

Associations Between Malaria in Pregnancy and Neonatal Neurological Outcomes

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19 Highlights

- 20 1. Prospective study of *in utero* malaria exposure and neonatal neurological function.
- 21 2. *In utero* malaria exposure may increase risk of suboptimal reflex in term neonates.
- 22 3. Impact of *in utero* malaria exposure on child neurodevelopment must be established.

23

24 Abstract

25 **Objective:** To compare neurological functioning of neonates born to mothers with and without malaria
26 in pregnancy.

Methods: Pregnant women presenting at Korle Bu Teaching Hospital, Ghana were recruited into this prospective observational study. Malaria exposure was determined by clinically-documented antenatal malaria infection; parasitemia in maternal, placental, or umbilical cord blood; or placental histology. Neurological functioning was assessed using the Hammersmith Neonatal Neurological Examination within 48 hours of birth. Performance was classified as “optimal” or “suboptimal” by subdomain and overall.

Results: Between 21st November 2018 and 10th February 2019, 211 term-born neonates, of whom 27 (13%) were exposed to malaria, were included. In the reflexes subdomain, exposed neonates tended to score lower (adjusted mean difference: -0.34, 95% CI: -0.70–0.03) with increased risk (adjusted risk ratio: 1.63, 95% CI: 1.09–2.44) of suboptimal performance compared to unexposed neonates. There were no significant between-group differences in scores or optimality classification for the remaining subdomains and overall.

Conclusion: Malaria-exposed neonates had similar neurological functioning relative to unexposed neonates, with differences confined to the reflexes subdomain, suggesting potential underlying neurological immaturity or injury. Further studies are needed to confirm these findings and determine the significance of malaria in pregnancy on long-term neurological outcomes.

Keywords

Brain; Infant; Malaria; Neurodevelopment; Sub-Saharan Africa

Abbreviations: HNNE: Hammersmith Neonatal Neurological Examination; IPTp-SP: Intermittent preventative treatment in pregnancy using sulfadoxine-pyrimethamine

Associations Between Malaria in Pregnancy and Neonatal Neurological Outcomes

49 During pregnancy, naturally acquired immunity to malaria is compromised and pregnant women in
50 endemic regions are at higher risk of malaria infection than their nonpregnant peers (Doolan et al.,
51 2009). It is well-established that malaria in pregnancy is associated with adverse pregnancy outcomes
52 (including miscarriage and stillbirth) (Saito et al., 2020) and maternal and fetal/neonatal complications
53 including malarial anemia, fetal growth restriction, preterm birth, and low birthweight (Rogerson, 2017).
54 Approximately 11 million pregnant women in sub-Saharan Africa were infected with malaria in 2018
55 resulting in 16% of all low birthweight deliveries in the region (World Health Organization, 2019). While
56 the adverse neurodevelopmental outcomes of children who have suffered from cerebral malaria during
57 childhood have been extensively investigated (Carter et al., 2004, Idro et al., 2010), relatively little is
58 known regarding the impact of malaria in pregnancy on neonatal neurological outcomes. Published
59 reviews have theorized that malaria exposure can impair fetal neurological development and
60 subsequent neurodevelopment (Lawford et al., 2019, McDonald et al., 2013); a number of
61 socioenvironmental and biological pathways are hypothesized to be involved, which we recently
62 summarized in a conceptual framework (Lawford et al., 2019).

63 Human and animal studies suggest some neurological impact of malaria exposure in pregnancy.
64 Cerebral blood flow redistribution (Arbeille et al., 1998) and faster development in the cingulate gyrus
65 (Rijken et al., 2012) have been documented in fetuses in response to maternal malaria infection, while
66 neurocognitive deficits are evident in the offspring of malaria-infected mice relative to uninfected mice
67 (McDonald et al., 2015). However, only one study to date has reported the neurodevelopmental impact
68 of malaria-exposure among infants. This case-report investigated neurodevelopmental outcomes at 12
69 and 24 months postpartum in dizygotic twins whose placentas were discordant for parasitemia; the
70 placental malaria-exposed twin demonstrated consistently lower motor, cognitive, and language scores
71 relative to the unexposed twin at both time points (Conroy et al., 2019). However, there was marked
72 discordance in fetal growth with the malaria-exposed twin exhibiting lower birthweight (1,320 g vs.

1,920 g) and head circumference (27 cm vs. 32 cm). As neurodevelopmental disadvantage has previously been reported in the smaller twin of discordant twin pairs regardless of malaria status (Halling et al., 2016), it is unclear whether the neurodevelopmental outcomes reported occurred as a component of the pathophysiology of malaria or was an independent confounder.

To date, no studies have reported neurological functioning of neonates exposed to malaria *in utero*. We conducted a prospective observational study to compare the neurological functioning of neonates ≤ 48 hours of age born to mothers with and without malaria in pregnancy. We hypothesized that exposure to malaria in pregnancy adversely affects neonatal neurological functioning.

