

1 **Malaria during pregnancy and newborns outcome in an unstable transmission area in Brazil:**  
2 **a population-based record linkage study**

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23

24 **Running Head:** Low birth weight in malaria

25 **Keywords:** malaria, newborn, low birth weight, prematurity, record linkage, database

26 **ABSTRACT**

27 **Background:** Malaria during pregnancy is one of the major causes of mortality in tropical regions,  
28 causing maternal anemia, intrauterine growth retardation, preterm birth, and low birth weight  
29 (LBW). The integration of the information systems is crucial to assess the dimension of gestational  
30 malaria in a wide and useful way, to improve decision making and maternal-child health.

31 **Methods and Findings:** An observational population-based study acquired information  
32 retrospectively from all live births that occurred between 2006 and 2014 in Cruzeiro do Sul (Acre,  
33 Brazil). Social and clinical data of the mother and newborn was extracted from the Information  
34 System of Live Births. Malaria episodes information was obtained from the Brazilian  
35 Epidemiological Surveillance Information System Malaria. A deterministic record linkage was  
36 performed to assess malaria impact on pregnancy. The studied population presented a malaria  
37 incidence of 8.9%, of which 63.9% infected by *Plasmodium (P.) vivax*. Reduction of newborns  
38 birth weight at term (small for gestational age (SGA) and LBW) has been found associated with *P.*  
39 *vivax* infection during pregnancy (SGA - OR 1.24, 95% CI 1.02-1.52, p=0.035; term LBW - OR  
40 1.39, 95% CI 1.03-1.88, p=0.033). Additionally, *P. falciparum* infection during pregnancy has been  
41 found to be associated with preterm births (OR 1.54, 95% CI 1.09-2.18, p=0.016), which is related  
42 with late preterm births (OR 1.59, 95% CI 1.11-2.27, p=0.011).

43 **Conclusions:** Despite the decrease of malaria cases during the evaluated period, we present  
44 evidence of the deleterious effects of gestational malaria in a low transmission area in the  
45 Amazonian region. Regardless of *Plasmodium* species, malaria during pregnancy poses a risk for  
46 newborns birth weight reduction, highlighting the impact that *P. vivax* has on the fetus.

47 **Funding:** São Paulo Research Foundation – FAPESP/Brazil.

## 48 INTRODUCTION

49 Malaria is a severe and potentially fatal parasitic disease that constitutes a major public health issue,  
50 being one of the greatest causes of mortality in tropical regions. Pregnant women are particularly  
51 vulnerable to malaria infection and are estimated that 125 million women are at risk of malaria in  
52 pregnancy each year <sup>1</sup>. Malaria can be devastating for both mother and fetus, leading up to 10,000  
53 maternal and 75,000 to 200,000 child deaths each year <sup>2</sup>. Maternal malaria presents a significant  
54 impact on the neonates, being the primary cause of abortion, stillbirth, premature delivery, fetal  
55 death, low birth weight (LBW) and fetal/child development retardation in malaria-endemic  
56 countries <sup>2</sup>.

57 LBW reflects an intra-uterine growth retardation (IUGR) and preterm delivery, which are  
58 compelling indicators of infant morbidity <sup>2-5</sup>. LBW has been linked to infant mortality and poor  
59 cognitive development, and the occurrence of non-communicable diseases later in life <sup>5,6</sup>. In fact,  
60 LBW in newborns due to malaria is related with up to 100,000 infant deaths each year in endemic  
61 countries <sup>7,8</sup>. These adverse birth outcomes have been extensively associated with *P. falciparum*  
62 infection during pregnancy. In contrast to *P. falciparum*, the *P. vivax* burden in pregnancy is less  
63 well described, and have been described as having less impact in the newborn <sup>2,9</sup>. Though, recent  
64 studies have presented the two species as similar threats to the mother and fetus <sup>10</sup>. Despite the  
65 efforts to reduce malaria the prevalence of these adverse birth outcomes remains high.

66 Therefore, it is crucial to have an efficient epidemiological surveillance of malaria during  
67 pregnancy. The linkage of two or more health public surveillance record databases with shared  
68 variables presents an important and effective strategy to plan preventive measures. Currently, most  
69 of the malaria-endemic countries have malaria public surveillance record databases since it is  
70 compulsory notification disease. This will contribute to the identification of epidemics and areas  
71 most affected. Thus, allowing to direct and intensify the control and preventive measures to the

72 affected communities, and reduce negative birth outcomes <sup>11</sup>. In fact, due to the potential assemble  
73 with other information systems it can be recognized as an important tool for research <sup>12,13,14</sup>.  
74 In 2003, the Brazilian Epidemiological Surveillance Information System (SIVEP)-Malaria was  
75 implemented to systematize the flow and quality of the information on malaria. This system gathers  
76 information on malaria morbidity according to gender, age, *Plasmodium* species, site of residence,  
77 the probable site of infection, treatment, and pregnancy status <sup>15</sup>. Another essential Brazilian  
78 information system of national coverage is the Information System of Live Births (SINASC),  
79 implemented in 1990. This system collects and systematizes information on maternal, pregnancy,  
80 delivery and newborns data <sup>16,17</sup>. Linkage of record databases is still scarcely used in Brazil, despite  
81 being an easy to perform technique with low operational cost. Here we present the first study that  
82 evaluates the association between gestational malaria and adverse birth outcomes in the Brazilian  
83 Amazonian region for nine years (2006-2014), using information obtained through the linkage of  
84 SINASC and SIVEP-Malaria.

## 85 **METHODS**

### 86 **Study design and data collection**

87 This is a population-based observational study developed in the city of Cruzeiro do Sul - Acre  
88 (Brazil), located in the Brazilian Amazonian region (7°37'51''S, 72°40'12''W) (Fig 1). Cruzeiro do  
89 Sul has an estimated population of 82,075 inhabitants and an average of 1,650 births per year <sup>18</sup>.  
90 Together with Porto Velho and Manaus, the three cities are responsible for 21.9% of the malaria  
91 cases notified in Brazil <sup>19</sup>. It is a high transmission risk city, with an annual parasitic incidence of  
92 214 cases per 1,000 inhabitants, with the prevalence of *P. vivax* infection <sup>19</sup>. The universe of the  
93 studied population was composed of all live newborns delivered by women living in the city,  
94 between January 2006 and December 2014. The information regarding the mother, newborn and  
95 delivery was extracted from SINASC, and the information on the malaria episodes and parasite  
96 species was obtained from the SIVEP-Malaria. By knowing that the primary health care is provided  
97 free of cost in Brazil and that the information systems of the Ministry of Health (MoH) offer wide  
98 coverage, we can presume that these datasets are reliable.

99

100 **Figure 1. Map showing the geographic location of Cruzeiro do Sul, Acre State, Brazilian**  
101 **Amazon.** Cruzeiro do Sul has an estimated population of 82,075 inhabitants. The map also  
102 indicates Rio Branco, the capital of Acre state.

103

### 104 **Ethical considerations**

105 According to the Resolution n° 196/96 of the Brazilian National Health Committee, ethical  
106 clearance was provided by the committees for research of the University of São Paulo and the  
107 Federal University of Acre (Plataforma Brasil, CAAE: 03930812.8.0000.5467 and  
108 03930812.8.3001.5010, respectively). The authors have agreed to maintain the confidentiality of the

109 data collected from the medical records and databases, by signing the Term of Commitment for the  
110 Use of Data from Medical Records.

111

### 112 **Exclusion criteria**

113 In this study, the SINASC database was considered the reference. Before performing the record  
114 linkage, curation was performed, and newborns with double entries, lack of information on birth  
115 weight, presenting congenital diseases or twins were excluded. Upon the linkage of SINASC with  
116 SIVEP-Malaria database, newborns with less than 22 weeks (miscarriage) or with no information  
117 on the gestational age at birth were excluded (Fig 2).

118

119 **Figure 2. Flowchart detailing exclusion criteria applied to the evaluation of the enrolled**  
120 **maternal-child pairs.** Mixed infection – *P. vivax*- and *P. falciparum*-infection occurring at the  
121 same time and/or at different times during pregnancy.

122

### 123 **Screening of malaria infection**

124 In Brazil, whenever individual show suspicious malaria symptoms, it is tested by qualified endemic  
125 agents that monitor micro-regions. The gold standard method for malaria diagnosis is the thin and  
126 thick blood smear, which is screened by trained microscopists from the System of Epidemiological  
127 Surveillance of the MoH, and further revised by senior experts, to confirm the results. Infections  
128 were categorized per parasite species: *P. falciparum*, *P. vivax*, or mixed infections. All women who  
129 had malaria during pregnancy were treated with antimalarial drugs under medical prescription,  
130 according to the Brazilian MoH guidelines.

