) + 120) / 5] (32, 33). SGA was defined as a birth weight below the 10^{th} percentile of sex-specific Schmiegelow charts [20]. Anaemia in the child was considered as a chronic condition and defined as an Hb level less than 14 g/dL at birth or less than 11g/dL at 6 months of age (for the first time period), and less than 11g/dL at 9 or at 12 months of age (for the second time period). For each infant, the level of exposure to mosquitoes was averaged for each specific infant's age period and was log-transformed because of non-normal distribution of the variable.

The following procedure was used for each malaria outcome (i.e., malaria infection and clinical malaria). All variables with a p-value below 0.25 in univariate analysis were selected for the multivariate multilevel analysis. Maternal malaria at delivery was forced into the multivariate model since it is known to be a risk factor for malaria during infancy [21–23]. Then, a manual backward selection procedure was used to obtain the final multivariate model, a p-value of <0.05 was considered statistically significant.

Stata version 13 for Windows (Stata Corp., College Station, TX) was used for all statistical analyses.

Ethics statement

The MiPPAD trial and APEC study have been approved by the Ethics Committee of the Health Sciences Faculty of Cotonou in Benin. Women and their infants were included after providing a signed written informed consent.

Results

Study profile

Among the 400 infants who were enrolled in the APEC study, 398 were included in our analysis because of 2 missing birth weights in women who delivered outside the participating health facilities (Figure 2). SGA at birth accounted for 12.3% (49/398, 95%CI: 9.4-15.9) of cases. During the one-year follow-up, 4 (1.0%) infants were lost to follow-up, 33 (8.3%) withdrew their consent, 22 (5.5%) migrated outside study area and 15 (3.8%) died. The maternal (age, gravidity, socioeconomic status) and infant's (sex, weight and gestational age at birth) characteristics of children who completed the 12 month follow-up and those who did not were similar (data not shown). The reasons for withdrawing consent were similar between SGA and non-SGA infants. The proportion of deaths was more than 2 times higher in SGA than in non-SGA infants (8.1% vs. 3.2%, respectively, p=0.21). At the end, 324 (81.4%) infants had completed the study.

Our analysis was based on 1261 (1261/1592, 92.3%) screenings for malaria during scheduled visits, and 580 screenings for malaria during unscheduled visits (of a total of 981 unscheduled visits).

Maternal and infant's characteristics

Mothers of SGA infants were significantly younger, more likely to be primigravidae and thinner than mothers from non-SGA infants (Table 1).

Mean gestational age at birth was similar between SGA and non-SGA infants. Expectedly, SGA infants had a significantly far lower birth weight than non-SGA infants (2396 g vs. 3123 g, respectively, p<0.001). More than two-thirds (33/49) of SGA infants had also a LBW compared to 9% of non-SGA infants. The overall proportion of preterm birth (<37 weeks) was 5.8%, and there was not statistically difference between SGA and non-SGA infants (8.5% vs 5.5%, p=0.34). During the one-year follow-up, the mean level of exposure to mosquitoes was similar between SGA and non-SGA infants. SGA infants were significantly more likely

to had wasting and stunting compared to non-SGA infants. The majority of infants were exclusively breastfed until 6 months of age and most families used an ITN.

Malaria morbidity in infants

The incidence rate of malaria infection was 3.66 (95%CI: 3.03–4.42) and 4.18 (95%CI: 2.48–7.06) per 100 person-months in non-SGA and SGA infants, respectively. For clinical malaria, the incidence rate was 2.82 (95%CI: 2.28–3.49) and 3.56 (95%CI: 2.02–6.24) per 100 person-months in non-SGA and SGA infants, respectively. Clinical malaria accounted for 71% of all malaria episodes. From birth to 6 months of age, non-SGA infants have a higher proportion of malaria than SGA infants (Figure 3), although the difference was not statistically significant (7.2% vs. 3.7% of infants with at least one malaria infection, p=0.351 and 4.0% vs. 1.5% of infants with at least one episode of clinical malaria, p=0.221, respectively). In contrast, after 6 months of age, SGA infants have a higher proportion of malaria compared to non-SGA infants, but the difference was only significant for malaria infection (24.0% vs. 15.1% for malaria infection, p=0.048 and 12.9% vs. 7.8% for clinical malaria, p=0.086, respectively) (Figure 3).