Methods

Sample

The Impact of Malaria in Pregnancy on Infant Neurodevelopment (IMPRINT) study was a prospective observational study conducted at Korle Bu Teaching Hospital in Accra, Ghana. This is the largest tertiary teaching hospital in Ghana and the leading regional referral center, with additional referrals from primary and secondary health facilities in the southern region. It has a catchment population of >3 million in an area of 50 km radius (Adu-Bonsaffoh et al., 2017) and approximately 10,000 live births annually.

Six physicians were recruited and trained to perform study assessments. Pregnant women presenting in the early stages of labor were approached for written informed consent. If granted and a member of the study team was available, neonates that met eligibility criteria were enrolled. Women were not approached if they were <15 years of age, HIV-positive, or had sickle cell disease. A nested sample of singleton neonates was selected for this study by further excluding those who were 1) born preterm or post-term ($<37+0$ or $>42+6$, weeks + days gestation), 2) had an Apgar score <7 at 5 minutes, 3) any

recorded admission to the Neonatal Intensive Care Unit, and 4) any recorded diagnosis of congenital anomalies. Ethical approval was obtained from institutional review boards of the University of Ghana and The University of Queensland, Australia.

Malaria Diagnosis

Malaria infection during pregnancy was the primary exposure measured as a binary variable. At Korle Bu Teaching Hospital, pregnant women are routinely tested for malaria at their antenatal visits. If tested positive, women were treated as per the national malaria treatment guidelines for pregnant women. A neonate was classified to be in the “exposed” group if they met one or more of the following conditions: 1) medical records of antenatal malaria infection confirmed by Rapid Diagnostic Test (RDT) or microscopy; 2) positive maternal, placental, or umbilical cord blood samples tested by RDT and/or microscopy; or 3) placental histology. Supplementary File–Appendix 1 further describes how malaria was diagnosed in the “exposed” group.

Neurological Evaluation

The primary outcome was performance on the Hammersmith Neonatal Neurological Examination (HNNE). The HNNE can identify neonates at risk of neurological dysfunction and later neurodevelopmental impairment (Dubowitz et al., 1984, Molteno et al., 1995, Molteno et al., 1999, Setanen et al., 2016, Tuhkanen et al., 2019), and exhibits good sensitivity (88%) to identify significant neuropathology detected by magnetic resonance imaging (Woodward et al., 2004). The HNNE has a total of 34 items stratified into six subdomains: tone, tone patterns, reflexes, movements, abnormal signs/patterns, and orientation and behavior. A scoring system was developed in 1998 based on reference values from a low-risk, term-born sample of 224 British neonates (Dubowitz et al., 1998). This scoring system allows the classification of neonates’ performance as “optimal” or “suboptimal” by each subdomain and overall. A score >10th centile of reference values is considered optimal. The HNNE

administration and scoring have been described in detail in the original publication (Dubowitz et al., 1998).

The HNNE was administered to all neonates in the IMPRINT study (irrespective of inclusion in this nested sample) ≤ 48 hours after birth by trained physicians in the postnatal ward using the standardized assessment proforma (Dubowitz et al., 1998). Details regarding physician training for this study have been described in previous publication (Lawford Harriet LS et al., 2020, Lawford H. L. S. et al., 2020). Examiners were not routinely blinded to gestational age at birth but were blinded to malaria status.

Sociodemographic, Clinical, and Placental Characteristics

Sociodemographic information was collected using a standardized questionnaire administered when participants were not in active labor and following birth. Maternal and neonatal clinical data were extracted from medical records, and the placenta was characterized by examination. Further details are described in Supplementary File–Appendix 1.

Statistical Analysis

Differences in sociodemographic, clinical, and placental characteristics between included and excluded neonates, and malaria-exposed and unexposed neonates were described as mean \pm standard deviation (SD), median [interquartile range], or n (%), and were tested using Student's *t*-test or Mann-Whitney U test for continuous data and χ^2 or Fisher's exact tests for categorical data. The association between malaria exposure and mean raw scores for the six HNNE subdomains and overall were assessed using linear regression and standardized effect sizes were reported as Cohen's *d* values. The association between malaria exposure and the proportion of neonates classified as suboptimal for the HNNE subdomains and overall was assessed using a Poisson regression with robust error variance. Multivariable models were adjusted for covariates determined by our previously published conceptual framework (Lawford et al., 2019), summarized in a qualitative causal model designed using

141 www.dagitty.net (Supplementary File–Appendix 2). The selected covariates are shown in red
 142 (socioeconomic status, education, maternal age, and social risk). There was no adjustment for covariates
 143 on the causal pathway (shown in green). Measures of association were expressed as unadjusted and
 144 adjusted mean differences and risk ratios. Statistical analysis was conducted using Stata 16.0 (Stata
 145 Corp, College Station, TX) and a significance level of .05 was used throughout inferential analysis.