131

### 132 **Definitions and gestational age estimation**

133 LBW was defined as birth weight < 2500 grams (g). WHO child growth standards were used to  
134 classify the small for gestational age newborns, weight  $\leq 10^{\text{th}}$  centile (boys  $\leq 2758$  g, girls  $\leq 2678$ g).  
135 The very preterm birth was defined as birth between  $\geq 28$  and <32 weeks' gestation; late preterm  
136 birth was defined as birth between  $\geq 32$  and <37 weeks' gestation, and total preterm birth was  
137 defined as birth <37 weeks' gestation. The gestational age was established by the woman's last  
138 menstrual period and, when possible, adjusted by ultrasound during antenatal visit care. In SINASC  
139 database, gestational age is categorized as follows: less than 22 weeks' gestation, 22-27 weeks, 28-  
140 31 weeks, 32-36 weeks, 37-41 weeks, and 42 weeks or more.

141

#### 142 **Record linkage strategy**

143 The record linkage was performed by using the RecLink III software through the deterministic  
144 method (manual search). For the data preprocessing, standardization of both databases was  
145 performed by withdrawing accentuations, extra spaces, special characters, and prepositions. After,  
146 databases were unified only by two shared variables that presented the appropriate fulfillment. Each  
147 year of the record linkage corresponds to one year of the SINASC (containing births records)  
148 assembled with two years of the SIVEP-Malaria, to identify all malaria cases presented by women  
149 during pregnancy. The linked database gathered the variables from SINASC (mother age,  
150 gestational age at delivery, parity, number of antenatal visits, birth weight, and type of birth), with  
151 variables from SIVEP-Malaria (infection by *Plasmodium* spp. (yes / no) and parasite species).

152

#### 153 **Statistical analysis**

154 Data were extracted into Microsoft Excel, and Stata 14.2 and GraphPad Prism software were used  
155 for statistical analyses. We used descriptive statistics to assess the distribution of all continuous  
156 (means and standard deviation [SD] or median and interquartile ranges [IQR]), and categorical  
157 (frequencies and percentages) variables. Differences between groups were evaluated using Mann-

158 Whitney U-tests, accordingly. Categorical data and proportions were analyzed using chi-square  
159 tests. Every p values were 2-sided at a significance level of  $<0.05$ . To assess the association  
160 between malaria and birth weight reduction or prematurity, adjusted odds ratios (OR) with 95%  
161 confidence intervals (CI) were estimated using a multivariate logistic regression approach. These  
162 models included infections by malaria (yes / no), maternal age ( $\geq 18$  years old /  $\leq 17$  years old),  
163 gravidity (primigravida / multigravida), and years of formal education ( $\geq 4$  years /  $\leq 3$  years) as  
164 explanatory variables, and birth weight [ $\leq 10^{\text{th}}$  centile] (yes / no) or LBW (yes / no) as response  
165 variables. The first category for each explanatory variable was considered as reference<sup>20</sup>.

166

### 167 **Role of the funding source**

168 The funders of this study played no part in the study design, data collection, data analysis, data  
169 interpretation, or writing of the manuscript. The corresponding author had full access to all the data  
170 in the study and had final responsibility for the decision to submit for publication.



171 **RESULTS**

172 **Study Population and Baseline Characteristics**

173 Between January 2006 and December 2014, 16,444 births occurred in Cruzeiro do Sul (Acre) with a  
174 total of 3,021 malaria cases notified during pregnancy. After applying the exclusion criteria, 14,487  
175 maternal-child pairs remained for further analysis (Fig 2). Table 1 shows maternal characteristics  
176 according to infection status (detailed by year in the S1 Table). To highlight that: circa 35% of  
177 women were primigravida; above 40% had at least 8 years of formal education (despite the high  
178 proportion of no-schooling women); and more than 70% had a minimum of four antenatal visits  
179 (Table 1). Nevertheless, it was possible to observe that there were no major differences between  
180 non-infected and infected mothers. Malaria incidence in the studied population was 8.9%, with *P.*  
181 *vivax* contributing to 63.9% of the cases (Fig 2). Time series of malaria cases in pregnant women  
182 allowed to detect three epidemic peaks along the studied period, one in 2007 with more than 500  
183 cases, and other two in 2010 and 2013 (Fig 3A and S2 Table). Interestingly, the significant  
184 reduction of cases from 2007 to 2008 coincides with the introduction of artemisinin combined  
185 therapy in Brazil <sup>15</sup>. Though, *P. falciparum* infections represented on average more than 30% of  
186 cases reported during pregnancy, in the assessed years (S2 Table).

187

188 **Table 1. Baseline characteristics of mothers at delivery.**

Characteristics	Non-infected (N=13,204)	Malaria <sup>a</sup> (N=1,283)	<i>P. vivax</i> (N=820)	<i>P. falciparum</i> (N=350)	Mixed (N=113)
Maternal age (years), mean (SD) <sup>b</sup>	24.3 ± 6.4	23.3 ± 6.0	23.3 ± 5.9	24.0 ± 6.3	21.9 ± 5.8
Primigravida, no. (%) <sup>c</sup>	4798 (36.3)	439 (34.2)	299 (36.5)	98 (28.0)	42 (37.2)
Male newborns, no. (%)	6860 (52.0)	675 (52.6)	425 (51.8)	189 (54.0)	61 (54.0)
Gestational age, no. (%)					
22-27 weeks	15 (0.1)	3 (0.2)	3 (0.4)	0	0
28-31 weeks	69 (0.5)	12 (0.9)	9 (1.1)	2 (0.6)	1 (0.9)
32-36 weeks	884 (6.7)	97 (7.6)	52 (6.3)	35 (10.0)	10 (8.9)
37 weeks or more	12236 (92.7)	1171 (91.3)	756 (92.2)	313 (89.4)	102 (90.2)
Years of formal education, no. (%) <sup>d,f</sup>					
No formal education	1894 (14.5)	215 (16.9)	117 (14.4)	75 (21.7)	23 (20.5)
1-3 years	1204 (9.2)	120 (9.5)	73 (9.0)	35 (10.1)	12 (10.7)
4-7 years	2866 (22.0)	338 (26.6)	219 (27.0)	90 (26.1)	29 (25.9)
8-11 years	5041 (38.6)	467 (36.8)	308 (37.9)	122 (35.4)	37 (33.0)
12 or more	1990 (15.2)	122 (9.6)	91 (11.2)	21 (6.1)	10 (8.9)
Antenatal care visit, mean (SD) <sup>e,f</sup>					
None	1295 (9.9)	86 (6.7)	39 (4.8)	39 (11.1)	8 (7.1)
1-3 visits	2100 (16.0)	211 (16.5)	130 (16.0)	65 (18.6)	16 (14.3)
4-6 visits	4004 (30.5)	417 (32.7)	281 (34.5)	109 (31.1)	27 (24.1)
7 or more	5676 (43.2)	560 (43.9)	363 (44.6)	136 (38.9)	61 (54.5)

189 N, number of individuals; SD, standard deviation; no., number of events.

190 <sup>a</sup> Malaria group consists of total pregnant women who had an infection (*P. falciparum* and *P. vivax* or both).

191 <sup>b</sup> Maternal age was recorded in 13,202 non-infected pregnant women.

192 <sup>c</sup> Information generated based on the number of live births and deaths, reported by the mother.

193 <sup>d</sup> Years of formal education were recorded in 13,054 non-infected and 1,269 infected pregnant women (812 *P. vivax* and 345 *P. falciparum*).

194 <sup>e</sup> Antenatal visits were recorded in 13,138 non-infected and 1,276 infected pregnant women (814 *P. vivax*).

195 <sup>f</sup> These variables have ignored values.

196

197 **Figure 3. Time-series of gestational malaria cases between 2006-2014.** (A) Number of  
198 gestational malaria cases per species, (B) mean birth weight of newborns from non-infected and  
199 infected women during pregnancy.

200

### 201 **Association of gestational malaria with reduction of the newborns' birth weight**

202 The analysis of the newborns birth weight across the nine years period, allowed to observe a  
203 significant reduction in the mean weight of babies born from women that had malaria during  
204 pregnancy (Fig 3B, Table 2, and S3 Table). Newborns from *P. falciparum*-infected mothers  
205 presented a more prominent difference of approximately 150 g ( $p<0.0001$ ) when compared to  
206 newborns from non-infected women (Table 2). Notably, the comparison of each group by year  
207 evidenced that newborns from *P. vivax*-infected mothers showed higher weight reduction when  
208 compared with non-infected (S3 Table). These differences can be explained by the higher  
209 prevalence of newborns with LBW among *P. vivax*-infected women (term LBW: NI 4.8%, Pv  
210 6.5%,  $p=0.031$ ; all LBW: NI 6.8%, Pv 8.9%,  $p=0.020$ ) (Table 2 and S4 Table). Although this  
211 prevalence occurred throughout the assessed years, it was more evident in 2006 and 2013 (S4  
212 Table).

