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Effectiveness of intermittent preventive treatment with sulfadoxine–pyrimethamine during pregnancy on placental malaria, maternal anaemia and birthweight in areas with high and low malaria transmission intensity in Tanzania

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Abstract

OBJECTIVE To assess the effectiveness of IPTp in two areas with different malaria transmission intensities.

METHODS Prospective observational study recruiting pregnant women in two health facilities in areas with high and low malaria transmission intensities. A structured questionnaire was used for interview. Maternal clinic cards and medical logs were assessed to determine drug intake. Placental parasitaemia was screened using both light microscopy and real-time quantitative PCR.

RESULTS Of 350 pregnant women were recruited and screened for placental parasitaemia, 175 from each area. Prevalence of placental parasitaemia was 16.6% (CI 11.4–22.9) in the high transmission area and 2.3% (CI 0.6–5.7) in the low transmission area. Being primigravida and residing in a high transmission area were significant risk factors for placental malaria (OR 2.4; CI 1.1–5.0; $P = 0.025$) and (OR 9.4; CI 3.2–27.7; $P < 0.001$), respectively. IPTp was associated with a lower risk of placental malaria (OR 0.3; CI 0.1–1.0; $P = 0.044$); the effect was more pronounced in the high transmission area (OR 0.2; CI 0.06–0.7; $P = 0.015$) than in the low transmission area (OR 0.4; CI 0.04–4.5; $P = 0.478$). IPTp use was not associated with reduced risk of maternal anaemia or low birthweight, regardless of transmission intensity. The number needed to treat (NNT) was four (CI 2–6) women in the high transmission area and 33 (20–50) in the low transmission area to prevent one case of placental malaria.

CONCLUSION IPTp may have an effect on lowering the risk of placental malaria in areas of high transmission, but this effect did not translate into a benefit on risks of maternal anaemia or low birthweight. The NNT needs to be considered, and weighted against that of other protective measures, eventually targeting areas which are above a certain threshold of malaria transmission to maximise the benefit.

keywords IPTp-SP, placental malaria, anaemia, low birthweight

Introduction

Pregnancy-associated malaria (PAM) is an important cause of maternal and neonatal morbidity such as severe maternal anaemia, intrauterine growth retardation, low birthweight (LBW), premature delivery, intra-uterine death and stillbirth, and can lead to maternal or neonatal mortality (Desai *et al.* 2007). Apart from malaria, anaemia in pregnancy may be secondary to iron, folate and vitamin B deficiency, sickle cell diseases, HIV or helminthic, which may also lead to LBW (Savage *et al.* 2007).

The placenta is a preferred site for *Plasmodium falciparum* to accumulate and cause placental insufficiency due to sequestration, with deleterious consequences for both mother and foetus (Brabin *et al.* 2004). Placental parasitaemia, maternal anaemia and LBW are more frequent in areas with stable than unstable malaria transmission because of the considerably higher level of acquired malaria immunity among women (Nosten *et al.* 2004).

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Use of at least two doses of sulfadoxine–pyrimethamine (IPTp-SP) after quickening for intermittent preventive treatment during pregnancy has long been recommended by WHO for malaria control (WHO 2004). The IPTp regimen has recently been modified: it is now suggested that the first IPTp-SP dose to be administered as early as possible during second trimester and that each SP dose should be given at least a month apart until delivery (WHO 2012). There is a growing concern that IPTp-SP effectiveness may be jeopardised by the high degree of resistance of *P. falciparum* to SP, which is a major concern in East Africa and hence questions the viability of IPTp-SP use in this area (Menendez *et al.* 2008; Feng *et al.* 2010; Harrington *et al.* 2011). However, a meta-analysis by Kayentao *et al.* (2013) supports the beneficial effects of three or more doses of IPTp in reducing the risk of LBW.

With the reported significant decline of malaria in most areas of East Africa including Tanzania (O'meara *et al.* 2010; D'acremont *et al.* 2011), it becomes essential to evaluate the benefit of routine IPTp-SP, especially in areas with low malaria transmission. This may assist decision-making on the relevance of advocating universal IPTp in areas where SP adverse reactions may outweigh the benefit of the treatment. Little is known regarding effectiveness of IPTp-SP over other preventive measures for PAM morbidity in areas with low malaria transmission. The aim of this study was to assess the effect of IPTp on placental malaria, PAM morbidity and birth outcomes in areas with high and low malaria transmission intensity.