146 **Results**

147 Figure 1 displays the sample recruitment. Between 21st November 2018 and 10th February 2019, a total
 148 of 302 mothers and 310 (8 twin births) neonates were recruited. In total, 36/310 neonates met study
 149 criteria for exposure to malaria in pregnancy. The HNNE was administered to 296/310 neonates (34/36
 150 exposed to malaria and 262 unexposed) within 48 hours of birth. Of the 14 neonates that were not
 151 administered the HNNE, eight were lost to follow-up, five were too unwell, and there was one neonatal
 152 death.

153 After exclusion of 7 exposed and 78 unexposed neonates that did not meet the criteria for this nested
 154 sample, the study sample comprised 211 eligible neonates of whom 27 (13%) were exposed to malaria.
 155 Demographic and clinical characteristics of included mother-neonate dyads (n=211) and dyads that
 156 either did not have the HNNE administered (n=14) or did not meet the inclusion criteria (n=85) are
 157 compared in Supplementary File–Appendix 3 and Appendix 4, respectively.

158 **Characteristics of Mother-Neonate Dyads**

159 Table 1 displays sociodemographic, clinical, and placental characteristics of the 211 included mother-
 160 neonate dyads by malaria exposure. Compared with mothers of unexposed neonates, significantly more
 161 mothers of exposed neonates had no other children (p=.003) and lived in overcrowded dwellings with
 162 >1 person per room (p=.03). Mothers of exposed neonates had a smaller average middle-upper arm

163 circumference compared with mothers of unexposed neonates ($p=.03$). Significant differences were
 164 evident in the timing of first intermittent preventative treatment in pregnancy using sulfadoxine-
 165 pyrimethamine (IPTp-SP); while the majority of mothers of exposed and unexposed neonates took their
 166 first IPTp-SP dose in the first/second trimester, fewer mothers of exposed neonates took no IPTp-SP but
 167 more took their first IPTp-SP in the third trimester relative to mothers of unexposed neonates ($p=.03$).
 168 Mothers of exposed and unexposed neonates did not differ significantly for the remaining
 169 sociodemographic or maternal clinical variables, and exposed and unexposed neonates did not differ
 170 significantly with regards to clinical or placental characteristics.

171 Of the 27 mothers who had malaria in pregnancy, 14 of 27 (52%) had active malaria infection at birth
 172 (positive RDT and/or blood smear). The timing and type of antimalarial treatment for these cases was
 173 not recorded. There were five cases of past-chronic placental infection and one case of active-chronic
 174 placental infection. Eleven (41%) mothers had evidence of malaria infection from medical records; of
 175 these, two were in the first trimester, two in the second trimester, and three in the third trimester.
 176 Timing of infection was not recorded for four infections.

177 **Neurological Functioning of Neonates**

178 Unadjusted and adjusted mean differences in raw scores on the six HNNE subdomains and overall were
 179 similar for exposed and unexposed neonates (Table 2). However, in both unadjusted and adjusted
 180 models exposed neonates tended to score lower on the reflexes subdomain (adjusted mean difference -
 181 0.34, 95% CI: -0.70–0.03).

182 As shown in Table 3, a large proportion of neonates were considered to be demonstrating “suboptimal”
 183 performance [using the original British scoring thresholds (Dubowitz et al., 1998)] by HNNE subdomain:
 184 67% for tone, 67% tone patterns, 37% reflexes, 82% movements, 61% abnormal signs/patterns, 75%
 185 orientation and behavior, and 95% overall. In the reflexes subdomain, significantly more neonates

exposed to malaria scored suboptimally than unexposed neonates (55.6% vs. 34.3%; adjusted risk ratio 1.63, 95% CI: 1.09–2.44). There were no significant differences between exposed and unexposed neonates in the risk of suboptimal scores for tone, tone patterns, movements, abnormal signs/patterns, or orientation and behavior. Finally, the association between scoring suboptimally by HNNE subdomain and overall was investigated separately for active (n=14) and past (n=13) malaria infection; however, no significant difference was evident.

Discussion

The objective of this study was to compare neurological functioning of malaria-exposed and unexposed neonates with a widely-used, validated, structured neurological assessment tool. Examining neonates prior to hospital discharge allowed us to assess the impact of malaria without the risk of confounding from subsequent exposure to family socioeconomic adversities and illnesses that may affect studies of outcomes in childhood. Further, assessing neonates within the first 48 hours of life has the advantage of allowing early detection of neurological abnormalities, which can lead to opportunities for targeted intervention.

We found that malaria-exposed neonates ≤ 48 hours of age had similar total HNNE scores to their unexposed peers. Interestingly, in the reflexes subdomain only, we found a statistically significant higher risk for suboptimal scores (which persisted after adjusting for socioeconomic status, education, maternal age, and social risk), although the mean difference in raw scores was small and did not reach statistical significance. There were no significant associations between malaria exposure and mean raw scores or suboptimal functioning in the tone, tone patterns, movements, abnormal signs/patterns, or orientation and behavior subdomains of the HNNE. Finding a significant difference in only one of the six HNNE subdomains could signify a selective effect on specific neurological function, but also raises the possibility that the finding was due to chance alone since no adjustment of statistical significance was

209 made for multiple comparisons. These findings may also be a result of the study being underpowered
210 due to our small sample size, thus the study may not be adequately powered to detect patterns of
211 malaria-related abnormality but might support the finding with the reflexes subdomain only. Although
212 all statistical analyses were predetermined according to *a priori* hypotheses, we recognize the
213 limitations on the certainty of the current findings and as such, we emphasize the preliminary nature of
214 our findings and highlight that this study was designed for hypothesis generation.

