Minimal impact by antenatal subpatent *P. falciparum* infections on delivery outcomes in Malawian women: a cohort study

Steve M Taylor MD MPH[1,2*]

Mwayiwawo Madanitsa MD PhD[3,4*]

Kyaw-Lay Thwai[2]

Carole Khairallah[4]

Linda Kalilani-Phiri MD PhD[3]

Anna M. van Eijk[4]

Victor Mwapasa MD PhD[3]

Feiko O ter Kuile MD PhD[4]

Steven R Meshnick MD PhD[2]

[1] Division of Infectious Diseases, Duke University Medical Center and Duke Global Health Institute, Durham, NC, USA

[2] Department of Epidemiology, UNC Gillings School of Global Public Health, Chapel Hill, USA

[3] Department of Community Health, College of Medicine, Blantyre, Malawi

[4] Department of Clinical Sciences, Liverpool School of Tropical Medicine, UK

* Authors SMT and MM contributed equally to this manuscript.

Corresponding author:

Steve M Taylor

Box 102359 DUMC

Durham, NC 27710

Tel: 919-684-5815

FAX: 919-684-8902

steve.taylor@duke.edu

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ABSTRACT

Antenatal malaria screening with a rapid diagnostic test (RDT) and treatment only of RDT-positive women may potentially prevent low birthweight resulting from malaria. The consequences of subpatent antenatal infections below the detection limit of RDTs are incompletely understood. In Malawi, pregnant women of any gravidity were tested at each antenatal visit for *P. falciparum* using RDT and PCR and followed until delivery. Associations between antenatal infections and delivery outcomes were assessed with Poisson regression or ANOVA. Compared to women with no detected antenatal *P. falciparum* infections, women with RDT-positive infections delivered babies with lower mean birthweights: 2960 vs 2867 grams[g] (mean difference[MD]: -93g; 95% confidence interval[CI]: -27,-159; p=0.006); this was not observed among women with only subpatent infections (mean: 3013g; MD: +54; 95% CI: -33,+140; p=0.2268). These differences were apparent early in pregnancy: At second trimester enrollment, compared to uninfected women, RDT-positive women delivered babies with lower mean birthweight (MD: -94g; 95% CI: -31,-156; p=0.003), but women with subpatent infections did not (MD: +36g; 95% CI: -49,+122; p=0.409). Subpatent antenatal *P. falciparum* infections were not associated with adverse delivery outcomes. The association of patent infections at enrollment with low birthweight suggests the importance of early-pregnancy *P. falciparum* prevention.

Background

Innovative approaches are continually needed to prevent placental malaria. In sub-Saharan Africa, placental *P. falciparum* infection causes low birth weight (LBW), small for gestational age (SGA), and preterm (PT) births; the risks of these adverse outcomes are mitigated by intermittent preventive therapy with sulfadoxine-pyrimethamine (IPTp-SP), which in Africa is widely recommended[1] but sub-optimally administered[2, 3] and continually threatened by resistance to SP.[4-6] One possible alternative strategy to IPTp-SP is intermittent antenatal screening for parasites with rapid diagnostic tests (RDTs) and the treatment of RDT-positive women with antimalarials (known as intermittent screening and treatment during pregnancy, or ISTp). Although ISTp results in more maternal antenatal infections[7], ISTp with artemisinin combination therapies was non-inferior to IPTp-SP to prevent LBW in two trials in low SP-resistance areas in West Africa,[7, 8] and ISTp with dihydroartemisinin-piperaquine was inferior to IPTp-SP in preventing parasitemia at delivery in Kenya and Malawi.[9] [10] Although WHO does not currently recommend ISTp as an alternative to IPTp-SP,[11] it is either being implemented[12] or planned[13] in low-transmission settings. With broad declines in malaria transmission[14] and increasing resistance to SP,[15] ISTp may offer an alternative to IPTp-SP in some epidemiologic settings for the prevention of LBW in malaria-endemic Africa.

However, there exists concern that the ISTp approach may be undermined by low-density antenatal infections that are undetected by screening tests and therefore remain untreated. The lower limits of detection for *P. falciparum* vary by diagnostic method, and are generally considered highest for light microscopy, slightly lower for RDTs, and lowest for molecular

detection assays like PCR. Antenatal subpatent infections are defined as negative by light microscopy or RDTs but positive by PCR, and result from parasite densities which fall between the limits of detection of diagnostic methods. In cross-sectional studies, subpatent infections have been associated with pregnancy outcomes: they have been associated with maternal anemia during pregnancy [16] or at delivery,[17] and with lower birthweight when detected at delivery.[18, 19] These cross-sectional studies provide limited ability to infer causality, but only a limited number of longitudinal studies have investigated subpatent infections and delivery outcomes. In Benin, these submicroscopic infections were associated with higher risks of LBW and preterm birth[20] and in Malawi with an increased risk of placental malaria, but not with adverse maternal or fetal outcomes.[21] In one Ghanaian study, sub-RDT (or subpatent) antenatal infections were not associated with LBW.[22] Before ISTp can be considered as a potential viable alternative to IPTp in any settings, the potential impact of subpatent infections, more especially sub-RDT infections, on a variety of endpoints in multiple cohorts needs to be determined.