Methods

Study area

This observational study was carried out in Moshi municipal in northeastern Tanzania and in Rufiji District in the eastern, coastal area of the country. Moshi is a low malaria transmission area with a malaria prevalence of 1.0%, whereas Rufiji is a moderate to high malaria transmission area with prevalence of 20.8% (TACAIDS 2013). The prevalence of *P. falciparum* dihydropteroate synthase (Pfdhps) gene 581G mutation was 56% in infected malaria cases, according to an evaluation conducted 6 years ago in Tanga, a region adjacent to the two study areas (Alifrangis *et al.* 2009). This same area had a day 14 SP treatment failure rate as high of 68% among children (Gesase *et al.* 2009). Mawenzi Hospital in Moshi and Kibiti Health Centre (HC) in Rufiji were involved to recruit study participants. In 2012, malaria accounted for 4% of the total outpatient cases in Mawenzi Hospital and 51% in Kibiti Health Centre (MOH 2013). Both facilities are publicly owned and provide free antenatal care and delivery services. The standard of care and capacity to handle obstetric emergences in the two facilities are similar.

Study design

A prospective study was conducted from July to October 2012, enrolling pregnant women who came for delivery in Mawenzi Hospital and Kibiti HC obstetric wards. The selection criteria for recruiting participants were as follows: residency in the study area for at least 1 year, gestational age of 28 weeks and presence of up-to-date medical information. Cases of multiple pregnancies and severe conditions such as eclampsia were excluded. A structured questionnaire was used to interview women. Information from the mother's medical registry and Reproductive and Child Health (RCH) clinic card was used to verify and complement the generated information. In case of discrepancies on IPTp-SP status between RCH log and what the participant had reported, the participant's information was considered the truth after further interview to verify specifications of the reported medicine. Other recorded information included social-demographic characteristics, parity, ITNs use, history of malaria illness during pregnancy, use of haematinics and anthelmintic drugs. Gestational age was estimated based on the date of last normal menstrual period and compared with the estimated fundal height recorded during the first RCH booking. Low birthweight was defined as below 2500 g, preterm birth as gestational age below 37 weeks and maternal anaemia as a haemoglobin level below 11 g/dl. Placental malaria infection was defined as parasite positive results based on either blood slide smear reading or polymerase chain reaction (PCR) results.

Sample collection and examination

Placental blood was collected within 1 h after delivery. An incision was made on at least three sites of placenta on the maternal side, where accumulated intervillous blood was collected using a blunt syringe. About two drops of collected blood (about 100 μl) were spotted onto a 3MM® Whatman filter paper, air dried and preserved in plastic zipped locked bags for PCR genotyping. Filter papers were then transferred to the laboratory, and DNA was extracted using the Chelex® method (Plowe *et al.* 1995). The DNA was stored at −20 °C until further use. Malaria parasite positivity was determined by quantitative real-time PCR targeting the *P. falciparum* S-type gene as described by Wampfler *et al.* (2013).

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Thick and thin blood smears were also prepared and stained with Giemsa. Blood slides were examined independently by two experienced laboratory technicians using a light microscope. Discrepant findings were reviewed by a third technician until consensus on positivity was reached. Parasites in thick film fields were counted per 200 leukocytes, and the parasite count was multiplied by a factor of 40 to give parasites per μl of blood.

Statistical analysis

Data analysis was performed using STATA® 12.0 (Stata Corporation, College Station, TX, USA). Numerical variables were summarised into median and range. Categorical variables were summarised using cross-tabulation to estimate different proportion. The primary outcome was the proportion with placental malaria. The bivariable models included IPTp, maternal age, gravidity, transmission intensity level, history of malaria illness in pregnancy, HIV status and ITNs as explanatory variables. Variables associated with the outcome having a $P < 0.2$ in the bivariable model were retained in the final adjusted logistic regression model to estimate odds ratio (OR) and 95% confidence intervals (CI). The same method was performed for secondary outcomes, that is maternal anaemia and LBW.

The absolute risk reduction (ARR) was calculated to estimate difference between the risk of placental malaria in IPTp-SP exposure and non-exposure women. Number needed to treat (NNT) was estimated based on ARR (Schechtman 2002).

Ethics

Ethical approval for the study was granted by the Kilimanjaro Christian Medical University College (KCMUCo) Research Ethics Committee. Written informed consent was obtained from all participants.

Results

A total of 350 pregnant women were recruited and screened for placenta parasitaemia, 175 from the high malaria transmission area (Rufiji) and 175 from the low malaria transmission area (Moshi). There were no early maternal deaths or referrals to a tertiary health facility during the study period. At the time of recruitment, the mean maternal age was 25.2 years (standard deviation [SD] 6.9) and the mean gestational age 37.2 (SD 2.2) weeks. 319 (91%) recruited women reported to have used one or more dose of IPTp. The median (interquartile range [IQ]) gestational age when the first IPTp dose was administered was 24 weeks (19–32), and the median (IQ) gestational age at the second administration of IPTp dose was 30 weeks (24–36). The participants' main characteristics are presented in Table 1.