Effect of SGA on malaria morbidity according to infant's age

Results of the univariate analysis are presented in table 2. From birth to 6 months of age, the following maternal, infant and environmental characteristics were associated with a higher risk of malaria infection in the infant: a low maternal age, malaria at delivery, infant's anaemia and level of exposure to mosquitoes, maternal inflammatory syndrome at delivery and rainy season at birth (only marginally significant for the latter two). After 6 months of age, factors associated with a risk of malaria with a P-value less than 0.25 were maternal age, SGA, infant's level of exposure to mosquitoes, maternal socioeconomic level and an inadequate gestational weight gain (GWG), only the two latter being statistically significant.

188 Women with a high or medium socioeconomic level compared to those with a relatively low
189 level had children with a lower risk of malaria (only the medium category in relation with
190 malaria infection was statistically significant).
191 In the multivariate multilevel analysis, we did not find any association between SGA status
192 and the risk of malaria infection or clinical malaria until 6 months of age (aOR= 0.46, 95%CI:
193 0.10–2.08, p=0.316 and aOR= 0.37, 95%CI: 0.08–1.57, p=0.176, for malaria infection and
194 clinical malaria respectively) (Table 3). However, after 6 months of age, SGA infants had a
195 significantly 2 times higher risk of malaria infection and clinical malaria than non-SGA
196 infants (aOR= 2.16, 95%CI: 1.04–4.51, p=0.039 and aOR= 2.33, 95%CI: 1.09–4.98, p=0.030,
197 for malaria infection and clinical malaria respectively). The other factors significantly
198 associated with a higher risk of malaria infection differed according to the infant's age. Until
199 6 months of age, maternal age and infant's anaemia remained significantly associated with
200 malaria infection. After 6 months of age, the infant's level of exposure to mosquitoes was
201 significantly associated with a higher risk of malaria infection; a medium (compared to a low)
202 maternal socioeconomic level and an inadequate GWG were associated with a lower risk of
203 malaria infection. Children born form mothers infected with malaria at delivery presented a
204 higher risk of malaria infection until 6 months of age, but this association was only marginally
205 significant (aOR= 2.17, 95%CI: 0.95–4.93, p=0.065). The same factors and associations were
206 found for clinical malaria according to the infant's age, except for socioeconomic status and
207 infant's level of exposure to mosquitoes, which were only marginally significant.
208

209 ## Discussion

210 To our knowledge, this is one of the few prospective longitudinal studies that have evaluated
211 the effect of SGA on infant's malaria morbidity in SSA. During infancy, malaria screening
212 included both active and passive case detection. Important maternal determinants that may

influence the infant health were prospectively collected such as malaria, nutritional status and socio-demographic characteristics. Also, we took into account postnatal conditions such as the infant's nutritional status and level of exposure to malaria over the entire follow-up. SGA, and not only LBW, was considered as the main variable of exposure. Indeed, SGA is more informative than LBW by taking into account both infant birthweight and gestational duration and then is a more specific indicator of infant's morbidity and mortality than LBW. Finally, SGA was defined using recent sex-specific foetal weight charts established in Tanzania. In our population, the prevalence of SGA was 12.3%, which is in accordance with the prevalence range (10-35%) recently reported in SSA [2].

In HICs, SGA has been associated with an increased risk of infections during childhood [9,10]. The increased susceptibility of SGA infants to infectious diseases may be explained by immune function impairment, which is maximum until 12 months of age [24]. This excess risk has been particularly evidenced for severe respiratory and diarrhoeal infectious diseases [9,10,25,26]. To account for this, we chose to assess malaria infection (either symptomatic or not) and clinical malaria (i.e., only symptomatic infections) separately. In our study, clinical malaria accounted for 71% of all malaria infections; we did not find a greater effect of SGA on clinical malaria than on malaria infection overall.