We investigated the impact of subpatent (RDT-negative/PCR-positive) *P. falciparum* infections in a cohort of Malawian women who were enrolled in a trial and randomized to the arm that received ISTp using a commercial RDT that detects the *Plasmodium* antigens HRP2 and pLDH.[10] We tested the impact of antenatal subpatent infections on maternal and newborn birth outcomes, including birthweight, gestational age, placental malaria, and maternal hemoglobin at delivery. We hypothesized that, relative to uninfected women, the presence of

subpatent antenatal infections would be associated with a decrease in mean birthweight and with growth retardation, in particular in paucigravidae.

Methods

Study cohort

We used specimens collected from participants in a published randomized clinical trial in Malawi conducted between 2011-14 that compared IPTp-SP with ISTp-DP (PACTR.org: 201103000280319; ISCRTN.com: 69800930).[10] Briefly, women of all gravidae presenting for antenatal care between 16-28 weeks gestation to three health clinics in Southern Malawi were eligible to participate. Women were randomized (1:1) to either intervention, which was administered open-label. Prior to delivery, all women were seen again at 2 to 3 additional scheduled visits and encouraged to return for unscheduled visits if they felt unwell between scheduled visits.

We used specimens only collected from women allocated to receive ISTp. At each visit, venous blood was collected from these women for parasite detection by light microscopy, RDT, and PCR. Those who tested positive by RDT were administered a standard 3-day course of dihydroartemisinin-piperaquine.

Outcome assessments

At delivery, maternal venous blood was tested for parasites using the same methods; placental histology was assessed for placental malaria using standard methods;[23] placental blood from the maternal side was tested for malaria parasites using light microscopy, RDT, and PCR; and newborns were weighed and gestational age was assessed using a modified Ballard score.[24]

Maternal hemoglobin was measured from venous blood using the Hemocue 301; a hemoglobin concentration < 11g/dL defined maternal anemia.

Birthweights obtained more than 24 hours after birth were corrected for the physiologic fall in weight in breastfed children[25] to obtain a corrected birthweight, which was used in all analyses. Birthweights were measured using digital weigh scales reporting weight to the nearest 10g. Low birthweight (LBW) was defined as < 2500g. We estimated gestational age using the following hierarchy, which varied between participants: ultrasound at enrollment, newborn Modified Ballard's Score clinical exam within 96 hours of delivery, last menstrual period, or fundal height at enrollment. Preterm (PT) birth was defined as delivery at less than 37 weeks. Small for gestational age (SGA) was defined as a birthweight below the tenth percentile for the gestational age and sex of the newborn, using a Tanzanian reference population; from this reference, z-scores of birthweight for gestational age were computed.[26]

Laboratory procedures

Microscopy was performed at a central laboratory at the University of Malawi by two independent readers who assessed 200 high powered fields of thick smear preparations. A positive microscopic test was defined as the presence of any asexual *Plasmodium* spp. parasites. RDT testing was performed at point-of-care using the HRP2/pLDH combination RDT (FirstResponse Malaria pLDH/HRP2 Combo Test, Premier Medical Corporation Ltd, USA) per the manufacturer's recommendation. A positive test was defined as the presence of the control band as well as at least one HRP2 or pLDH band. Placental sections of 2.5cm^3 were used for

histologic analysis, for which hematoxylin and eosin staining was used to score for the presence of parasites, parasite pigment, and intervillous inflammation;[23] histologic analysis was performed by a trained technician masked to microscopy, RDT, and outcome data.

PCR detection of parasites was performed using a real-time PCR assay[27] targeting the *P. falciparum* lactate dehydrogenase gene (*pfldh*) in genomic DNA extracted from dried blood spots using Chelex-100. Real-time PCR assays were performed in duplicate in 384-well reaction plates on a BioRad CFX384 platform, threshold lines were set manually, and each reaction plate included gDNA from parasite strain 3D7 as a positive control. PCR detection was performed by personnel masked to microscopy, RDT, and outcome data.

Data analyses

The main exposure of interest was subpatent (i.e. RDT-negative and PCR-positive) infection with *P. falciparum*. Exposure classifications were i) infections at antenatal enrollment, based upon RDT and PCR (uninfected v. RDT-positive v. subpatent) and ii) cumulative antenatal infections (never infected v. RDT-positive infections only v. subpatent infection only). The continuous outcomes analyzed were maternal hemoglobin at delivery, birthweight, gestational age, and birthweight-for-age Z-score; the dichotomous outcomes analyzed were LBW, SGA, PT, the composite endpoint of LBW, SGA, or PT, placental malaria (parasites detected by microscopy, RDT, PCR, or histology in placental specimens), and maternal anemia at delivery (hemoglobin concentration < 11g/dL). We compared continuous outcomes using oneway ANOVA and expressed results as the mean difference and corresponding 95% confidence

intervals (CIs). We compared dichotomous outcomes using Poisson regression and expressed results as Risk Ratios (RRs) with 95% CIs. We compared proportions of placental histologic features between groups using the chi-squared test. All analyses were conducted overall (all gravidae) and by gravidity strata (pauci- or multigravidae). The analysis involving all gravidae, included gravidity as a binary co-variable (pauci- or multigravidae). All statistical analyses were performed with Stata/IC (v14, StataCorp, College Station, TX, USA).