215 If there is a true differential impact on primitive reflexes over tone, movements, and behavior, the
216 mechanism and implications are uncertain. HNNE reflexes scores have been strongly associated with
217 motor and cognitive outcomes in preterm-born infants assessed at 32 weeks postmenstrual age (George
218 et al., 2021). Suboptimal reflex subdomain scores have also predicted poor neurodevelopmental
219 outcomes, including lower mental and psychomotor development indices (Molteno et al., 1995, Sanchez
220 et al., 2017) and structural brain abnormalities, including reduced biparietal diameter, increasing
221 severity of cerebral white and gray matter abnormalities, and cerebellar abnormalities (Eeles et al.,
222 2017, George et al., 2018, Sanchez et al., 2017, Woodward et al., 2004). Indeed, a recent study in Brazil
223 reported reduced head circumference in neonates born to malaria-infected mothers (Dombrowski et al.,
224 2017), however there was no intergroup difference in head circumference in our study. We can
225 speculate that exposure to malaria in pregnancy results in adverse neurodevelopmental outcomes
226 and/or subtle alterations in brain development. Unlike changes in gross brain structure, subtle changes
227 would not manifest as differences in HNNE scores across all domains. However, without incorporating
228 neurodevelopmental follow-up of exposed neonates, or including neuroimaging into our study, we
229 cannot determine whether any such brain pathology or long-term neurological adversities exist in
230 malaria-exposed infants.

231 An alternative explanation for why we found so little difference between malaria-exposed and
232 unexposed neonates is the heterogeneity of malaria exposure in our sample and the lack of dense
233 placental inflammatory response with pigmented monocytes that may be mitigating possible effects of
234 malaria infection. An important pathway identified in our previously published conceptual framework
235 was the role of maternal immune-inflammatory dysfunction and the downstream effects of
236 inflammatory factors and the immune system on fetal brain development (Lawford et al., 2019).
237 However, if there was only clinically mild malaria in our sample with little acute or chronic placental
238 malaria infection, it is unlikely that heightened maternal immuno-inflammatory responses would occur,
239 which would be responsible for impaired fetal brain development and subsequent neonatal neurological
240 functioning. Possibly, replicating this study in a population with denser placental parasitization would
241 find different results. However, this approach presents the serious ethical challenges common to other
242 studies of “natural history” of disease, in that a duty of care would be owed to mothers participating in
243 research to provide them with optimal treatment if malaria is diagnosed early in pregnancy. While there
244 are no major ethical challenges around recruiting women with intense placental inflammation in the
245 labor ward, as in this study, this does increase the challenge of determining the importance of timing of
246 malaria infection on neurological outcomes.

247 A limitation of this study is that exposure to antimalarial treatment among women with active malaria at
248 birth was not recorded. According to the standard treatment guidelines for malaria in Ghana, pregnant
249 women are administered either artesunate + amodiaquine, artemether + lumefantrine or oral quinine
250 for uncomplicated malaria in the second or third trimester (Ministry of Health & Ghana Health Services,
251 2014), all of which have a good safety profile. Maternal treatment could have reduced the impact of
252 exposure to malaria on the neonate, biasing our study towards finding no difference between the
253 groups (whereas a study of women without access to treatment might have shown differences).

254 However, if antimalarial drugs adversely affected the neonates' neurological function, we would have
255 expected this to have exaggerated differences between the malaria-exposed and unexposed groups.

256 It is important to acknowledge that, despite being the largest study published to date investigating the
257 impact of malaria in pregnancy on neonatal neurological functioning, our study may be underpowered
258 given the small sample size (particularly the sample of neonates exposed to malaria in pregnancy). Given
259 the small sample size (particularly in the malaria-exposed group) and the multiple comparisons in the
260 study, we advise caution in interpreting statistical significance. It is possible that the finding of a
261 difference in neonates meeting the threshold for suboptimal performance in only one of six subdomains
262 is the result of a type 2 error. It is also possible that the increased risk of suboptimal reflexes seen in
263 neonates exposed to malaria could be due to chance (a type 1 error), subtle biases, or unmeasured
264 confounders. The adjusted mean difference between groups for raw scores for the reflexes subdomain
265 was only about a third of a standard deviation and was not statistically significant. The difference we
266 found may or may not be clinically significant and a much larger sample size might find subtle (and yet
267 clinically significant) differences in other subdomains or in total HNNE scores that this study was too
268 small to detect. Ultimately, longitudinal studies are needed to determine the significance of malaria
269 exposure during pregnancy on childhood neurodevelopment, and to distinguish the effects of maternal
270 malaria infection from concomitant comorbid conditions. This will allow an understanding of both the
271 childhood impact of malaria in pregnancy and the specificity and predictive value of neurological
272 assessments at birth in this context.