We showed that SGA was significantly associated with a 2 time-higher risk of both malaria infection and clinical malaria after 6 months of age, whereas no excess risk was evidenced from birth to 6 months of age. In the literature, there are limited findings on the effect of SGA or LBW on malaria during infancy. In their study in Uganda, de Beaudrap *et al*. found a lower, but non-significant, risk of malaria in SGA infants during the first 12 months of life [26]. Sylvester *et al* in Tanzania and Le Port *et al* in Benin did not find any association between LBW and clinical malaria in the infant during the first or the first two years of life [21,27]. In contrast to previous studies, we chose to stratify on infant's age to account for the

variation in malaria susceptibility with age. Indeed, during the very first months of life (from birth to 6 months of age), malaria infection is modulated by the presence of both protective maternal antibodies [18] and foetal haemoglobin that is not favourable to the development of *Plasmodium* parasites [19]. Malaria history during pregnancy may then have a greater role in the occurrence of malaria in the infant during this period compared to other factors not related to malaria such as SGA. In contrast, after 6 months of age, both maternal and infant conditions—including SGA—significantly influenced the risk of malaria in the infant. This period is probably a period of transition regarding the risk of malaria since the infant has lost his maternal protective antibodies, builds his own immunity, is no longer breastfed and interacts more with his environment. How long SGA children are at increased risk of malaria warrants further analysis. Children of this cohort were actually followed from 12 until 24 months of age as a part of the TOLIMMUNPAL study [28]. However, because of the very different infant's follow-up (in terms of malaria and other medical conditions/possible confounding factors screening and treatment), we chose to not pool data collected during the second year of life with the present ones. In particular, screening for malaria was performed at least monthly during scheduled visits, with possible additional screenings during fortnightly home visits. Interestingly, while restricting the analysis to the second-year follow-up, the association between SGA and malaria did not seem to persist after the first year. This result may partly be due to the fact that SGA infants become more comparable to non-SGA infants over time because of growth catch-up [29,30], as observed in our data, and correction of immune disorders [24]. However, these exploratory results warrant further confirmation.

Our results suggested that maternal malaria at delivery may be associated with a higher risk of malaria until 6 months of age independently of SGA. However, this association was not statistically significant, possibly due to a lack power. We chose to define maternal malaria at delivery as either placental malaria or peripheral malaria at delivery to minimise missed

infections at the end of pregnancy. Indeed, in longitudinal studies, only malaria occurring during the third trimester of pregnancy, and not placental malaria, was associated with malaria in the infant [26,31]. Since women were treated repeatedly for malaria during pregnancy (as part of intermittent preventive treatment and in case of malaria infection), it is likely that placental malaria only reflected recent infections at the end of pregnancy. Our results are in accordance with the literature. Indeed, several studies have reported an association between malaria during pregnancy and a higher risk of malaria during infancy [21,23,27,32,33]. One hypothesis is that *in utero* exposure to soluble *Plasmodium* antigens may alter the fetal and neonatal immune development, resulting in a higher susceptibility to malaria later in life [34,35]. In a recent study in Benin, infants born to mothers with a placental malaria had an increased risk for the first malaria attack (HR = 1.37; p= 0.048), but not for subsequent attacks later in life (HR = 0.88; p= 0.49) [36].

The higher risk of malaria in SGA infants was found after adjustment for the level of exposure to mosquitoes. Environmental characteristics highly influence the level of transmission of malaria and the risk of infection at population level [37]. Seasonality (dry *vs.* rainy season) is usually used as a proxy for malaria transmission and, by extension, as a proxy for the subject's level of exposure to mosquitoes [38]. In our study, the level of exposure to malaria was predicted for each infant and more accurately than with seasonality alone by combining climatic, geographical and entomological parameters. We showed that a higher level of exposure to mosquitoes was associated with a higher risk of malaria morbidity. Similar findings have been reported by Le Port *et al*. and Bouaziz *et al*. in Benin [21,36].

Our study has some limitations that should be considered. First, GA at birth was estimated using the Ballard method, which may have underestimated GA and, therefore, misclassified some SGA as non-SGA infants [39]. However, this should not have biased the association between SGA and malaria since misclassification was probably non-differential regarding

malaria. Second, the infant's follow-up was different between the first (mainly unscheduled visits) and second semester (quarterly scheduled screenings plus unscheduled visits) of life. During the first six months of life, malaria cases were mainly detected through a passive follow-up, leading to possible malaria (especially malaria infection) underdetection.

In conclusion, we showed that SGA infants were more susceptible to malaria than non-SGA infants after 6 months of life, after adjustment for the infant's level of exposure to mosquitoes. This result highlights the detrimental effect of fetal conditions on the infant health later in life, as stated by the DOHaD paradigm. They argue for a better follow-up after birth of SGA infants as currently done for preterm babies.

Conflict of interest

None declared

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Authors' contributions

G.A., M.C., and V.B. conceived and designed the study. G.A. and V.B. analyzed the data. G.A., M.A., G.C., Y-M.P., J.M., S.O., D.C., A.M., A.G., M.C. and V.B. contributed reagents/materials/analysis tools. G.A., M.C., and V.B. drafted and finalized the manuscript. The final manuscript was read and approved by all authors.