Prevalence of placental malaria and associated factors

Prevalence of placental malaria was 16.6% (29/175) in the high transmission area and 2.3% (4/175) in the low transmission area. In high malaria transmission area, the prevalence of placenta malaria was 8% (14/175) by light microscopy and 15.4% (27/175) by PCR, whereas in low transmission area, it was 1.1% (2/175) and 1.7% (3/175), respectively.

Table 1 Characteristics of study participants from the Moshi and Rufiji study sites

Characteristics	Moshi (n = 175) n (%)	Rufiji (n = 175) n (%)	Total 350 (%)
Age (years)			
<20	35 (20.0)	50 (28.6)	85 (24.3)
20–35	126 (72.0)	104 (59.4)	230 (65.7)
>35	14 (8.0)	21 (12.0)	35 (10.0)
Gravidity			
Primigravida	73 (41.7)	58 (33.1)	131 (37.4)
Multigravida	102 (58.3)	117 (66.9)	219 (62.6)
IPTp use			
Not at all	19 (10.9)	12 (6.9)	31 (8.9)
Single dose	66 (37.7)	72 (41.1)	138 (39.4)
≥Two doses	90 (51.4)	91 (52.0)	181 (51.7)
ITNs use			
Yes	161 (92.0)	170 (97.1)	331 (94.6)
No	14 (8.0)	5 (2.9)	19 (5.4)
HIV status			
Positive	8 (4.6)	4 (2.3)	12 (3.4)
Negative	160 (91.4)	171 (97.7)	331 (94.6)
No results	7 (4.0)	0 (0.0)	7 (2.0)
Haemoglobin level (g/dl)*	11.1 (1.7)	10.5 (1.4)	10.7 (1.6)
Parasite density (count/μl)*	18 (14.1)	269.9 (336.5)	238.4 (324.9)
Pregnancy outcome			
Birth outcome			
Live birth	172 (98.3)	172 (98.3)	344 (98.3)
Stillbirth	3 (1.7)	3 (1.7)	6 (1.7)
Birthweight			
≥2500 g	168 (96.0)	164 (93.7)	332 (94.9)
<2500 g	7 (4.0)	11 (6.3)	18 (5.1)
Gestational age at birth			
Term	149 (85.1)	150 (85.7)	174 (49.7)
Preterm	26 (14.9)	25 (14.3)	176 (50.3)

*Haemoglobin level and placenta parasite density presented in mean (SD).

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Details of variables associated with placental malaria by bivariable and logistic regression model are shown in Table 2. Women living in high transmission areas were nine times more likely to have placental malaria than those living in low transmission areas (adjusted OR 9.4; CI 3.2–27.7; $P < 0.001$). Primigravidae were twice as likely to have placental malaria as multigravidae (adjusted OR 2.4; CI 1.1–5.0; $P = 0.025$). There was no evidence of the association between placental malaria and HIV status or history of malaria during pregnancy.

Effectiveness of IPTp on placental malaria

In the high transmission area, of the 163/175 (93.1%) women who reported to have used at least one dose of IPTP, twenty-four (14.7%) were found to have placental malaria, while 139 (85.3%) had no placental malaria. Among the 12 of 175 (6.9%) who reported not to have used IPTp during their pregnancy, five (41.7%) were found to have placental malaria. In the low transmission area, of the 156/175 (89%) women who reported to have used at least one dose of IPTp, three (2.0%) were found to have placental malaria. Among the 19 (10.9%) who reported not to have used IPTp, one had placental malaria. In multivariate analysis, one dose or more of IPTp had 80% protective efficacy against placental malaria in the high transmission area (adjusted OR 0.2; CI 0.06–0.7; $P = 0.015$), and 60% protective efficacy in the low transmission area (adjusted OR 0.4; CI 0.04–4.5; $P = 0.478$) (Table 3a,b). There was no significant relationship between the number of IPTp doses taken and the prevalence of placental malaria in either high or low transmission area (Figure 1).