213

214

**Table 2. Clinical outcomes of newborns at birth.**

Characteristics	Non-infected (N=13,204)	Malaria <sup>a</sup> (N=1,283)	p value <sup>b</sup>	<i>P. vivax</i> (N=820)	p value <sup>b</sup>	<i>P. falciparum</i> (N=350)	p value <sup>b</sup>	Mixed (N=113)	p value <sup>b</sup>
All birth weight (g)			<0.0001		<0.0001		<0.0001		0.0002
Mean (SD)	3200.1 ± 514.7	3090.1 ± 524.2		3118.9 ± 532.4		3049.9 ± 506.7		3005.8 ± 503.9	
Median (IQR)	3215.0 (2900.0-3530.0)	3100.0 (2785.0-3420.0)		3132.5 (2800.0-3447.5)		3030.0 (2780.0-3350.0)		3095.0 (2690.0-3330.0)	
Term birth weight (g) <sup>c</sup>			<0.0001		<0.0001		<0.0001		0.004
Mean (SD)	3236.1 ± 482.2	3139.6 ± 471.6		3159.5 ± 486.0		3106.4 ± 447.9		3094.4 ± 426.9	
Median (IQR)	3240.0 (2940.0-3550.0)	3130.0 (2840.0-3430.0)		3150.0 (2842.5-3452.5)		3060.0 (2850.0-3380.0)		3155.0 (2770.0-3348.0)	
All low birth weight, no. (%)	896 (6.8)	120 (9.4)	0.001	73 (8.9)	0.020	31 (8.9)	0.130	16 (14.2)	0.002
Term low birth weight, no. (%) <sup>c</sup>	581 (4.8)	74 (6.3)	0.017	49 (6.5)	0.031	17 (5.4)	0.575	8 (7.8)	0.144
Prematurity, no. (%)	968 (7.3)	112 (8.7)	0.069	64 (7.8)	0.614	37 (10.6)	0.022	11 (9.7)	0.330
Very preterm birth, no. (%)	69 (7.1)	12 (10.7)	0.058	9 (14.1)	0.032	2 (5.4)	0.901	1 (9.1)	0.596
Late preterm birth, no. (%)	884 (91.3)	97 (86.6)	0.239	52 (81.3)	0.694	35 (94.6)	0.015	10 (90.9)	0.362
Very preterm birth weight (g)			0.868		0.863		0.627		0.638
Mean (SD)	2036.3 ± 722.2	2032.3 ± 625.5		1978.9 ± 692.0		2112.5 ± 576.3		2353.0	
Median (IQR)	1880.0 (1460.0-2575.0)	2045.0 (1532.5-2547.5)		1915.0 (1360.0-2575.0)		2112.5 (1705.0-2520.0)		2353.0	
Late preterm birth weight (g)			0.093		0.838		0.164		0.0009
Mean (SD)	2814.1 ± 621.6	2683.1 ± 677.2		2839.0 ± 645.6		2598.6 ± 703.5		2167.5 ± 444.1	
Median (IQR)	2840.0 (2422.5-3232.5)	2720.0 (2240.0-3100.0)		2797.5 (2397.5-3267.5)		2765.0 (2320.0-3075.0)		2225.0 (1860.0-2500.0)	

215

N, number of individuals; no., number of events; SD, standard deviation; IQR, interquartile range.

216

<sup>a</sup> Malaria group consists of total pregnant women who had an infection (*P. falciparum* and *P. vivax* or both).

217

<sup>b</sup> Statistical tests were applied according to the type of variable (Mann-Whitney or Chi-square).

218

<sup>c</sup> Term indicates all babies born at 37 weeks' gestation or later.

219

220 Further, multivariate logistic regression analysis disclosed the association of malaria with the  
221 likelihood of occurring newborns small for gestational age (SGA) at term (weight  $\leq$  10<sup>th</sup> centile,  
222 boys  $\leq$  2758g and girls  $\leq$  2658g) (Odds ratio [OR] 1.23, 95%, confidence interval [CI] 1.05-1.45,  
223  $p=0.013$ ), which relates to *P. vivax* infection (OR 1.24, 95% CI 1.02-1.52,  $p=0.035$ ) (Fig 4).  
224 Moreover, LBW at term was significantly increased in newborns from malaria-infected mothers,  
225 (OR 1.34, 95% CI 1.04-1.72,  $p=0.024$ ), which was evidenced when mothers were infected by *P.*  
226 *vivax* (OR 1.39, 95% CI 1.03-1.88,  $p=0.033$ ) (Fig 4). Additionally, segregation by gravidity showed  
227 that newborns at term from both primigravida and multigravida presented reduced birth weight  
228 when mothers had malaria during pregnancy, irrespective of species (Fig 5A-B, and S5 Table).  
229 Nevertheless, newborns from primigravida showed a more prominent birth weight reduction upon  
230 infection (Fig 5B, and S5 Table).

231

232 **Figure 4. Forest plot of the Odds Ratio for weight reduction in newborns from women**  
233 **infected during pregnancy compared to babies from non-infected women, according to**  
234 ***Plasmodium* species.** Each model adjusting for maternal age, parity and years of formal education  
235 (less than 4 years); mixed infection (*P. vivax* and *P. falciparum*-infection).  $p$  values were estimated  
236 through logistic regression methods.  $n$ , number of events;  $N$ , total number in each group; CI,  
237 confidence interval; SGA, small for gestational age; LBW, low birth weight.

238

239 **Figure 5. Impact of malaria on birth weight at term according to gravidity.** Tukey boxplots  
240 show the gravidity effect on the weight of newborns from malaria-infected women (A), and on  
241 newborns from women infected according with *Plasmodium* species (B). The bottom and the top of  
242 the box are the first and third quartiles, the line inside the box is the median, and the whiskers  
243 represent the lowest and the highest data within 1.5 IQR of the first and upper quartiles. The line  
244 indicates the cut-off of low birth weight. Differences between each group were examined with

245 Mann-Whitney or Kruskal-Wallis test with a Dunn's post hoc test. (A) P - NI x Infec ( $p < 0.0001$ ); M  
246 - NI x Infec ( $p < 0.0001$ ); NI- P x M ( $p < 0.0001$ ); and Infec - P x M ( $p = 0.0004$ ). (B) P - NI x Pv  
247 ( $p = 0.0001$ ); NI x Pf ( $p = 0.0003$ ); M - NI x Pv ( $p = 0.0009$ ); NI x Pf ( $p < 0.0001$ ); NI x Mix ( $p = 0.003$ );  
248 Pv x Pf ( $p = 0.025$ ); Pv - P x M ( $p = 0.0009$ ). P, primigravida; M, multigravida; NI, non-infected  
249 pregnant women; Infec, infected pregnant women; Pv, *P. vivax*-infection; Pf, *P. falciparum*-  
250 infection; Mix, mixed-infection.

### 251

### 252 ***P. falciparum* infection during pregnancy increases preterm births**

253 The assembly of databases unveiled increased prematurity among babies born from *P. falciparum*-  
254 infected women during pregnancy (Table 2). Prematurity prevalence increased around 3% when  
255 women were infected with *P. falciparum*, and the association was evidenced by multivariate logistic  
256 regression analysis (OR 1.54, 95% CI 1.09-2.18,  $p = 0.016$ ), which corresponded with late preterm  
257 births (OR 1.59, 95% CI 1.11-2.27,  $p = 0.011$ ) (Fig 6). Moreover, *P. vivax* infections were related to  
258 very preterm births in women with malaria during pregnancy (OR 2.09, 95% CI 1.04-4.20,  
259  $p = 0.039$ ) (Fig 6).

260 Together, these results demonstrate that linkage of national record databases is a valuable research  
261 tool, which disclosed adverse neonatal outcomes upon malaria infection during pregnancy in Brazil.

262

263 **Figure 6. Forest plot of the Odds Ratio for prematurity in newborns from women infected**  
264 **during pregnancy compared to babies from non-infected women, according to *Plasmodium***  
265 **species.** Each model adjusting for maternal age, parity and years of formal education (less than 4  
266 years). Mixed infection (*P. vivax* and *P. falciparum*-infection). p values were estimated through  
267 logistic regression methods. n, number of events; N, total number in each group; CI, confidence  
268 interval.

## 269 **DISCUSSION**

270 Malaria during pregnancy is known as an important risk factor for miscarriage, stillbirth, LBW and  
271 maternal anemia<sup>8,21-23</sup>. Nevertheless, little is known about malaria in pregnancy in the Americas  
272 endemic regions, where it predominates *P. vivax* infections. This work is the first to assess the  
273 effect of gestational malaria in Brazil through the linkage of national databases of the Brazilian  
274 Ministry of Health, SINASC and SIVEP-Malaria. Interestingly, despite the decrease in the number  
275 of gestational malaria cases through the studied period (2006-2014), the impact of malaria during  
276 pregnancy is still evident. The reduction of the mean of the weight was maintained throughout the  
277 years and the higher prevalence of preterm births among newborns from women that presented  
278 malaria during pregnancy.