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313 # References

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Figure legends

Figure 1: Study procedures

[a] Plasmodium parasitaemia was quantified by the Lambaréné method. [b] Hb level was determined using a Hemo-Control photometer (EKF Diagnostics, Magdeburg, Germany) device. [c] CRP level was determined by rapid slide test (CRP Latex; Cypress Diagnostics Inc.). Infants with malaria infection were treated with artemether-lumefantrine or quinine according to national guidelines.

Figure 2: Flow chart diagram of follow-up

Infants who were absent more than 3 consecutive months were considered as lost to follow-up. The main causes of death were: acute respiratory infection (n=5), neonatal icterus (n=2), severe malaria (n=2), severe anaemia (n=2) and unknown disease (n=4). The children who left the cohort before 12 months of age were included in the analysis.

Figure 3: Proportion of infants with at least one malarial infection or one clinical malaria episode according to SGA status and age. Allada, Benin 2010-2014

(I 95 % confidence interval)

439 **Table 1:** Characteristics of the mothers during pregnancy and of their children at birth and
440 during the first year of life according to small-birth-weight for gestational age (SGA) status.
441 Allada, Benin, 2010-2014 (n=398)

Characteristics	At birth		From birth to 6 months		Between 6 and 12 months	
	SGA + (n=49)	SGA – (n=349)	SGA + (n=41)	SGA – (n=294)	SGA + (n=33)	SGA – (n=291)
Maternal characteristics						
Age (years) (M±SD)	24.3±5.2*	26.2±5.5	–	–	–	–
Primigravidae (%)	26.5*	14.3	–	–	–	–
≥ primary school (%)	28.6	29.5	–	–	–	–
Low socioeconomic status[a] (%)	55.1	63.3	–	–	–	–
BMI at inclusion (kg/m²) (M±SD)	21.4±2.2*	22.1±2.8	–	–	–	–
Gestational age at inclusion (weeks) (M±SD)	22.1±4.1	22.8±4.0				
Adequate GWG (≥1 Kg/month)[b] (%)	20.8	33.6				
Inflammatory syndrome at delivery[c] (%)	36.2	30.4	–	–	–	–
Anaemia at delivery (Hb < 110g/L) (%)	40.8	51.6				
≥ 1 episode(s) of malaria in pregnancy (%)	36.7	27.2	–	–	–	–
Placental malaria (%)	10.2	11.0	–	–	–	–
Malaria at delivery (%) [£]	18.4	12.2				
Infant's characteristics						
Sex male (%)	42.9	47.9	–	–	–	–
Term at birth (weeks) (M±SD)	39.4±0.9	39.2±1.1	–	–	–	–
Weight at birth (g) (M±SD)	2396 ±183*	3123 ±363	–	–	–	–
Low birth weight (< 2500 g) (%)	67.3*	9.1				
Birth during the dry season[d] (%)	28.6	36.4	–	–	–	–

ITN use (%)	–	–	79.3	87.4	78.8	65.1
Exclusive breastfeeding (%)	–	–	93.1	93.2	–	–
Anaemia at birth (Hb < 140g/L)	30.6*	48.4				
Anaemia (Hb < 110g/L) (%)	–	–	49.0	57.3	79.0	81.7
Iron deficiency[e] (%)	–	–	12.2	20.9	57.6	59.5
Wasting (WLZ < -2SD)	–	–	56.3*	30.0	25.8	18.7
Stunting (LAZ < -2SD)	–	–	27.3*	14.5	41.9*	17.7
≥ 1 episode(s) of malaria infection ‡ (%)	–	–	6.1	11.5	36.4	28.0
≥ 1 episode(s) of clinical malaria‡ (%)	–	–	4.1	10.0	33.3*	19.6
Mean level of exposure to mosquitoes	1.5	1.4	1.5	1.3	1.3	1.3
(M±SD)¥	±0.9	±1.2	±0.9	±1.1	±0.6	±0.8
Mean number of unscheduled visits (M±SD)			1.9 ±0.2	2.2 ±0.1	1.7 ±0.2	1.6 ±0.1

Missing data: 8 for GWG, 2 for inflammatory syndrome at delivery, 4 for malaria at delivery and 9 for infant anaemia between 6-12 months.