Ethical statement

The clinical study was approved by the ethical review boards of the National Health Sciences Research Committee, Malawi, and the Liverpool School of Tropical Medicine. Testing of specimens was approved by the University of North Carolina.

Results

Epidemiology of antenatal infections

Of 923 women allocated to the ISTp study arm, the mean (SD) age was 22.5 (5.1) years, the mean (SD) estimated gestational age at enrollment was 146.8 (23.3) days, 34% were primigravidae, and 18% had slept under a bednet the previous night. At enrollment, 51.2% (n=473) were uninfected, 34.5% (n=318) had an RDT-positive infection, and 14.3% (n=132) had a subpatent infection. The prevalence of RDT-positive infections declined at subsequent scheduled visits to 6.1% at the 1st, 7.0% at the 2nd, and 10.3% at the 3rd. In contrast, the prevalence of subpatent infections remained largely unchanged at these visits: 12.5% (1st), 13.2% (2nd), and 14.3% (3rd) (**Figure 1A**). At unscheduled visits, the prevalence of RDT-positive infections was higher than that of subpatent infections (**Figure 1A**).

Overall, women had RDT-positive infections on up to 4 separate visits, and subpatent infections on up to 6 separate visits (**Figure 1B**). Of the 923 women, 474 (51.4%) had at least 1 RDT-positive infection and 323 (35%) had at least 1 subpatent infection. Compared with multigravidae, paucigravidae did not have more subpatent infections (pauci: 36.4%, multi: 32.7%; p = 0.47).

Maternal and newborn outcomes

The overall mean (SD) birthweight was 2921g (423), mean (SD) maternal hemoglobin at delivery was 12g/dL (1.56), mean (SD) gestational age was 38.1 weeks (2.4), and mean (SD) birthweight-for-age Z-score was 0.14 (0.94) (**Supplemental Table 1**). The prevalence of LBW was 12%

(98/818), the composite LBW/SGA/PT 29.9% (254/849), placental malaria 40.9% (337/825), and maternal anemia at delivery 24% (196/817) (**Supplemental Table 2**).

Associations of birth outcomes with infections at antenatal enrollment

Among all gravidae, compared to uninfected women, those with RDT-positive infections at enrollment delivered babies with similar gestational age but lower mean birthweights (mean difference [MD]: -94g; 95% confidence interval [CI]: -156, -31; p = 0.0033) and lower birthweight-for-age Z-scores (MD: -0.17; 95% CI: -0.31, -0.03; p = 0.0194); in contrast, subpatent infections were not associated with any of these outcomes (**Figure 2**). In paucigravidae, RDT-positive infections were associated with lower maternal hemoglobin at delivery (MD: -0.33g/dL; 95% CI: -0.63, -0.03; p = 0.0308), but not significantly associated with birthweight or Z-scores (**Supplemental Table 1**). On dichotomized outcomes, compared to uninfected women at enrollment, the presence of an RDT-positive infection was associated with an increased prevalence of LBW (RR 1.67; 95% CI: 1.08 – 2.58) and placental malaria (RR 1.73; 95% CI: 1.36 – 2.19); subpatent infections were not associated with any increased risk of adverse birth outcomes, including LBW (RR 0.93; 95% CI: 0.46 – 1.87) (**Figure 3; Supplemental Table 2**). Among paucigravidae specifically, relative to uninfected women, an RDT-positive infection was only associated with an increased prevalence of placental malaria (RR 1.81; 95% CI: 1.38 – 2.37). In these women, a subpatent infection was not significantly associated with any outcome, including LBW (RR 0.64; 95% CI: 0.25 – 1.66) (**Figure 3; Supplemental Table 2**).

Associations of birth outcomes with cumulative antenatal infections

Compared to infants born to women who were never infected, women with RDT-positive infections during pregnancy delivered babies with lower birthweight (MD: -93g; 95% CI: -159, -27; p = 0.0061) and birthweight-for-age Z-scores (MD: -0.20; 95% CI -0.34, -0.05; p = 0.008); in contrast, neither outcome was associated with having suffered only subpatent infections (**Figure 2; Supplemental Table 3**). In analyses stratified by gravidity, compared to women who were never infected, women with RDT-positive infections had non-significant reductions in mean birthweight amongst both paucigravidae (MD: -39g; 95% CI: -129, +50; p = 0.3916) and multigravidae (MD: -79g; 95% CI: -184, +25; p = 0.1369), while women with only subpatent infections had non-significant increases in birthweight (**Supplemental Table 3**). Notably, there were no differences in gestational age between women who were never infected and those who either suffered RDT-positive or only subpatent infections.