279 The number of studies estimating the real frequency of malaria in pregnant women is still limited,  
280 both in Brazil and in other regions of the Americas, which are considered low transmission areas<sup>2</sup>.  
281 The prevalence (8.9%) of malaria during pregnancy in our study was similar to the findings of a  
282 multi-centric study that enrolled data from the Americas (Guatemala, Colombia, and Brazil)  
283 between 2008-2011, and another study performed in Urubá (Colombia) between 2005-2009<sup>24,25</sup>.  
284 Though, the prevalence is higher in relation to reports from Iquitos (6.6%) (Peru), and from other  
285 Brazilian cities, such as Manaus (6.1%) and Coari (4.3%) in the Amazonas state, and Rio Branco  
286 (1.4%) in Acre state<sup>26-29</sup>. The discrepancies may encompass differential study designs and  
287 endemicity of studied areas.

288 Prematurity is one of the adverse effects commonly observed in malaria during pregnancy<sup>6,30,31</sup>.  
289 Usually, it correlates with infections occurring during the third trimester of pregnancy and  
290 contributes to increasing the number of newborns with LBW, which is more likely to be observed in  
291 low transmission areas<sup>2,32</sup>. In fact, our data show that *P. falciparum* infections during pregnancy are  
292 responsible for a high proportion of preterm births, mainly late preterm births ( $\geq 32$  and  $< 37$  weeks

293 of gestation). However, it was not possible to correlate the time of infection with the gestational  
294 trimester.

295 Newborns reduced weight at birth either classified as LBW or SGA, is an important predictive  
296 marker of neonatal and child survival, and can result from two basic factors: intrauterine growth  
297 restriction and preterm births<sup>33,31</sup>. In gestational malaria, birth weight reduction is the main adverse  
298 outcome observed in studies involving *P. falciparum* infections<sup>2,30,34,35</sup>. In our observations,  
299 malaria infection during pregnancy represents a critical morbidity that impacts newborns' weight.

300 The records show that malaria in pregnant women increases the number of babies born at term with  
301 SGA by 19.3% and LBW by 28.6% (SGA – NI 14.0%, Malaria 16.7%; term LBW – NI 4.9%,  
302 Malaria 6.3%). Strikingly, *P. vivax* infection during pregnancy represents the higher odds for the  
303 occurrence of birth weight reduction (SGA - OR 1.24, 95% CI 1.02-1.52, p=0.035; term LBW - OR  
304 1.39, 95% CI 1.03-1.88, p=0.033). The absence of the association between *P. falciparum* infections  
305 and the occurrence of SGA or LBW newborns can be related with the restricted pool of variant  
306 genes of the Amazonian parasite, which can explain the mild outcomes observed in the Americas,  
307 substantially different from other endemic regions in the world<sup>36</sup>. Nevertheless, our data  
308 corroborate some findings in Southeast Asia from Moore *et al.* that show that *P. vivax* infection is  
309 associated with SGA and *P. falciparum* infection with late preterm, although we could not correlate  
310 with time of infection<sup>34</sup>.

311 The reduction of newborns birth weight is multifactorial, and it can be related to social-economic,  
312 environmental, nutritional, and clinic factors during pregnancy. However, in this study, it was not  
313 possible to assess other risk factors, once these variables were absent in the databases used. Of note,  
314 it is important to highlight that it is impossible to compare this study with other carried out in  
315 Africa. There, *P. falciparum* infections are predominant and, in general, the health systems that  
316 diagnose and treat malaria have several limitations, summed up with the high rate of co-infection  
317 with other diseases, such as HIV and tuberculosis. The Brazilian Amazonian region has a health



318 care system with effective strategies to control, diagnose, and treat malaria, despite being a low  
319 transmission area with predominance of *P. vivax* infections. These characteristics make our findings  
320 even more interesting, as we observed a substantial impact of infection during pregnancy in  
321 newborns.

322 In Brazil, malaria is a mandatory notification disease, and SIVEP-Malaria is essential to plan health  
323 interventions that enable effective control and preventive strategies to eradicate the disease. For  
324 pregnant women, the early diagnosis is essential to prevent adverse outcomes. In 2014, it was  
325 enforced, by Brazilian MoH, a malaria routine screen during antenatal care and at delivery, in  
326 women living in Brazilian Amazonian region states<sup>37</sup>. This initiative brought important benefits for  
327 both mother and fetus, enabling early treatment and preventing gestational adverse outcomes.

328 This work present potential limitations. First, the databases used have only two shared variables  
329 with adequate fulfillment, and this hampered the identification of all women. Therefore, the number  
330 of pregnant women with malaria can be underestimated. Second, the reduction of birth weight has  
331 different etiologies. Although we used important exclusion criteria, it was not possible to identify  
332 through SINASC women presenting other infections, such as TORCHs, as well as, nutritional or  
333 other risk factors.

334 In conclusion, this work allowed us to observe through a time-lapse study, the effect of gestational  
335 malaria on newborns birth weight in a region considered of low transmission and with *P. vivax*  
336 infections predominance. During the evaluated period (2006-2014), malaria infections continue to  
337 be an important risk factor for prematurity and reduction of newborns' birth weight, despite the  
338 decline in the number of cases reported in the region. We have shown that the SINASC and the  
339 SIVEP-Malaria databases linkage allow to estimate the extent of malaria adverse effects, which  
340 permit to improve information and further plan interventions. These findings reinforce the urgent  
341 need for health programs and actions to prevent and protect pregnant women against the  
342 consequences of malaria, especially during the antenatal care.

343

344 **Acknowledgement**

345 We thank Health Surveillance Secretariat of Acre for authorizing the data collection. Also, we thank  
346 the Municipal Health Secretariat of Cruzeiro do Sul, which promptly welcome us and provided us  
347 access to the SINASC database, and to the Brazilian Epidemiological Surveillance/Administration  
348 of Endemics, which authorized the assess to SIVEP-Malaria information.

349

350 **Funding**

351 This work was primarily funded by grants from São Paulo Research Foundation (FAPESP), CRFM  
352 (2009/53889-0 and 2014/09964-5) and SE (2014/20451-0). JGD, AB, and LAG were supported by  
353 FAPESP fellowships (2012/04755-3, 2017/03939-7 and 2015/06106-0, respectively).

354

355 **Contributors**

356 JGD, LAG, and CRFM designed the study and were involved in data acquisition and scientific  
357 input. JGD, RMS, NRMS, AB, SE, LAG, and CRFM contributed to the analysis and interpretation  
358 of data. JGD, LAG, and CRFM wrote the manuscript. CRFM and SE were the main funders of this  
359 work. CRFM had full access to all the data in the study and takes responsibility for the integrity of  
360 the data and the accuracy of the data analysis. All authors reviewed and approved the final version  
361 of this manuscript.

362

363 **Declaration of interests**

364 All authors declare no competing interests.

365

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- 463

464 **SUPPORTING INFORMATION CAPTIONS**

465 **S1 Table. Characteristics of mothers and newborns per year in Cruzeiro do Sul, 2006-2014.**

466 Data from the System Information of Live Births provided by the Cruzeiro do Sul Municipal  
467 Secretariat of Health. <sup>a</sup> Information generated based on the number of live births and deaths  
468 reported by the mother. <sup>b</sup> There are other groups with ignored values.

469 **S2 Table. Trends in malaria infection during pregnancy in Cruzeiro do Sul, 2006-2014.**

470 N, number of malaria cases. Data are N or N (%). Values correspond to the total number of malaria  
471 episodes reported between 2006 and 2014.

472 **S3 Table. Description of the birth weight of newborns from Non-Infected and Infected  
473 pregnant women per year.**

474 N, number of individuals; IQR, interquartile range. <sup>a</sup> Malaria group consists of total pregnant  
475 women who had an infection (*P. falciparum*, *P. vivax*, and Mixed infections). <sup>b</sup> Differences between  
476 Non-Infected and the other groups were evaluated using Mann-Whitney rank sum tests.