M: Mean; SD: Standard deviation; WLZ: Weight-for-length z-score; LAZ: Length-for-age z-score; £ Peripheral malaria at delivery or placental malaria; * Statistically significant difference (p-value<0.05) between SGA and non-SGA children using Student's t-test or Chi-squared test or Fisher exact test; ‡Malaria episodes that were detected either during scheduled or unscheduled visits. ¥ Quantitative level of exposure to mosquitoes that was estimated using a predictive model. [a] Maternal socioeconomic status was classified as low, medium and high depending on the number (0-1, 2-3, and 4) of assets (having electricity, a television, a refrigerator or a bicycle) owned. [b] Weight gain ≥ 1 Kg per month from the end of the first trimester of pregnancy until delivery. [c] Inflammation was defined as a CRP concentration more than 6mg/mL. [d] Season of birth was defined as rainy (from April to July and from October to November) or dry (from December to March and from August to September). [e] Iron deficiency was defined as a ferritin level < 12 µg/L or between 12-70 µg/L in an inflammatory context.

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445 **Table 2:** Factors associated with malaria in the infant according to age. Univariate analysis. Allada, Benin, 2010-2014 (n=398)

Variables	Categories	≤ 6 months of age (N=776)				> 6 months of age (N=1065)			
		Malaria infection‡		Clinical malaria‡		Malaria infection‡		Clinical malaria‡	
		OR [95%CI]	p	OR [95%CI]	p	OR [95%CI]	p	OR [95%CI]	p
Maternal characteristics									
Age (*years*)	*≤ 20*	2.68 [1.37;5.24]	0.004	2.71 [1.37;5.37]	0.004	1.59 [0.88;2.89]	0.125	0.95 [0.50;1.80]	0.869
	*20-30**	1		1		1		1	
	> 30	0.65 [0.23;1.86]	0.422	0.79 [0.28;2.22]	0.656	1.27 [0.67;2.42]	0.469	1.27 [0.66;2.43]	0.470
Socioeconomic status	*Low**	1							
	Medium	0.72 [0.37;1.42]	0.344	0.63 [0.31;1.31]	0.217	0.55 [0.33;0.93]	0.026	0.62 [0.36;1.07]	0.088
	High	1.56 [0.28;8.68]	0.609	0.70 [0.08;6.04]	0.747	0.61 [0.13;2.85]	0.534	0.29 [0.03;2.47]	0.256
Malaria at delivery£	*No**	1		1		1		1	
	Yes	2.36 [1.01;5.50]	0.047	2.03 [0.88;4.68]	0.097	0.67 [0.29;1.54]	0.350	0.60 [0.24;1.49]	0.274
Gestational weight gain	*Inadequate**	1		1		1		1	
(GWG)	*Adequate*	1.44 [0.75;2.76]	0.275	1.15 [0.57;2.30]	0.702	0.48 [0.28;0.83]	0.009	0.40 [0.22;0.75]	0.004
Inflammatory syndrome	*No**	1		1		1		1	
at delivery	*Yes*	1.80 [0.95;3.40]	0.070	1.70 [0.88;3.28]	0.117	0.81 [0.46;1.44]	0.481	0.65 [0.35;1.21]	0.176

Infant's characteristics									
SGA	*No**	1		1		1		1	
	Yes	0.47 [0.13;1.69]	0.249	0.36 [0.08;1.57]	0.172	1.86 [0.87;3.98]	0.108	1.88 [0.88;4.02]	0.102
Season of birth	*Dry**	1		1		1		1	
	Rainy	1.84 [0.90;3.78]	0.096	1.81 [0.85;3.84]	0.125	1.24 [0.74;2.07]	0.408	1.46 [0.84;2.53]	0.184
Anaemia	*No**	1		1		1		1	
	Yes	2.26 [1.09;4.67]	0.028	2.22 [1.04;4.73]	0.039	1.42 [0.71;2.82]	0.323	1.06 [0.55;2.06]	0.862
Stunting	*No**	1		1		1		1	
	Yes	1.41 [0.59;3.40]	0.440	1.42 [0.59;3.41]	0.430	1.73 [0.98;3.04]	0.057	1.75 [0.98;3.12]	0.057
Wasting	*No**	1		1		1		1	
	Yes	0.76 [0.36;1.58]	0.455	0.80 [0.37;1.71]	0.563	1.63 [0.91;2.92]	0.098	1.73 [0.96;3.08]	0.066
Environmental factors									
Mean level of exposure to mosquitoes		3.29 [1.36;8.01]	0.008	3.22 [1.34;7.74]	0.009	1.66 [0.87;3.18]	0.128	1.49 [0.76;2.93]	0.244

Missing data: 8 for GWG, 2 for inflammatory syndrome at delivery, 4 for malaria at delivery and 9 for infant anaemia after 6 months.