There was no statistically-significant difference in the prevalence of LBW between those who were never infected (9.7%), those with RDT-positive infections (14.7%; RR 1.28, 95% CI: 0.78 – 2.08), and those with subpatent infections only (7.6%; RR 0.78, 95% CI: 0.38 – 1.60) (**Figure 3; Supplemental Table 4**). The prevalence of placental malaria was 23.6% in women who were never infected antenatally, 51.6% in those with RDT-positive infections at least once (RR 1.93, 95% CI 1.43 – 2.59), and 37.6% in those with subpatent infections only (RR 1.59, 95% CI 1.10 – 2.30) (**Figure 3; Supplemental Table 4**). Among the 334 women with placental malaria, intervillous inflammation was not associated with infections at enrollment or with cumulative antenatal infections, but malaria pigment was more common among women with RDT-positive infections at enrollment (66.7%; 112/168) compared to women not infected (24.4%; 30/123) or

with subpatent infections (20.9%; 9/43; $p < 0.001$) (**Table 1**). Similarly, malaria pigment was also more common amongst women with RDT-positive infections at least once antenatally (61%; 136/223) compared to those who were never infected (8.9%; 5/56) or those with only subpatent antenatal infections (18.2%; 10/55; $p < 0.001$).

Discussion

In our cohort of over 800 delivering women in a malaria-hyperendemic setting in Malawi, PCR-positive sub-patent antenatal *P. falciparum* infections which were below the limit of detection of an RDT and remained therefore untreated, were not consistently associated with adverse maternal or newborn outcomes. In contrast, RDT-positive infections as expected were associated with lower birthweights and lower birthweight-for-age Z-scores, suggesting that antenatal *P. falciparum* infections that remain undetected by a commercial RDT targeting the pLDH/HRP2 antigens are not associated with an increased risk of adverse clinical birth outcomes.

This lack of an association between morbidity and subpatent infections was evident in multigravidae as well as paucigravidae, despite the fact that paucigravid women are at higher risk of malaria infections and their consequences. Our results are consistent with a prior Ghanaian trial of ISTp with artemether-lumefantrine in paucigravidae, which also showed no associations between subpatent infections and birthweight or maternal hemoglobin concentration.[22] Taken together, these data, coupled with our analyses of a broad range of outcomes in a cohort with a high prevalence of subpatent infections, suggest that untreated subpatent infections do not cause fetal growth restriction or maternal anemia in semi-immune pregnant women in highly endemic areas of sub-Saharan Africa. Furthermore, our data do not support the hypothesis that the non-superiority of ISTp-DP to IPTp-SP was mainly the result of a failure to detect and treat these subpatent infections. The continued efficacy of IPTp-SP to

improve birthweight may be the result of off-target or antibacterial effects of SP or cryptic factors.

Unlike a recent study in Benin,[20]we found no specific association between subpatent infections at antenatal enrollment and an increased prevalence of LBW or PT. Both our and the study in Benin enrolled women < 24 weeks gestation and detected parasites using real-time PCR assays, but key differences are the use of IPTp with SP in Benin and the differing definitions of subpatent between the two studies (submicroscopic in Benin, sub-RDT in our study). Both of these differences might be expected to exacerbate the biological effects of subpatent infections in our study: the absence of IPTp in our study would have allowed subpatent infections to persist during pregnancy, and the higher limit of detection of parasites for our RDT (approximately 200 parasites/ uL)[28] compared to microscopy (reported as 40 parasites/uL)[20] would permit higher-density infections to be classified as subpatent. Nevertheless, we observed no consistent impact of these sub-RDT infections.

Antenatal *P. falciparum* infections should offer a unique model by which to investigate the individual clinical impact of subpatent infections by means of the analysis of birth outcomes, but in light of our null results and those of Williams *et al*.,[22] what is the biological importance of sub-RDT infections? In a longitudinal study of Ugandan children,[29] subpatent *P. falciparum* infections (microscopy-negative and PCR-positive) were not associated with an increased risk of clinical disease, relative to uninfected children, suggesting that low-density subpatent infections may not presage clinical consequences. One hypothesis for this phenomenon in

children is that low-density infections may promote or maintain adaptive immunity to clinical disease.[30] By analogy, the presence of subpatent antenatal infections may promote the acquisition of immunity to placental-binding parasites, which develops during pregnancy in paucigravid Malawian women[31] and which is associated with protection from adverse birth outcomes.[32] Notably, although we observed a higher prevalence of placental malaria in women with subpatent infections compared to those who were never infected, the prevalence of malaria pigment between groups was similar, a finding associated with low birthweight in prior studies [23]. Therefore, partial immunity promoted by subpatent parasites could potentially attenuate the downstream effects of placental malaria and limit its deleterious impact on birthweight.