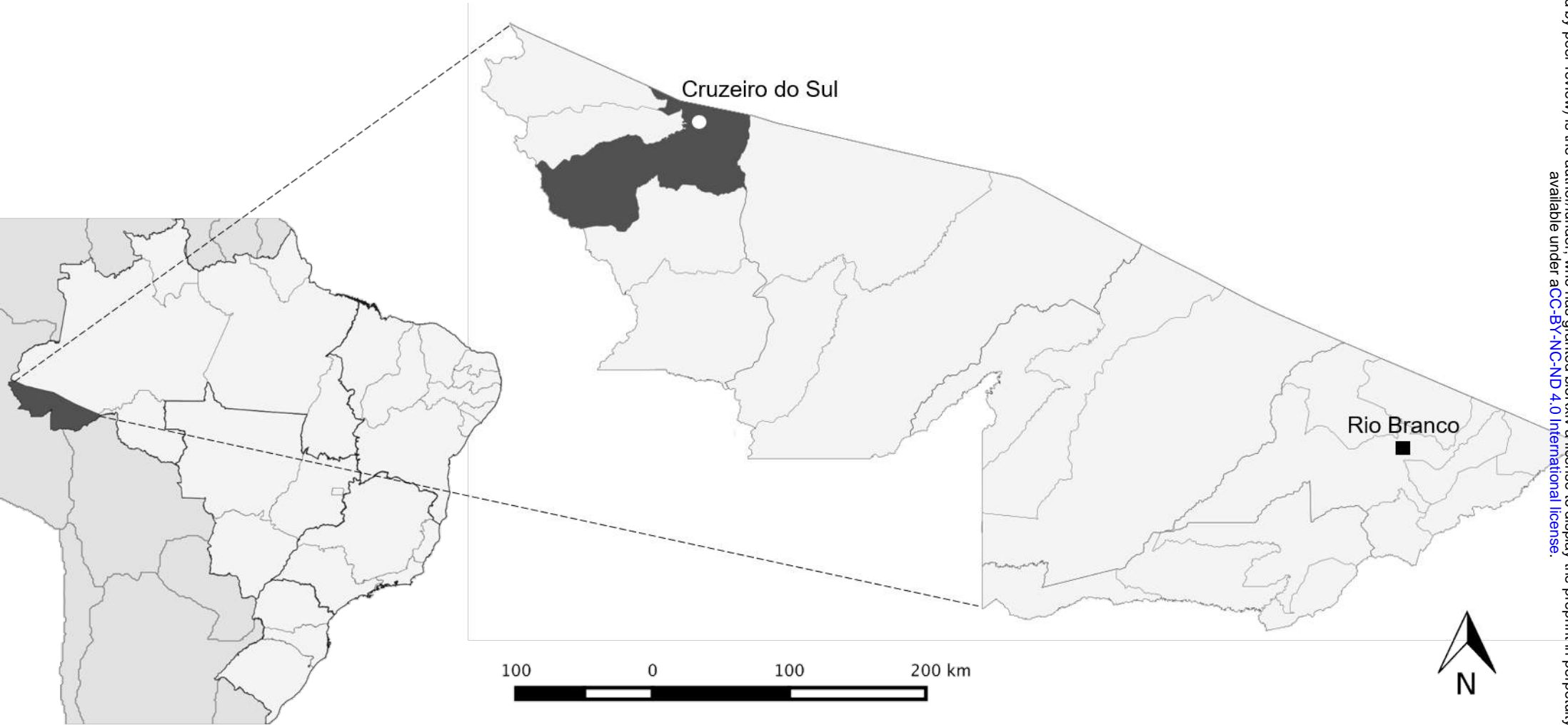
477 **S4 Table. Description of term low birth weight newborns from Non-Infected and Infected  
478 pregnant women per year.**

479 N, number of individuals; no., number of newborns with low birth weight. <sup>a</sup> Malaria group consists  
480 of total pregnant women who had an infection (*P. falciparum*, *P. vivax*, and Mixed infections). <sup>b</sup>  
481 Differences between Non-Infected and Infected groups were evaluated using Chi-square tests.

482 **S5 Table. Description of birth weight of term newborns from Non-Infected and Infected  
483 pregnant women per gravidity.**

484 N, number of individuals; SD, standard deviation; IQR, interquartile range. <sup>a</sup> Malaria group consists  
485 of total pregnant women who had an infection (*P. falciparum*, *P. vivax*, and Mixed infections). <sup>b</sup>  
486 Differences between each group were examined using Mann-Whitney or Kruskal-Wallis test with  
487 Dunn post hoc test. <sup>c</sup> p=0.025 for *P. vivax* versus *P. falciparum* groups.

Figure 1





**Figure 2**

**Linkage Study**

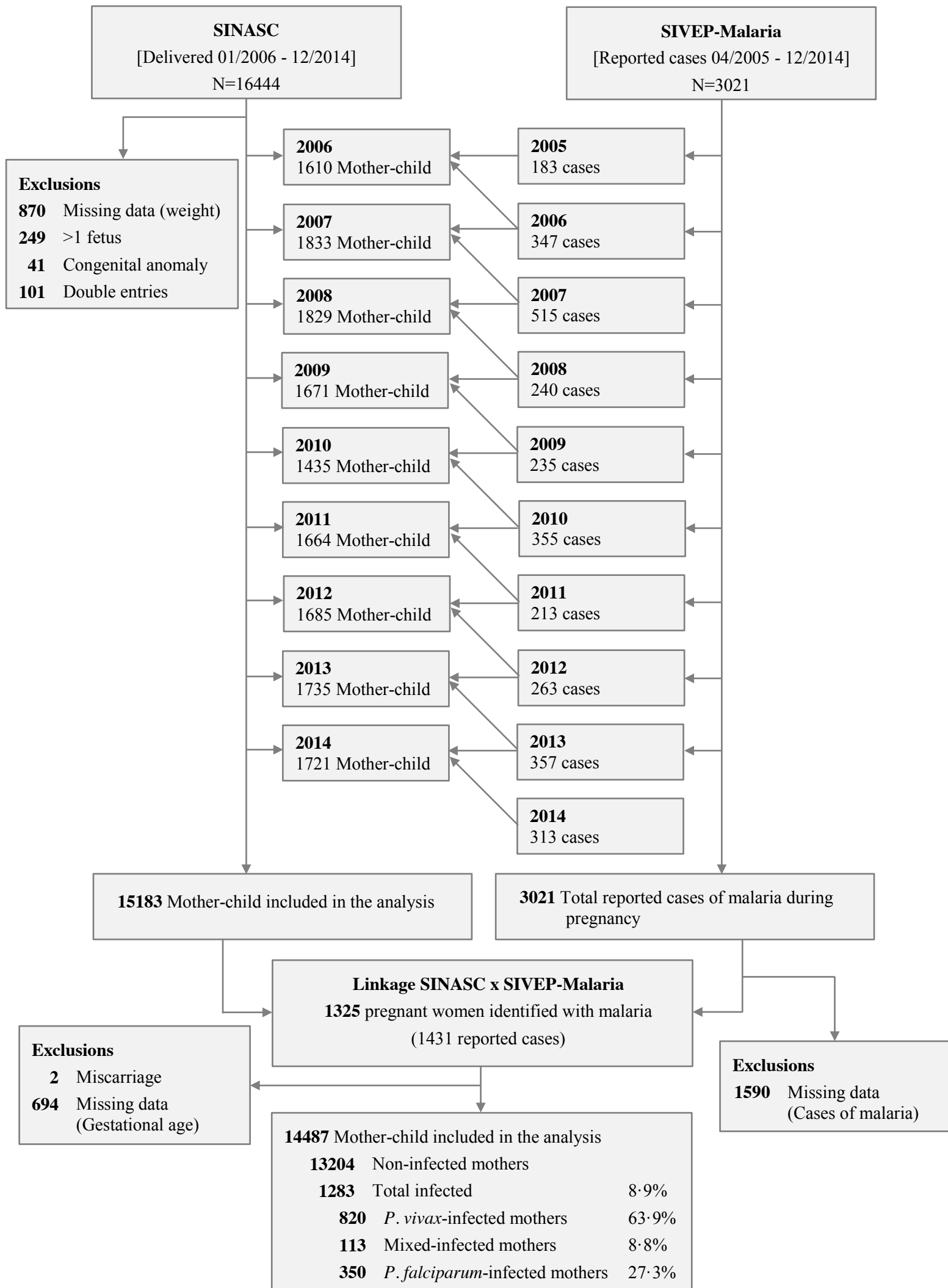
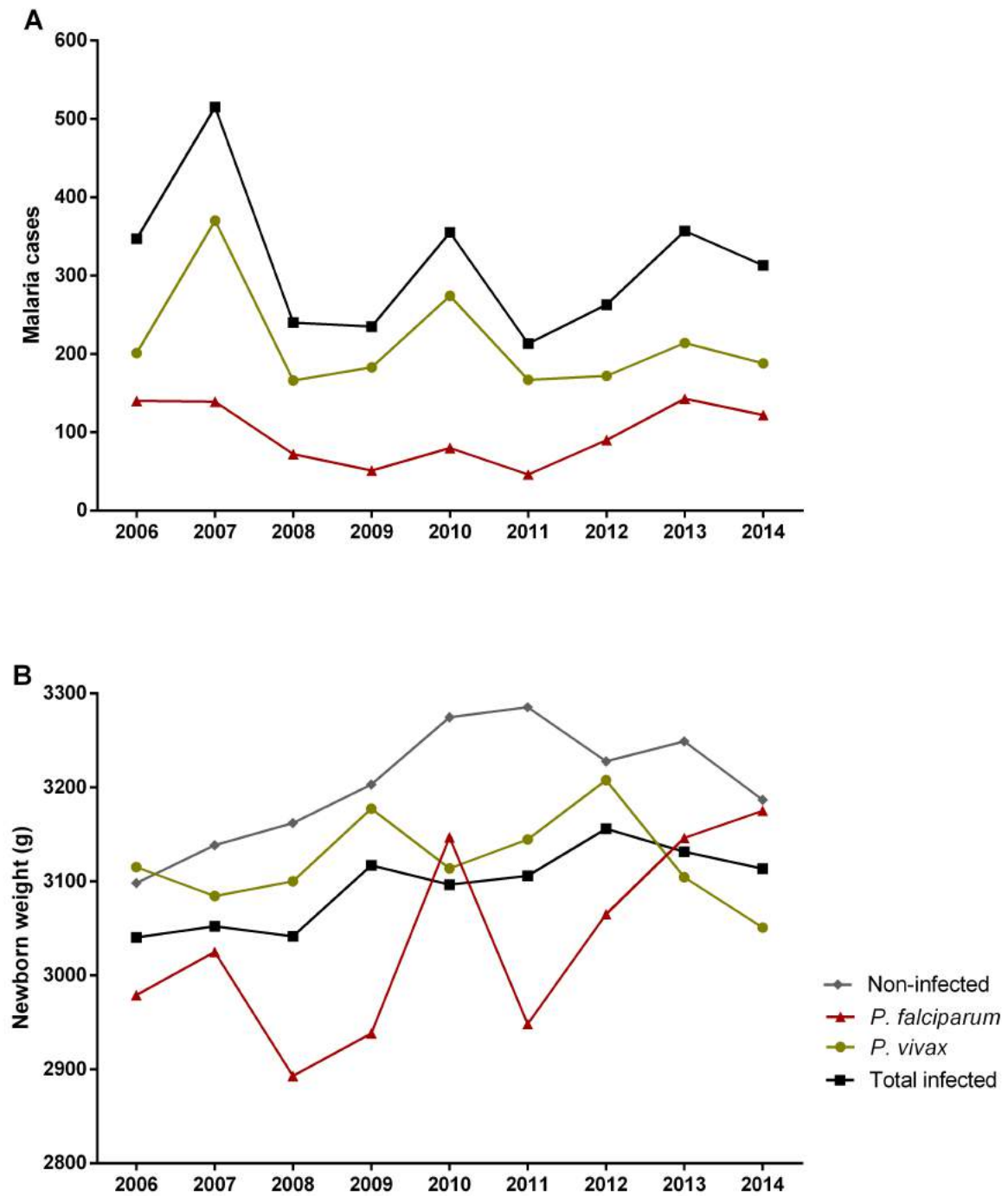