£ Peripheral malaria at delivery or placental malaria; ǂ Infections that were detected during both scheduled and unscheduled visits; p: p-value; * Category of reference; OR: Unadjusted odds ratio; 95%CI: 95% confidence interval. N: number of malaria screenings that were performed during each period of time (≤6 months and >6 months of age) and that were considered for the analyses. For each variable of interest, the analysis was conducted using a hierarchical logistic mixed model with random intercept. The crude OR was corrected for the clustering effect of the infant

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448 **Table 3:** Effect of SGA on infant malaria morbidity according to age. Multivariate analysis. Allada, Benin, 2010-2014

Characteristics	Categories	≤ 6 months of age (n=347)				> 6 months of age (n=322)			
		Malaria infection‡		Clinical malaria‡		Malaria infection‡		Clinical malaria‡	
		aOR [95%CI]	p	aOR [95%CI]	p	aOR [95%CI]	p	aOR [95%CI]	p
Fixed effects									
SGA	*No**	1		1		1		1	
	Yes	0.46 [0.10;2.08]	0.316	0.37 [0.08;1.57]	0.176	**2.16 [1.04;4.51]**	**0.039**	**2.33 [1.09;4.98]**	**0.030**
Infant anaemia	*No episode**	1		1					
	≥ 1 episode(s)	**3.41 [1.44;8.04]**	**0.005**	2.04 [0.98;4.29]	0.059	–		–	
Maternal age (*years*)	*≤ 20*	1.91 [0.91;4.02]	0.089	**2.27 [1.10;4.67]**	**0.026**	–		–	
	*20-30**	1		1					
	> 30	0.64 [0.22;1.81]	0.397	0.73 [0.26;2.02]	0.545	–		–	
Malaria at delivery£	*No**	1		1		1		1	
	Yes	2.18 [0.95;4.93]	0.065	1.62 [0.84;3.58]	0.130	1.31 [0.62;2.78]	0.482	0.91 [0.39;2.14]	0.834

Socioeconomic status	*Low**			1			
	Medium	–	–	**0.51 [0.28;0.92]**	**0.027**	0.57 [0.30;1.08]	0.086
	High	–	–	0.48 [0.10;2.18]	0.339	0.23 [0.02;2.06]	0.187
GWG	*Inadequate**			1		1	
	Adequate	–	–	**0.55 [0.31;0.98]**	**0.045**	**0.40 [0.20;0.82]**	**0.012**
Mean level of exposure to mosquitoes		–	–	**2.10 [1.11;3.97]**	**0.022**	1.82 [0.96;3.70]	0.068
Random effects							
Child-to-child variance (σ^2)		0.35 [0.01;11.22]	0.26 [0.01;20.93]	0.66 [0.19;2.33]		0.46 [0.08;2.58]	
Total variance explained by the model		90%	93%	83%		88%	

Missing data: 8 for GWG, 4 for malaria at delivery and 9 for infant anaemia after 6 months.

ǂ Infections that were detected during both scheduled and unscheduled visits; p: p-value; * Category of reference; aOR: adjusted odds ratio; 95%CI: 95% confidence interval; £ Peripheral malaria at delivery or placental malaria; List of the variables that were initially introduced in the multivariate model: SGA, maternal age, socioeconomic status, GWG, inflammatory syndrome at delivery, malaria at delivery, season of birth, infant's anaemia, infant's stunting and wasting, exposure to mosquitoes, study center.