Our results further highlight the need to prevent patent infections early in pregnancy. Compared to uninfected women, those harboring RDT-positive infections at enrollment delivered infants with lower birthweights and birthweight-for-age Z-scores, despite being treated with DP at that visit and being screened subsequently for parasites with RDTs. In our study, women were enrolled between 16 – 24 weeks gestation and there were no associations between antenatal or enrollment infections and gestational age, indicating that lower birthweights were likely the result of intrauterine growth retardation. Therefore, the associations with birthweight likely reflect the vulnerability of the placenta to parasitization during the first and early second trimesters, when placental pathology can disrupt the trajectory of fetal growth. Currently, with the exception of ITNs, antenatal malaria prevention is initiated during the second trimester owing to care-seeking customs, and the contraindication

to SP use in the first trimester.[33] Our data, taken together with similar findings in Benin,[20] suggest that the risk of LBW and placental malaria may be further reduced by initiating preventive measures earlier in pregnancy. This may be enhanced by recent changes to WHO's antenatal care guidelines which now recommend a minimum of eight antenatal care visits and encourage contacts at 13 weeks gestation in order to promote IPTp.[34]

Two additional points merit mention. The prevalence of antenatal subpatent infections remained largely unchanged, varying between 12 and 14% of women at each scheduled antenatal visit; this is in contrast to the prevalence of patent infections, which were most common at antenatal enrollment and uncommon thereafter, likely owing to the treatment of these RDT-positive women with DP. Although the direct effect of these subpatent infections on birth outcomes was not apparent in our study, ongoing gametocytemia may allow these women to remain reservoirs of overall malaria transmission. Secondly, the prevalence of placental malaria, as detected by microscopy, RDT, PCR, or histology, was 24% in the 242 women who tested negative by all methods at each visit; by comparison, the prevalence was 35% in women randomized to IPTp-SP in this study. This suggests that screening and treating in the second trimester, using any diagnostic method or treatment, will still result in a large proportion of women with placental infection. Therefore, prevention, using bednets and routine use of highly-effective prophylaxis or more effective antimalarials such as dihydroartemsinin-piperaquine for IPTp, may be more effective measures to reduce placental malaria.

In this cohort of pregnant Malawian women who were screened three to four times during the 2nd and 3rd trimester for malaria parasites using RDTs and who did not receive standard intermittent preventive antimalarial therapy, antenatal subpatent *P. falciparum* infections were common but not associated with adverse maternal or newborn delivery outcomes. In contrast, RDT-positive infections were associated with lower mean birthweights, and more LBW, and this association was already apparent at enrollment in the second trimester. These findings suggest that higher-density infections may account for the adverse sequelae of antenatal malaria infection, and that the prevention of these infections early in pregnancy may offer a new strategy to improve existing antenatal care programs in malaria-endemic Africa.

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Corresponding author:

Steve M Taylor

Box 102359 DUMC

Durham, NC 27710

Tel: 919-684-5815

FAX: 919-684-8902

steve.taylor@duke.edu

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Table 1. Impact of infections at enrollment and cumulative antenatal infections on placental histology among women with placental malaria

	Malaria pigment present, % (n)	Malaria pigment in free macrophages, % (n)	Malaria pigment within fibrin, % (n)	Intervillous inflammation leukocytes, % (n)			
				<5	6-10	11-25	>25
Infections at enrollment							
Not infected (n=123)	24.4 (30)	0.8 (1)	24.4 (30)	67.5 (83)	23.6 (29)	7.3 (9)	1.6 (2)
RDT-positive infection (n=168)	66.7 (112)	1.8 (3)	66.7 (112)	66.1 (111)	28.6 (48)	4.8 (8)	0.6 (1)
Subpatent infection (n=43)	20.9 (9)	0	20.9 (9)	65.1 (28)	32.6 (14)	2.3 (1)	0
p-value	< 0.001	0.558	< 0.001	0.650			
Cumulative antenatal infections							
Never infected (n=56)	8.9 (5)	1.8 (1)	10.7 (6)	66.1 (37)	26.8 (15)	7.1 (4)	0

RDT-positive infections (n=223)	61.0 (136)	1.4 (3)	61.0 (136)	66.4 (148)	26.9 (60)	5.4 (12)	1.4 (3)
Subpatent infections only (n=55)	18.2 (10)	0	16.4 (9)	67.3 (37)	29.1 (16)	3.6 (2)	0
p-value	< 0.001	0.647	< 0.001	0.899			

p-values computed using chi-squared tests. RDT: rapid diagnostic test for malaria parasites.

Figure 1. Prevalence of antenatal *P. falciparum* infections

A. Prevalence of uninfected women (green), RDT-positive infections (blue) and subpatent infections (turquoise) at enrollment, scheduled visits 1 (1st), 2 (2nd), and 3 (3rd), and unscheduled visits 1 (U1), 2 (U2), and 3 (U3). Width of columns is proportional to the number of women tested.

B. Distributions of the numbers of antenatal RDT-positive and subpatent infections.

Figure 2. Impacts of RDT-positive and subpatent infections at enrollment and cumulatively during pregnancy on continuous birth outcomes

g: grams; dL: deciliter; RDT: rapid diagnostic test for malaria parasites; CI: confidence interval. Differences are compared to uninfected women and were computed from pairwise comparisons of means using ANOVA. Details for the number of women contributing and the mean values are reported in Supplemental Tables 1 and 3.