Figure 3



**Figure 4**

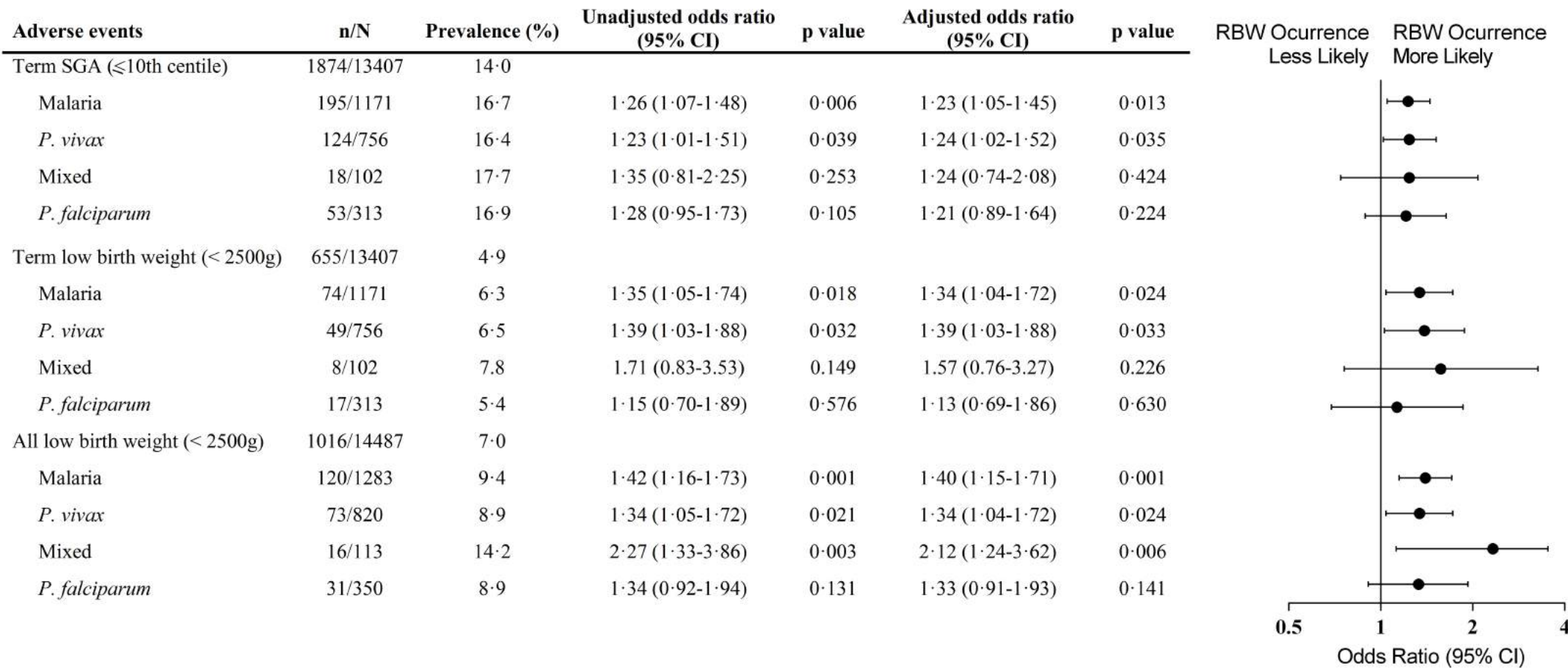


Figure 5

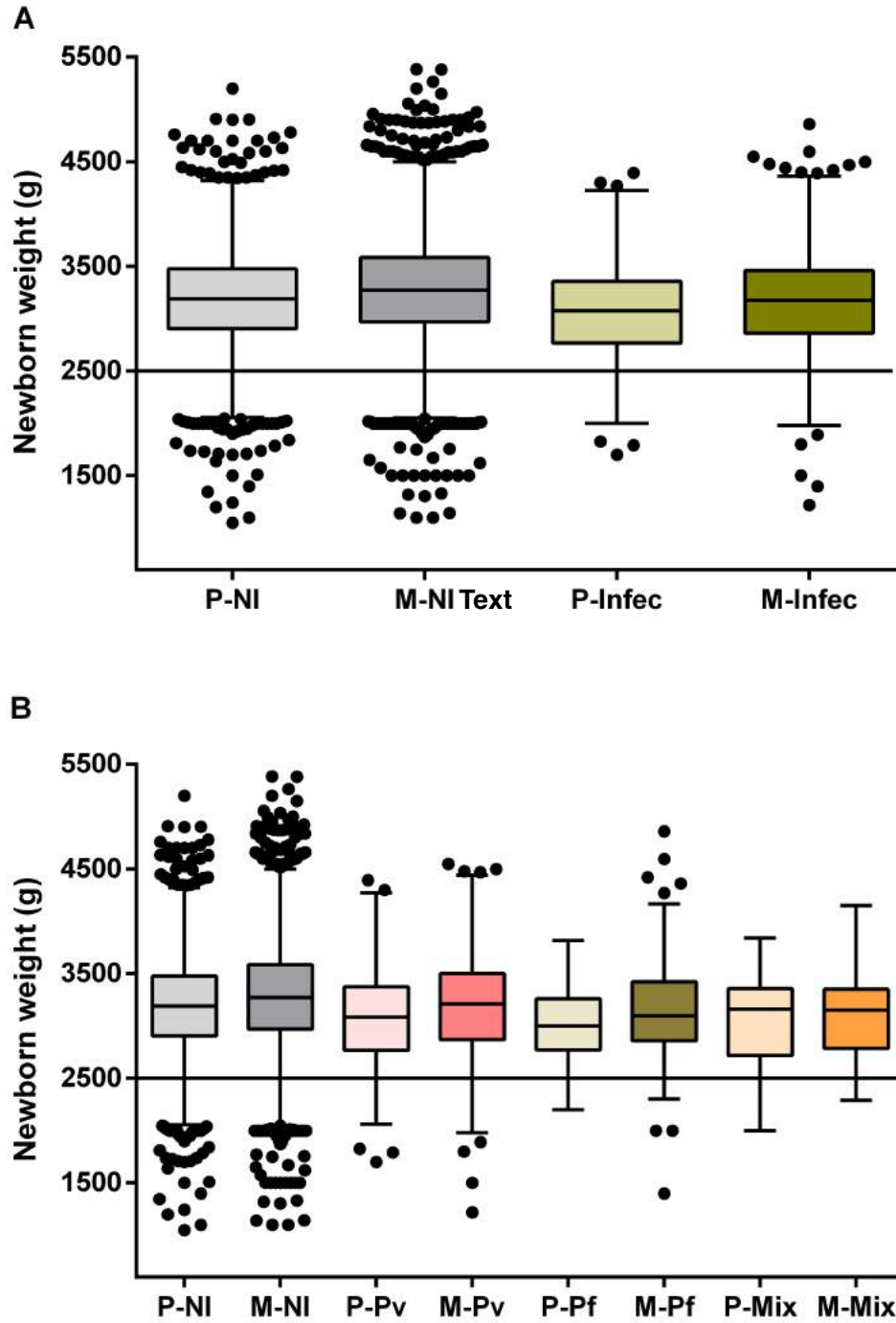
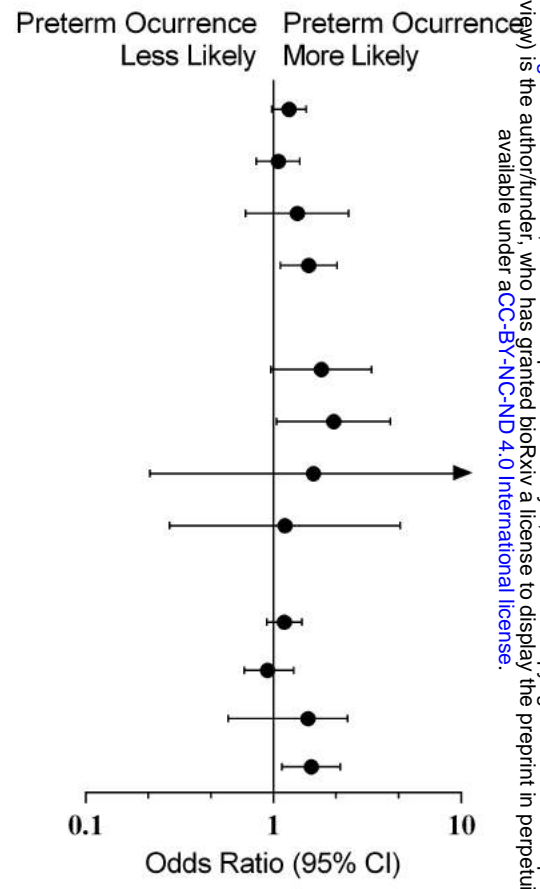