273 The HNNE was selected as the most appropriate neurological assessment tool for this study; it assesses
274 neurological functioning at birth, has been widely used both in clinical and research contexts, has
275 excellent (>96%) interrater reliability (Dubowitz et al., 1998) and has high predictive validity to identify
276 structural brain abnormalities and later neurological dysfunction. However, the HNNE has only

277 infrequently been used for research in low- and middle-income countries and has not been validated or
 278 standardized in Ghana. Therefore, we are hesitant to interpret Ghanaian neonates as performing
 279 “suboptimally” using this (original British) scoring system without more extensive validation of the HNNE
 280 in Ghana or follow-up of our sample to determine long-term neurological functioning. Because we are
 281 unsure of the reasons why such a high proportion of Ghanaian neonates in the comparison group scored
 282 suboptimally we also compared HNNE raw scores, but still found little difference between groups.

283 Based on the original HNNE scoring system established by Dubowitz *et al.* in 1998 (Dubowitz et al.,
 284 1998), we would expect that ~10% of our unexposed comparison group would be scoring suboptimally.
 285 However, we found a much higher proportion of unexposed neonates scored below the 10th centile
 286 when the British scoring system was applied, but we are very uncertain about whether this indicates a
 287 much higher baseline of adverse neurological functioning in term-born, malaria-unexposed neonates
 288 specific to our study site. We have discussed possible reasons for these findings in both the IMPRINT
 289 study (Lawford Harriet LS et al., 2020) and studies conducted in other low- and middle-income countries
 290 [Thailand, Myanmar (McGready et al., 2000), Vietnam (Hieu et al., 2006), and Uganda (Hagmann et al.,
 291 2015)], which have also reported differences from the original British norms. An important characteristic
 292 of the study population that should be noted is the mode of delivery. Overall, 66% of deliveries were by
 293 Caesarean section; as discussed in our previous work reasons for this could include the study setting
 294 (Korle Bu Teaching Hospital is a tertiary referral hospital), or it could be a reflection of higher
 295 socioeconomic status (Lawford Harriet LS et al., 2020). It is important to note that when neonates were
 296 stratified by mode of delivery, there was no difference in total HNNE score between neonates delivered
 297 by C-section vs. vaginally (25.3 ± 3.7 vs. 25.0 ± 3.7 ; $P=0.52$). Therefore, it is unlikely that C-section or the
 298 use of postpartum analgesia impacted HNNE scores in this study. Nevertheless, we consider that any
 299 confounding or bias in HNNE results in the Ghanaian setting caused by unmeasured comorbidities, test

conditions or conduct, or uncertainties in gestational age estimation should have applied equally to both arms of the current study, not just to the malaria-exposed group.

In conclusion, given the high burden of malaria infection in pregnancy, understanding whether *in utero* exposure to malaria adversely impacts neurological development is important. Our results suggest that a group of term-born neonates exposed to malaria in pregnancy (and whose mothers had generally received treatment) had HNNE scores similar to an unexposed comparison group born in the same hospital. However, we found a higher risk of suboptimal functioning in only the reflexes subdomain, which could be a result of malaria exposure in pregnancy.

Contributors' Statement

The corresponding author, Dr. Samudragupta Bora had full access to all of the study data and is primarily accountable for all aspects of the work, including the decision to submit for publication. The corresponding author, first author, and the statistical advisor, Ms. Alison Griffin verified all the reported data analysis.

Harriet L.S. Lawford conceptualized and designed the study protocol, coordinated data acquisition, performed data analyses, interpreted the results, drafted and revised the initial manuscript, and approved the final manuscript as submitted.

Mercy A. Nuamah designed the study protocol, coordinated and supervised data acquisition, interpreted the results, critically reviewed and revised the initial manuscript, and approved the final manuscript as submitted.

Helen G. Liley conceptualized the study, supervised data analyses, interpreted the results, critically reviewed and revised the initial manuscript, and approved the final manuscript as submitted.

Alison Griffin developed the statistical analysis plan, supervised preliminary data analyses, performed data analyses, interpreted the results, critically reviewed and revised the initial manuscript, and approved the final manuscript as submitted.

326 Cecilia E. Lekpor designed the study protocol, acquired data, interpreted the results, critically
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328 Felix Botchway designed the study protocol, acquired data, interpreted the results, critically
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330 Samuel A. Oppong supervised the designing of the study protocol, coordinated data acquisition,
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341 Anne CC Lee conceptualized the study, interpreted the results, critically reviewed and revised
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343 Richard K. Gyasi designed the study protocol, acquired data, interpreted the results, critically
344 reviewed and revised the initial manuscript, and approved the final manuscript as submitted.

345 Andrew A. Adjei supervised the designing of the study protocol, coordinated data acquisition,
346 interpreted the results, critically reviewed and revised the initial manuscript, and approved the
347 final manuscript as submitted.