Figure 3. Impacts of RDT-positive and subpatent infections at enrollment and cumulatively during pregnancy on dichotomous birth outcomes

Risk ratios computed with Poisson regression and adjusted for gravidity in the aggregated analysis. Subpatent infections were defined as RDT-negative and PCR-positive. LBW: low birth weight (< 2500g); SGA: small for gestational age; PT: preterm; RDT: rapid diagnostic test for malaria parasites. Maternal anemia defined as hemoglobin concentration < 11 grams/deciliter at delivery. Details for the number of women contributing, the number of events, and proportions are reported in Supplemental Tables 2 and 4.

Figure 1A

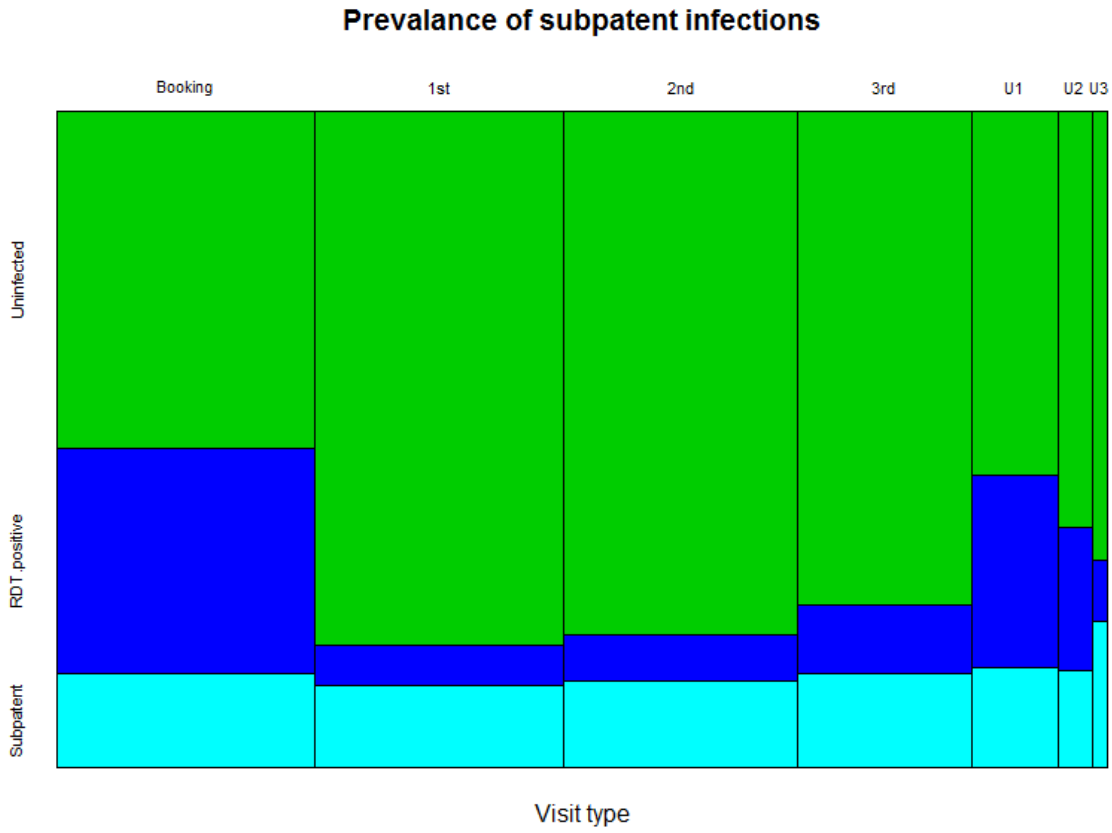


Figure 1B

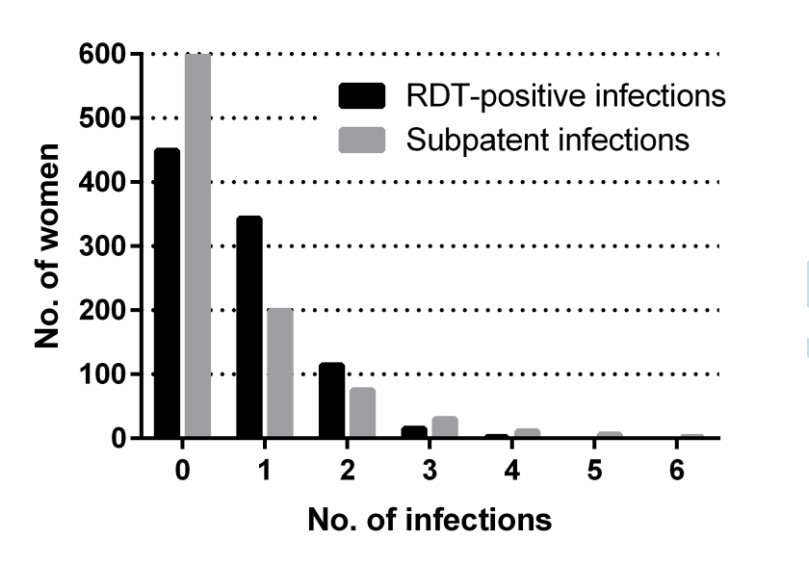


Figure 2

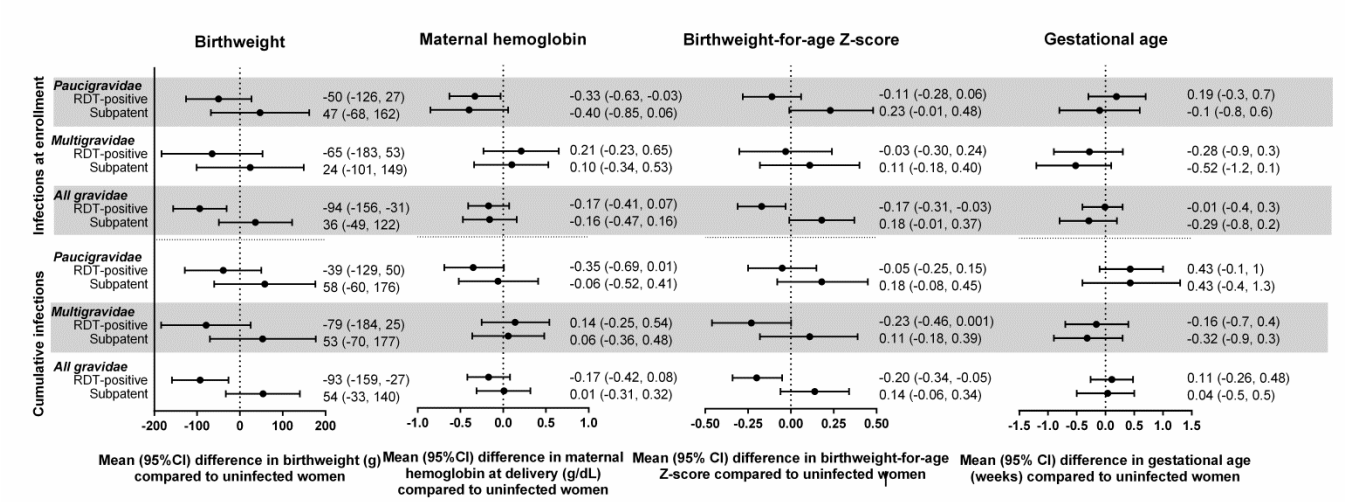
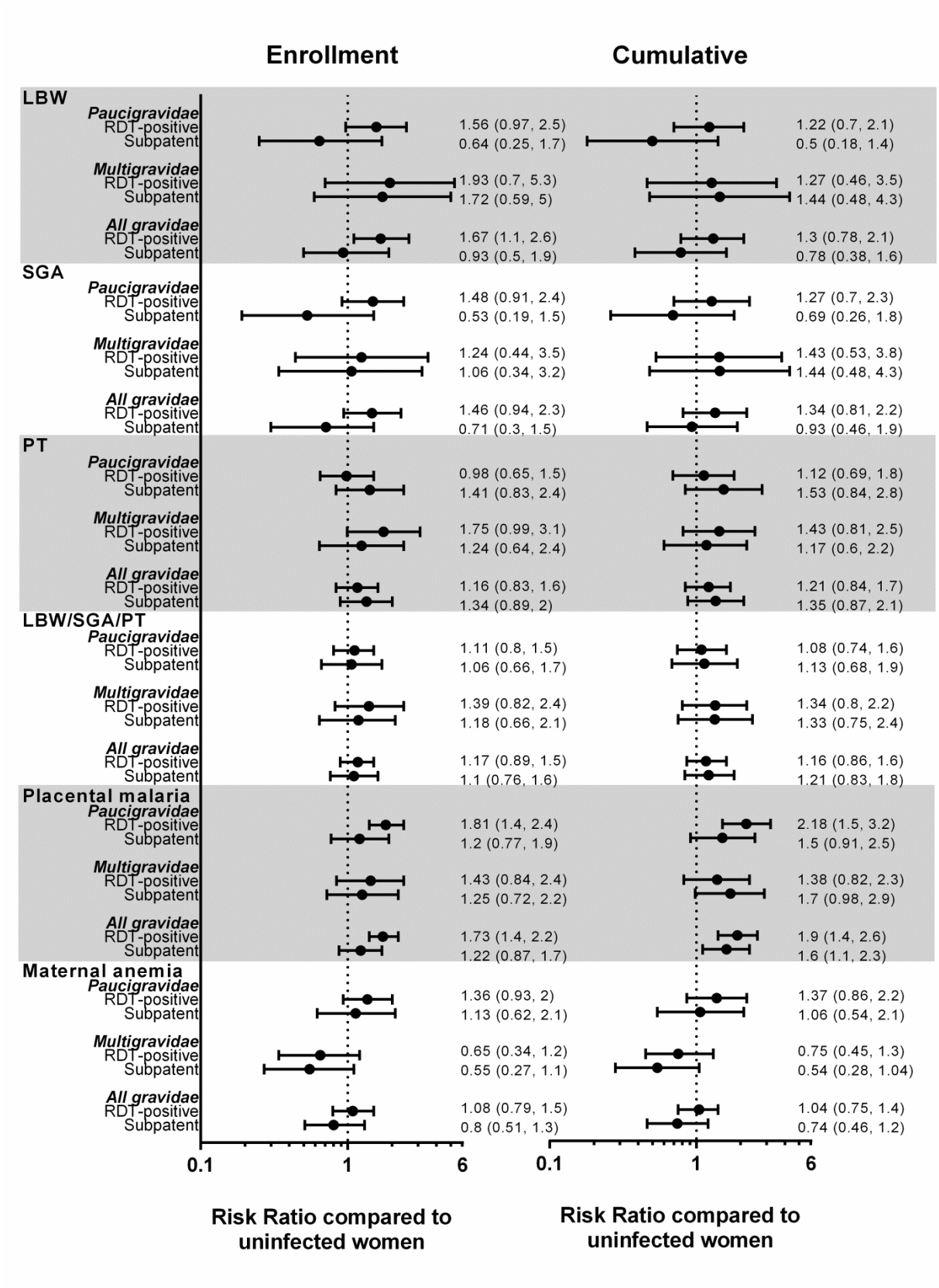