Figure 6

Adverse events	n/N	Prevalence (%)	Unadjusted odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Prematurity	1080/14487	7.5				
Malaria	112/1283	8.7	1.21 (0.99-1.48)	0.069	1.21 (0.98-1.49)	0.071
<i>P. vivax</i>	64/820	7.8	1.07 (0.82-1.39)	0.614	1.06 (0.81-1.38)	0.667
Mixed	11/113	9.7	1.36 (0.73-2.55)	0.332	1.34 (0.71-2.51)	0.363
<i>P. falciparum</i>	37/350	10.6	1.49 (1.06-2.11)	0.023	1.54 (1.09-2.18)	0.016
Very preterm birth	81/14487	0.6				
Malaria	12/1283	0.9	1.78 (0.97-3.33)	0.062	1.80 (0.97-3.34)	0.061
<i>P. vivax</i>	9/820	1.1	2.11 (1.05-4.25)	0.036	2.09 (1.04-4.20)	0.039
Mixed	1/113	0.9	1.70 (0.23-12.35)	0.600	1.63 (0.22-11.88)	0.631
<i>P. falciparum</i>	2/350	0.6	1.09 (0.27-4.48)	0.901	1.15 (0.28-4.73)	0.844
Late preterm birth	981/14487	6.8				
Malaria	97/1283	7.6	1.14 (0.92-1.42)	0.239	1.14 (0.92-1.42)	0.246
<i>P. vivax</i>	52/820	6.3	0.94 (0.71-1.26)	0.694	0.93 (0.70-1.28)	0.645
Mixed	10/113	8.9	1.35 (0.70-2.60)	0.364	1.33 (0.69-2.57)	0.391
<i>P. falciparum</i>	35/350	10.0	1.55 (1.09-2.21)	0.016	1.59 (1.11-2.27)	0.011



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**S1 Table. Characteristics of mothers and newborns per year in Cruzeiro do Sul, 2006-2014.**

Characteristics	2006 (N=1594)	2007 (N=1795)	2008 (N=1748)	2009 (N=1625)	2010 (N=1382)	2011 (N=1510)	2012 (N=1553)	2013 (N=1620)	2014 (N=1660)
<b>Age, years, mean (SD)</b>	23.6 (6.1)	23.7 (6.1)	24.4 (6.3)	24.5 (6.3)	24.3 (6.3)	24.3 (6.5)	24.1 (6.4)	24.3 (6.4)	24.4 (6.6)
<b>Primigravida, no. (%)<sup>a</sup></b>	551 (34.6)	481 (26.8)	534 (30.6)	530 (32.6)	520 (37.6)	644 (42.7)	632 (40.7)	659 (40.7)	688 (41.5)
<b>Gestational age, no. (%)</b>									
22-27 weeks	1 (0.1)	5 (0.3)	3 (0.2)	-	-	5 (0.3)	-	1 (0.1)	3 (0.2)
28-31 weeks	5 (0.3)	2 (0.1)	7 (0.4)	2 (0.1)	11 (0.8)	22 (1.5)	16 (1.0)	9 (0.5)	7 (0.4)
32-36 weeks	27 (1.7)	34 (1.9)	55 (3.1)	68 (4.2)	64 (4.6)	157 (10.4)	199 (12.8)	164 (10.1)	213 (12.8)
37 weeks or more	1561 (97.9)	1754 (97.7)	1683 (96.3)	1555 (95.7)	1307 (94.6)	1326 (87.8)	1338 (86.2)	1446 (89.3)	1437 (86.6)
<b>Marital status, no. (%)<sup>b</sup></b>									
Single	1408 (89.1)	1503 (84.3)	1390 (81.0)	1329 (83.3)	1021 (75.3)	516 (34.8)	414 (26.8)	378 (23.6)	369 (22.3)
Married or cohabiting	163 (10.3)	257 (14.4)	310 (18.1)	252 (15.8)	327 (24.1)	960 (64.6)	1120 (72.6)	1199 (74.9)	1272 (76.8)
<b>Years of formal education, no. (%)<sup>b</sup></b>									
No education	616 (38.8)	622 (34.9)	248 (14.4)	202 (12.7)	130 (9.5)	86 (5.8)	66 (4.3)	77 (4.8)	62 (3.8)
1-3 years	120 (7.6)	135 (7.6)	282 (16.4)	239 (15.0)	170 (12.5)	168 (11.2)	92 (6.0)	63 (3.9)	55 (3.4)
4-7 years	226 (14.2)	264 (14.8)	487 (28.3)	469 (29.4)	383 (28.1)	390 (26.1)	371 (24.0)	317 (19.8)	297 (18.1)
8-11 years	402 (25.3)	295 (16.6)	483 (28.1)	477 (29.9)	461 (33.9)	675 (45.2)	815 (52.7)	914 (57.1)	986 (60.2)
12 or more	222 (14.0)	461 (25.9)	219 (12.7)	206 (12.9)	217 (15.9)	170 (11.4)	196 (12.7)	206 (12.9)	215 (13.1)
<b>Antenatal visits, no. (%)<sup>b</sup></b>									
None	245 (15.6)	233 (13.1)	295 (16.9)	241 (15.0)	118 (8.6)	101 (6.7)	57 (3.7)	57 (3.5)	34 (2.0)
1-3 visits	147 (9.4)	132 (7.4)	332 (19.1)	399 (24.8)	366 (26.7)	285 (18.9)	235 (15.1)	213 (13.2)	202 (12.2)
4-6 visits	216 (13.7)	191 (10.8)	583 (33.5)	568 (35.4)	552 (40.2)	621 (41.1)	591 (38.1)	556 (34.3)	543 (32.7)
7 or more	960 (61.1)	1213 (68.3)	523 (30.0)	380 (23.7)	314 (22.9)	502 (33.3)	669 (43.1)	794 (49.0)	881 (53.1)
<b>Caesarean section, no. (%)</b>	317 (19.9)	418 (23.3)	469 (26.9)	509 (31.3)	543 (39.3)	525 (34.8)	623 (40.1)	744 (45.9)	752 (45.3)
<b>Birth weight (g), mean (SD)</b>									
Mean (SD)	3093.3 (523.6)	3128.3 (529.0)	3150.8 (506.7)	3197.3 (509.6)	3256.2 (524.0)	3271.7 (503.7)	3222.7 (515.0)	3237.5 (486.2)	3180.8 (521.9)
Median (IQR)	3100.0 (2700.0-3450.0)	3450.0 (2770.0-3480.0)	3170.0 (2850.0-3500.0)	3220.0 (2900.0-3515.0)	3270.0 (2950.0-3590.0)	3275.0 (2990.0-3585.0)	3225.0 (2930.0-3560.0)	3235.0 (2955.0-3537.5)	3210.0 (2907.5-3500.0)
<b>Low birth weight, no. (%)</b>	123 (7.7)	134 (7.5)	126 (7.2)	111 (6.8)	96 (7.0)	80 (5.3)	114 (7.3)	95 (5.9)	137 (8.3)
<b>Very low birth weight, no. (%)</b>	6 (0.4)	11 (0.6)	10 (0.6)	4 (0.3)	4 (0.3)	5 (0.3)	7 (0.5)	7 (0.4)	17 (1.0)

Data from the System Information of Live Births provided by the Cruzeiro do Sul Municipal Secretariat of Health.