348 Samudragupta Bora acquired funds and resources, conceptualized the study, designed the
349 study protocol, supervised data acquisition and data analyses, interpreted the results, critically
350 reviewed and revised the initial manuscript, and approved the final manuscript as submitted.

351

352

353 **Ethical Approval**

354 The study protocol was approved by the Institutional Review Board/Human Research Ethics Committee
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362 **Conflict of interest**

363 The authors have no conflict of interest relevant to this study to disclose.

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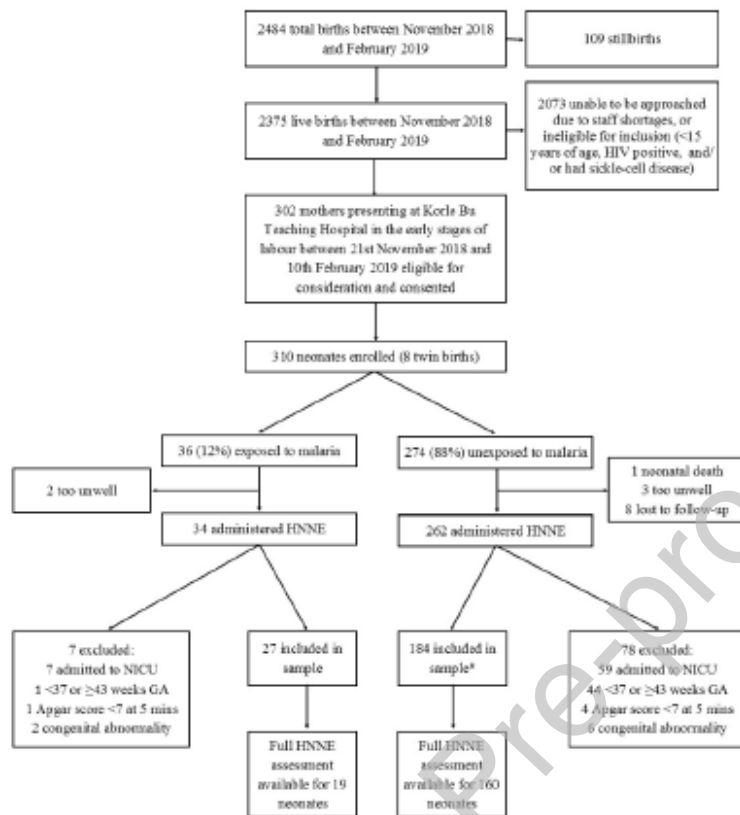
Figure 1: Sample Recruitment

Table 1: Sociodemographic characteristics of neonates assessed using the Hammersmith Neonatal Neurological Examination according to malaria exposure

| Characteristics [†] | All [n=211] | Malaria-Exposed [n=27] | Malaria-Unexposed [n=184] | p |
|------------------------------|----------------|---------------------------|------------------------------|-----|
| Maternal Demographics | | | | |
| Age, years | 31.4 ± 6.1 | 29.8 ± 7.0 | 31.7 ± 6.0 | .14 |
| Literate | | | | |

| Characteristics [†] | All [n=211] | Malaria-Exposed [n=27] | Malaria-Unexposed [n=184] | p |
|---|----------------|---------------------------|------------------------------|------|
| No | 46 (22.3) | 5 (18.5) | 41 (22.9) | .60 |
| Yes | 160 (77.7) | 22 (81.5) | 138 (77.1) | |
| Education | | | | |
| None/primary/secondary | 137 (66.2) | 22 (81.5) | 115 (63.9) | .07 |
| Higher | 70 (33.8) | 5 (18.5) | 65 (36.1) | |
| Amount worked | | | | |
| None/occasional/seasonal | 39 (18.8) | 5 (18.5) | 34 (18.9) | .96 |
| Full-time | 168 (81.2) | 22 (81.5) | 146 (81.1) | |
| Wealth quintile | | | | |
| Poorest [1 st –3 rd] | 100 (47.4) | 15 (55.6) | 85 (46.2) | .36 |
| Richest [4 th –5 th] | 111 (52.6) | 12 (44.4) | 99 (53.8) | |
| Health insurance | | | | |
| No | 6 (2.9) | 1 (3.7) | 5 (2.8) | .79 |
| Yes | 200 (97.1) | 26 (96.3) | 174 (97.2) | |
| Other children | | | | |
| None | 42 (20.5) | 11 (42.3) | 31 (17.3) | .003 |
| ≥1 | 163 (79.5) | 15 (57.7) | 148 (82.7) | |
| Overcrowding | | | | |
| ≤1 person per room | 51 (24.6) | 2 (7.4) | 49 (27.2) | .03 |