For each variable of interest, the analysis was conducted using a hierarchical logistic mixed model with random intercept. The adjusted OR was corrected for the clustering effect of the infant

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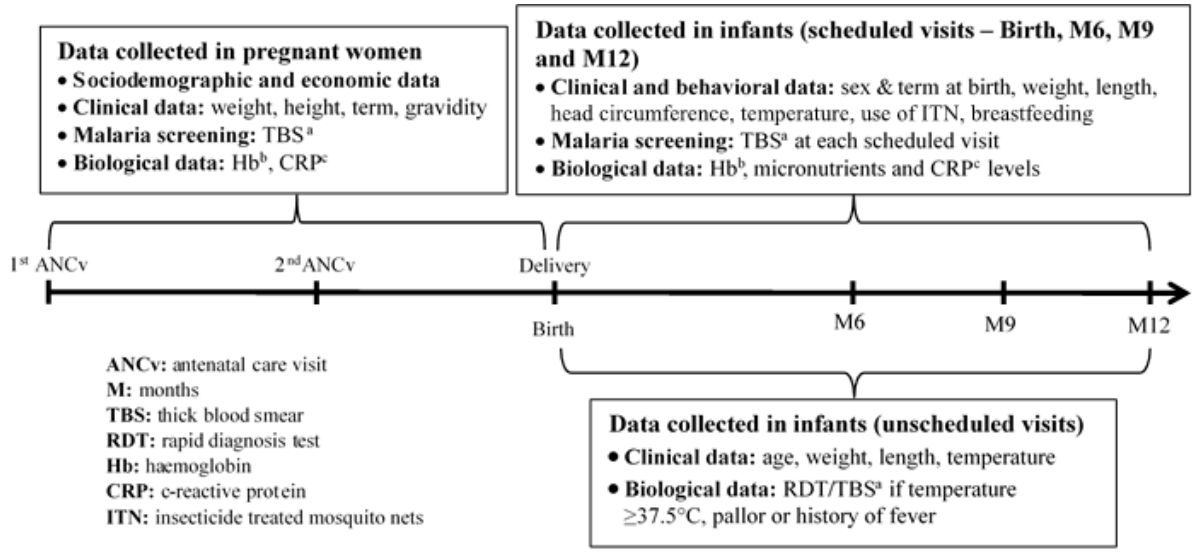
450 Figure 1



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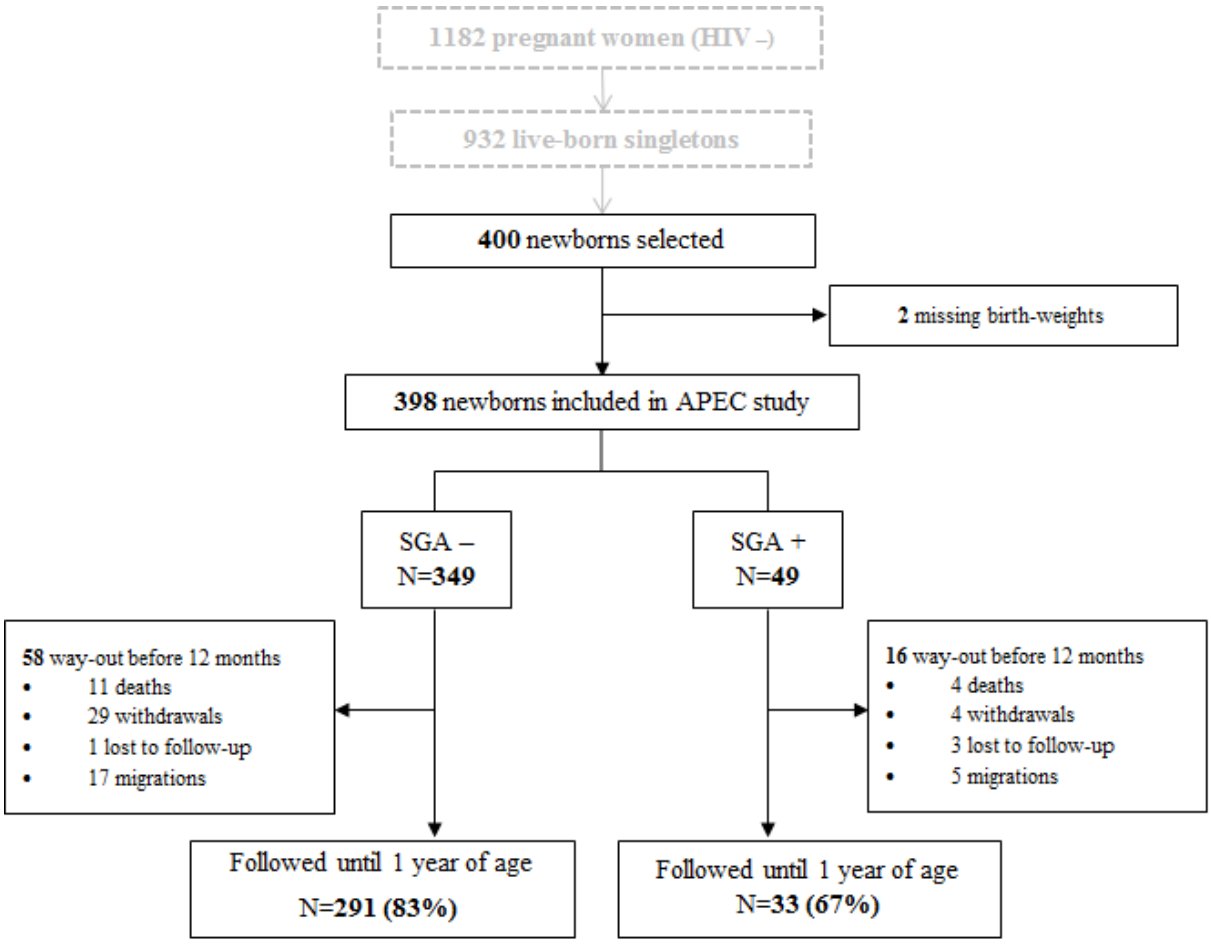
452 Figure 2