<sup>a</sup> Information generated based on the number of live births and deaths reported by the mother.

<sup>b</sup> There are other groups with ignored values.

**S2 Table. Trends in malaria infection during pregnancy in Cruzeiro do Sul, 2006-2014.**

Cases of malaria	2006	2007	2008	2009	2010	2011	2012	2013	2014
Overall	347	515	240	235	355	213	263	357	313
<i>P. falciparum</i>	140 (40.4%)	139 (27.0%)	72 (30.0%)	51 (21.7%)	80 (22.5%)	46 (21.6%)	90 (34.2%)	143 (40.1%)	122 (39.0%)
<i>P. vivax</i>	201 (57.9%)	370 (71.8%)	166 (69.2%)	183 (77.9%)	274 (77.2%)	167 (78.4%)	172 (65.4%)	214 (59.9%)	188 (60.0%)
Mixed	6 (1.7%)	6 (1.2%)	2 (0.8%)	1 (0.4%)	1 (0.3%)	0	1 (0.4%)	0	3 (1.0%)

N, number of malaria cases. Data are N or N (%). Values correspond to the total number of malaria episodes reported between 2006 and 2014.

**S3 Table. Description of the birth weight of newborns from Non-Infected and Infected pregnant women per year.**

Year	Non-infected		Malaria <sup>a</sup>		p value <sup>b</sup>	<i>P. vivax</i>		p value <sup>b</sup>	<i>P. falciparum</i>		p value <sup>b</sup>	Mixed		p value <sup>b</sup>
	N	Median (IQR)	N	Median (IQR)		N	Median (IQR)		N	Median (IQR)		N	Median (IQR)	
2006	1459	3100.0 (2700.0-3450.0)	135	3030.0 (2660.0-3370.0)	0.174	72	3135.0 (2770.0-3455.0)	0.071	51	3005.0 (2615.0-3300.0)	0.623	12	2827.5 (2612.5-3350.0)	0.259
2007	1581	3170.0 (2795.0-3500.0)	214	3077.5 (2690.0-3400.0)	0.047	147	3100.0 (2720.0-3445.0)	0.245	38	3017.5 (2640.0-3300.0)	0.816	29	3060.0 (2500.0-3340.0)	0.087
2008	1586	3190.0 (2860.0-3500.0)	162	3000.0 (2730.0-3390.0)	0.270	99	3100.0 (2770.0-3405.0)	0.521	45	2990.0 (2600.0-3165.0)	0.482	18	3055.0 (2770.0-3300.0)	0.338
2009	1517	3230.0 (2910.0-3530.0)	108	3117.5 (2850.0-3417.5)	0.559	83	3210.0 (2880.0-3460.0)	0.826	22	2900.0 (2750.0-3000.0)	0.664	3	2660.0 (2415.0-3200.0)	0.102
2010	1239	3300.0 (2970.0-3610.0)	143	3090.0 (2785.0-3385.0)	0.108	110	3095.0(2790.0-3430.0)	0.033	24	3185.0 (2995.0-3342.5)	0.362	9	2630.0 (2420.0-2920.0)	0.002
2011	1394	3287.5 (3010.0-3600.0)	116	3122.5 (2780.0-3420.0)	0.009	93	3150.0 (2800.0-3425.0)	0.008	18	2972.5 (2670.0-3245.0)	0.472	5	2880.0 (2760.0-3265.0)	0.133
2012	1442	3232.5 (2930.0-3560.0)	111	3100.0 (2845.0-3475.0)	0.107	73	3200.0 (2870.0-3480.0)	0.629	30	3030.0 (2745.0-3340.0)	0.463	8	3075.0 (2865.0-3190.0)	0.198
2013	1461	3245.0 (2975.0-3540.0)	159	3145.0 (2860.0-3520.0)	0.091	71	3210.0 (2810.0-3575.0)	0.181	74	3127.5 (2890.0-3475.0)	0.429	14	3270.0 (2920.0-3485.0)	0.772
2014	1525	3215.0 (2915.0-3510.0)	135	3160.0 (2855.0-3400.0)	0.087	72	3062.5 (2805.0-3395.0)	0.067	48	3205.0 (2957.5-3410.0)	0.932	48	3300.0 (3140.0-3470.0)	0.715

N, number of individuals; IQR, interquartile range.

<sup>a</sup> Malaria group consists of total pregnant women who had an infection (*P. falciparum*, *P. vivax*, and Mixed infections).

<sup>b</sup> Differences between Non-Infected and the other groups were evaluated using Mann-Whitney rank sum tests.

**S4 Table. Description of term low birth weight newborns from Non-Infected and Infected pregnant women per year.**

Year	Non-infected		Malaria <sup>a</sup>		p value <sup>b</sup>	<i>P. vivax</i>		p value <sup>b</sup>	<i>P. falciparum</i>		p value <sup>b</sup>	Mixed		p value <sup>b</sup>
	N	no. (%)	N	no. (%)		N	no. (%)		N	no. (%)		N	no. (%)	
2006	1429	82 (5.7)	132	13 (9.9)	0.059	72	9 (12.5)	0.019	49	3 (6.1)	0.910	11	1 (9.1)	0.635
2007	1551	91 (5.9)	203	16 (7.9)	0.259	141	10 (7.1)	0.557	37	3 (8.1)	0.568	25	3 (12.0)	0.199
2008	1528	81 (5.3)	155	10 (6.5)	0.546	97	6 (6.2)	0.707	40	4 (10.0)	0.195	18	0	0.316
2009	1449	80 (5.5)	106	4 (3.8)	0.442	82	2 (2.4)	0.228	22	1 (4.6)	0.842	2	1 (50.0)	0.006
2010	1175	57 (4.9)	132	7 (5.3)	0.820	105	5 (4.8)	0.967	19	0	0.325	8	2 (25.0)	0.009
2011	1229	32 (2.6)	97	5 (5.2)	0.142	77	3 (3.9)	0.496	15	1 (6.7)	0.330	5	1 (20.0)	0.016
2012	1247	53 (4.3)	91	5 (5.5)	0.574	63	5 (7.9)	0.165	22	0	0.323	6	0	0.606
2013	1306	38 (2.9)	140	9 (6.4)	0.026	60	4 (6.7)	0.099	67	5 (7.5)	0.037	13	0	0.533
2014	1322	67 (5.1)	115	5 (4.4)	0.734	59	5 (8.5)	0.249	42	0	0.135	14	0	0.387

N, number of individuals; no., number of newborns with low birth weight.

<sup>a</sup> Malaria group consists of total pregnant women who had an infection (*P. falciparum*, *P. vivax*, and Mixed infections).

<sup>b</sup> Differences between Non-Infected and Infected groups were evaluated using Chi-square tests.



**S5 Table. Description of birth weight of term newborns from Non-Infected and Infected pregnant women per gravidity.**

Birth weight (g)	Non-infected (N=12,236)	Malaria <sup>a</sup> (N=1,171)	p value <sup>b</sup>	<i>P. vivax</i> (N=756)	p value <sup>b</sup>	<i>P. falciparum</i> (N=313)	p value <sup>b</sup>	Mixed (N=102)	p value <sup>b</sup>
Primigravida									
Mean (SD)	3184.1 (454.8)	3072.1 (453.1)	<0.0001	3088.0 (478.0) <sup>c</sup>	0.0001	3021.6 (370.9)	0.0003	3070.1 (436.6)	0.104
Median (IQR)	3186.5 (2905.0-3475.0)	3075.0 (2769.0-3355.0)		3085.0 (2770.0-3370.0)		3000.0 (2769.0-3260.0)		3160.0 (2720.0-3348.0)	
Multigravida									
Mean (SD)	3265.1 (494.5)	3173.2 (477.2)	<0.0001	3199.0 (486.4) <sup>c</sup>	0.0009	3137.0 (469.5)	<0.0001	3108.2 (424.1)	0.003
Median (IQR)	3270.0 (2970.0-3585.0)	3175.0 (2860.0-3460.0)		3210.0 (2870.0-3500.0)		3095.0 (2860.0-3420.0)		3150.0 (2800.0-3340.0)	
p value (Primigravida x Multigravida)	<0.0001	0.0004		0.0009		0.083		0.862	

N, number of individuals; SD, standard deviation; IQR, interquartile range.

<sup>a</sup> Malaria group consists of total pregnant women who had an infection (*P. falciparum*, *P. vivax*, and Mixed infections).

<sup>b</sup> Differences between each group were examined using Mann-Whitney or Kruskal-Wallis test with Dunn post hoc test.

<sup>c</sup> p=0.025 for *P. vivax* versus *P. falciparum* groups.