| Characteristics [†] | All [n=211] | Malaria-Exposed [n=27] | Malaria-Unexposed [n=184] | p |
|------------------------------------|----------------|---------------------------|------------------------------|-----|
| >1 person per room | 156 (75.4) | 25 (92.6) | 131 (72.8) | |
| Social risk | | | | |
| Low risk (no risk factor) | 106 (50.2) | 15 (55.6) | 91 (49.5) | .55 |
| High risk (≥1 risk factor) | 105 (49.8) | 12 (44.4) | 93 (50.5) | |
| Maternal Clinical | | | | |
| Time of first antenatal visit | | | | |
| Second/third trimester | 70 (34.3) | 10 (37.0) | 60 (33.9) | .75 |
| First trimester | 134 (65.7) | 17 (63.0) | 117 (66.1) | |
| Gravidity | 3.3 ± 1.7 | 2.7 ± 1.9 | 3.3 ± 1.7 | .09 |
| Middle upper arm circumference, cm | 31.3 ± 4.1 | 29.6 ± 3.6 | 31.5 ± 4.1 | .03 |
| Hemoglobin level, g/dl | 10.2 ± 1.5 | 10.0 ± 2.0 | 10.3 ± 1.4 | .29 |
| Anxiety | 2 [0, 4] | 2 [0, 6] | 2 [0, 4] | .41 |
| Depression | 2 [0, 5] | 2 [0, 5] | 2 [0, 5] | .40 |
| Clinical risk | | | | |
| Low risk [no risk factor] | 152 (72.0) | 17 (63.0) | 135 (73.4) | .26 |
| High risk [≥1 risk factor] | 59 (28.0) | 10 (37.0) | 49 (26.6) | |
| Malaria Prevention | | | | |
| ITN use in pregnancy | | | | |
| Did not use/no bed net | 129 (62.3) | 16 (59.3) | 113 (62.8) | .72 |

| Characteristics [†] | All [n=211] | Malaria-Exposed [n=27] | Malaria-Unexposed [n=184] | p |
|--|-----------------|---------------------------|------------------------------|-----|
| Used in pregnancy | 78 (37.7) | 11 (40.7) | 67 (37.2) | |
| Total IPTp-SP doses | 2 [1, 3] | 2 [2, 3] | 2 [1, 3] | .28 |
| Trimester of first IPTp-SP | | | | |
| No IPTp-SP/not specified | 35 (16.7) | 1 (3.7) | 34 (18.6) | .03 |
| First or second trimester | 131 (62.4) | 16 (59.3) | 115 (62.8) | |
| Third trimester | 44 (21.0) | 10 (37.0) | 34 (18.6) | |
| Neonatal Clinical | | | | |
| Mode of delivery | | | | |
| Cesarean section | 134 (63.8) | 14 (51.9) | 120 (65.6) | .17 |
| Spontaneous vaginal/ vacuum extraction | 76 (36.2) | 13 (48.1) | 63 (34.4) | |
| Gestational age, weeks | 39 [38.1, 40.2] | 39.2 [38.1, 40.4] | 39 [38.1, 40.2] | .81 |
| Birthweight, kg | 3.2 ± 0.4 | 3.2 ± 0.4 | 3.1 ± 0.4 | .40 |
| Birthweight Z-score | -0.3 ± 0.9 | -0.2 ± 0.9 | -0.3 ± 0.9 | .44 |
| Low birthweight | | | | |
| No | 201 (95.7) | 25 (92.6) | 176 (96.2) | .39 |
| Yes | 9 (4.3) | 2 (7.4) | 7 (3.8) | |
| Apgar score 1 minute | 8 [7, 8] | 8 [7, 8] | 8 [7, 8] | .60 |
| Apgar score 5 minutes | 9 [8, 9] | 9 [8, 9] | 9 [8, 9] | .54 |
| Length, cm | 50 [49, 5] | 51 [50, 52] | 50 [49, 52] | .13 |

| Characteristics [†] | All [n=211] | Malaria-Exposed [n=27] | Malaria-Unexposed [n=184] | p |
|------------------------------|-----------------|---------------------------|------------------------------|-----|
| Chest circumference, cm | 33 [32, 34] | 33 [31, 34] | 33 [32, 34] | .18 |
| Head circumference, cm | 34 [33, 35] | 34 [33, 35] | 34 [33, 35] | .62 |
| Ponderal Index | 2.6 ± 0.8 | 2.5 ± 0.3 | 2.6 ± 0.9 | .50 |
| Sex | | | | |
| Male | 108 (51.4) | 12 (44.4) | 96 (52.5) | .44 |
| Female | 102 (48.6) | 15 (55.6) | 87 (47.5) | |
| Placental Assessment | | | | |
| Placental abnormality | | | | |
| None | 50 (23.7) | 10 (37.0) | 40 (21.7) | .16 |
| 1 abnormality | 82 (38.9) | 7 (25.9) | 75 (40.8) | |
| >1 abnormality | 79 (37.4) | 10 (37.0) | 69 (37.5) | |
| Cord length, cm | 52 [45.5, 60.0] | 55.5 [46, 60.5] | 51.6 [45.5, 59.2] | .37 |
| Cord diameter, cm | 1.2 [1, 1.5] | 1.3 [1, 1.5] | 1.2 [1, 1.5] | .69 |
| Umbilical coiling index | 0.08 ± 0.09 | 0.07 ± 0.08 | 0.08 ± 0.09 | .86 |
| Placental weight, kg | 472.1 ± 100.6 | 478.8 ± 105.4 | 471.2 ± 100.3 | .73 |
| Placental thickness, cm | 1.9 ± 0.4 | 1.9 ± 0.3 | 1.8 ± 0.4 | .48 |

[†]Data are number (%), median [interquartile range], or mean ± standard deviation.