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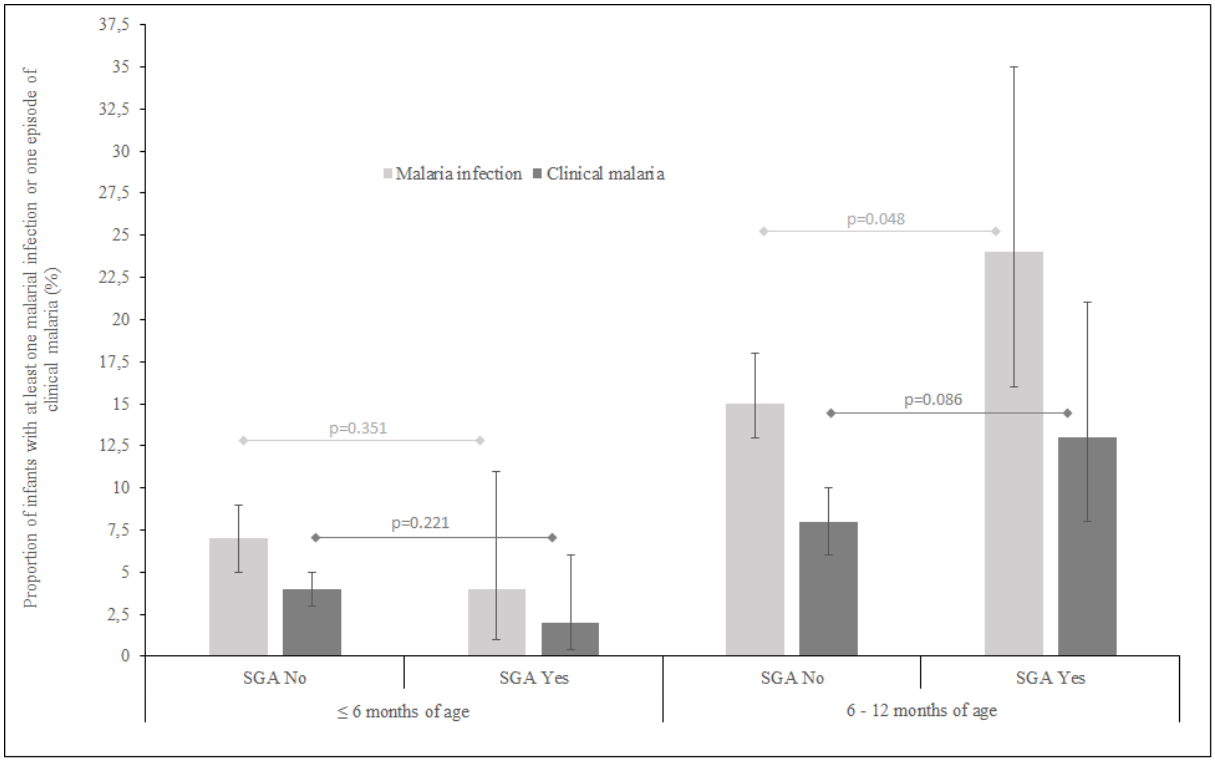
455 Figure 3



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