Figure 3


Enrollment
Cumulative
LBW
Paucigravidae
RDT-positive
1.56 (0.97, 2.5)
1.22 (0.7, 2.1)
Subpatent
0.64 (0.25, 1.7)
0.5 (0.18, 1.4)
Multigravidae
RDT-positive
1.93 (0.7, 5.3)
1.27 (0.46, 3.5)
Subpatent
1.72 (0.59, 5)
1.44 (0.48, 4.3)
All gravidae
RDT-positive
1.67 (1.1, 2.6)
1.3 (0.78, 2.1)
Subpatent
0.93 (0.5, 1.9)
0.78 (0.38, 1.6)
SGA
Paucigravidae
RDT-positive
1.48 (0.91, 2.4)
1.27 (0.7, 2.3)
Subpatent
0.53 (0.19, 1.5)
0.69 (0.26, 1.8)
Multigravidae
RDT-positive
1.24 (0.44, 3.5)
1.43 (0.53, 3.8)
Subpatent
1.06 (0.34, 3.2)
1.44 (0.48, 4.3)
All gravidae
RDT-positive
1.46 (0.94, 2.3)
1.34 (0.81, 2.2)
Subpatent
0.71 (0.3, 1.5)
0.93 (0.46, 1.9)
PT
Paucigravidae
RDT-positive
0.98 (0.65, 1.5)
1.12 (0.69, 1.8)
Subpatent
1.41 (0.83, 2.4)
1.53 (0.84, 2.8)
Multigravidae
RDT-positive
1.75 (0.99, 3.1)
1.43 (0.81, 2.5)
Subpatent
1.24 (0.64, 2.4)
1.17 (0.6, 2.2)
All gravidae
RDT-positive
1.16 (0.83, 1.6)
1.21 (0.84, 1.7)
Subpatent
1.34 (0.89, 2)
1.35 (0.87, 2.1)
LBW/SGA/PT
Paucigravidae
RDT-positive
1.11 (0.8, 1.5)
1.08 (0.74, 1.6)
Subpatent
1.06 (0.66, 1.7)
1.13 (0.68, 1.9)
Multigravidae
RDT-positive
1.39 (0.82, 2.4)
1.34 (0.8, 2.2)
Subpatent
1.18 (0.66, 2.1)
1.33 (0.75, 2.4)
All gravidae
RDT-positive
1.17 (0.89, 1.5)
1.16 (0.86, 1.6)
Subpatent
1.1 (0.76, 1.6)
1.21 (0.83, 1.8)
Placental malaria
Paucigravidae
RDT-positive
1.81 (1.4, 2.4)
2.18 (1.5, 3.2)
Subpatent
1.2 (0.77, 1.9)
1.5 (0.91, 2.5)
Multigravidae
RDT-positive
1.43 (0.84, 2.4)
1.38 (0.82, 2.3)
Subpatent
1.25 (0.72, 2.2)
1.7 (0.98, 2.9)
All gravidae
RDT-positive
1.73 (1.4, 2.2)
1.9 (1.4, 2.6)
Subpatent
1.22 (0.87, 1.7)
1.6 (1.1, 2.3)
Maternal anemia
Paucigravidae
RDT-positive
1.36 (0.93, 2)
1.37 (0.86, 2.2)
Subpatent
1.13 (0.62, 2.1)
1.06 (0.54, 2.1)
Multigravidae
RDT-positive
0.65 (0.34, 1.2)
0.75 (0.45, 1.3)
Subpatent
0.55 (0.27, 1.1)
0.54 (0.28, 1.04)
All gravidae
RDT-positive
1.08 (0.79, 1.5)
1.04 (0.75, 1.4)
Subpatent
0.8 (0.51, 1.3)
0.74 (0.46, 1.2)
0.1
1
6
0.1
1
6
Risk Ratio compared to uninfected women
Risk Ratio compared to uninfected women