Table 2: Unadjusted and adjusted mean differences in raw scores of the Hammersmith Neonatal Neurological Examination subdomain according to malaria exposure

| Malaria-Exposed | | Malaria-Unexposed | | Mean Difference | | | Adjusted [†] Mean Difference | | |
|-----------------|----------------|-------------------|----------------|--------------------------|-----|---------------------|---------------------------------------|-----|------------|
| N | Mean \pm SD | N | Mean \pm SD | Mean Difference (95% CI) | p | Cohen's d (95% CI) | Mean difference (95% CI) | p | Cohen's d |
| 27 | 7.1 \pm 2.6 | 182 | 7.3 \pm 2.2 | -0.18 (-1.09, 0.73) | .70 | -0.08 (-0.48, 0.33) | -0.00 (-0.93, 0.93) | .10 | -0.0 (-0.4 |
| 27 | 4.2 \pm 0.8 | 184 | 4.1 \pm 0.8 | 0.13 (-0.18, 0.44) | .41 | 0.17 (-0.24, 0.57) | 0.14 (-0.18, 0.46) | .40 | 0.18 (-0. |
| 27 | 4.6 \pm 1.0 | 178 | 5.0 \pm 0.9 | -0.33 (-0.69, 0.03) | .07 | -0.37 (-0.78, 0.03) | -0.34 (-0.70, 0.03) | .07 | -0.38 (-0 |
| 24 | 1.9 \pm 0.9 | 179 | 1.8 \pm 0.8 | 0.06 (-0.30, 0.42) | .75 | 0.06 (-0.36, 0.49) | 0.03 (-0.33, 0.40) | .85 | 0.04 (-0. |
| 27 | 2.4 \pm 0.6 | 181 | 2.3 \pm 0.7 | 0.06 (-0.21, 0.34) | .66 | 0.09 (-0.31, 0.50) | 0.07 (-0.21, 0.34) | .64 | 0.10 (-0. |
| d 20 | 4.7 \pm 1.5 | 165 | 4.5 \pm 1.6 | 0.19 (-0.54, 0.93) | .60 | 0.12 (-0.34, 0.59) | 0.28 (-0.47, 1.03) | .46 | 0.18 (-0. |
| 19 | 25.2 \pm 3.5 | 160 | 25.0 \pm 3.8 | 0.23 (-1.56, 2.02) | .80 | 0.06 (-0.41, 0.54) | 0.46 (-1.35, 2.27) | .62 | 0.12 (-0. |

465 [†] Adjusted for socioeconomic status, education, maternal age, and social risk.

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469 **Table 3:** Risk of suboptimal scores of the Hammersmith Neonatal Neurological
 470 Examination subdomain according to malaria exposure

| HNNE Subdomain | Neonates with suboptimal scores, n/N (%) | | | Unadjusted | | Adjusted Risk Ratio (95% CI) |
|----------------------|--|-------------------|----------------|---------------------|-----|------------------------------|
| | Malaria-Exposed | Malaria-Unexposed | All | Risk Ratio (95% CI) | p | |
| Tone | 17/27 (63.0) | 123/182 (67.6) | 140/209 (67.0) | 0.93 (0.69, 1.27) | .65 | 0.90 |
| Tone patterns | 16/27 (59.3) | 125/184 (67.9) | 141/209 (66.8) | 0.87 (0.63, 1.21) | .42 | 0.87 |
| Reflexes | 15/27 (55.6) | 61/178 (34.3) | 76/205 (37.1) | 1.62 (1.09, 2.41) | .02 | 1.63 |
| Movements | 18/24 (75.0) | 149/179 (83.2) | 167/203 (82.3) | 0.90 (0.71, 1.15) | .40 | 0.92 |

| | | | | | | |
|--------------------------|--------------|----------------|----------------|-------------------|-----|------|
| Abnormal signs/patterns | 17/27 (63.0) | 110/181 (60.8) | 127/208 (61.1) | 1.03 (0.76, 1.42) | .83 | 1.03 |
| Orientation and behavior | 14/27 (70.0) | 125/165 (75.8) | 139/185 (75.1) | 0.92 (0.68, 1.25) | .61 | 0.91 |
| Total HNNE score | 18/19 (94.7) | 152/160 (95.0) | 170/179 (95.0) | 1.00 (0.89, 1.12) | .96 | 1.00 |

471 † Adjusted for socioeconomic status, education, maternal age, and social risk.

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