NNT with IPTp to prevent placental malaria

In the high transmission area, 24 of 163 women who used IPTp had placental malaria *vs.* five of 12 women who did not use IPTp. This gives an ARR of 27% for women to have placental malaria after using at least one dose of IPTp. Thus, in the high malaria transmission area, four (CI 2–6) pregnant women need to be treated with IPTp to prevent one case of placental malaria (NNT=1/0.27 = 3.7). By stratifying for gravidity, 14 of 54 primigravidae who used IPTp in the same transmission area had placental malaria *vs.* two of four primigravidae who did not use IPTp. Among multigravidae, 10 of 109 who used IPTp had placental malaria *vs.* three of eight women who did not use IPTp. The ARR in primigravida in this area was 24% (0.5–0.26 × 100) and 29%

Table 2 Strength of association between placental malaria and other factors

	Placental malaria					
Variable	Yes 33 (%)	No 317 (%)	Crude OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*†
Age (years)						
<25	14 (42)	146 (46)	0.9 (0.4–1.8)	0.860	2.5 (0.7–9.5)	0.164
≥25	19 (58)	171 (54)				
Gravidity						
Primigravidae	17 (52)	114 (36)	1.9 (0.9–3.9)	0.083	2.4 (1.1–5.0)	0.025
Multigravidae	16 (48)	203 (64)				
Transmission						
High	29 (88)	146 (46)	8.5 (2.9–24.7)	<0.001	9.4 (3.2–27.7)	<0.001
Low	4 (12)	171 (54)				
History of malaria						
Yes	6 (18)	62 (20)	0.9 (0.4–2.3)	0.849	1.1 (0.4–2.9)	0.846
No	27 (82)	255 (80)				
HIV status‡						
Positive	1 (3)	11 (4)	0.9 (0.1–7.0)	0.904	1.2 (0.1–11.2)	0.883
Negative	31 (97)	300 (96)				
ITNs use						
Yes	33	317	–	–	–	–
No	0	0				

*Adjusted for gravidity and area of malaria transmission.
†Estimated from the logistic regression model.
‡Seven women had no HIV results.

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Table 3 IPTp use in relation to placenta malaria, maternal anaemia and low birthweight in (a) high (b) low malaria transmission areas

Variable	Frequency		Crude OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*†
	Yes	No				
(a)						
Placental malaria	29 (%)	146 (%)				
IPTp use						
Yes	24 (82.8)	139 (95.2)	0.2 (0.1–0.8)	0.023	0.2 (0.1–0.7)	0.015
No	5 (17.2)	7 (4.8)				
Maternal anaemia‡	81 (%)	53 (%)				
IPTp use						
Yes	76 (93.8)	49 (92.5)	1.2 (0.3–4.8)	0.756	1.2 (0.3–4.9)	0.755
No	5 (6.2)	4 (7.5)				
Low birthweight	11 (%)	164 (%)				
IPTp use						
Yes	9 (81.8)	154 (93.9)	0.3 (0.1–1.5)	0.146	0.3 (0.1–1.5)	0.146
No	2 (18.2)	10 (6.1)				
(b)						
Placental malaria	4 (%)	171 (%)				
IPTp use						
Yes	3 (75.5)	153 (89.5)	0.4 (0.03–3.6)	0.378	0.4 (0.04–4.5)	0.478
No	1 (25.5)	18 (10.5)				
Maternal anaemia§	39 (%)	50 (%)				
IPTp use						
Yes	36 (92.3)	42 (84.0)	2.3 (0.7–9.3)	0.247	2.6 (0.6–10.7)	0.191
No	3 (7.7)	8 (16.0)				
Low birthweight	7 (%)	168 (%)				
IPTp use						
Yes	6 (85.7)	150 (89.3)	0.7 (0.1–6.3)	0.767	0.7 (0.1–6.4)	0.757
No	1 (14.3)	18 (10.7)				

*Adjusted for gravidity.
†Estimated from the logistic regression model.
‡No haemoglobin level information in 41 women.
§No haemoglobin level information in 86 women.

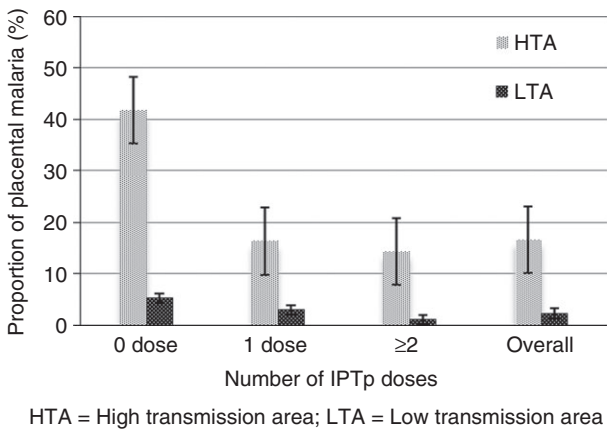


Figure 1 Prevalence of placental malaria in relation to IPTp doses taken in low and high malaria transmission areas. HTA, high transmission area; LTA, low transmission area.

(0.38–0.09 × 100) in multigravidae. Therefore, four (CI 2–4) primigravidae need to be treated in the high transmission area with at least one dose of IPTp to prevent one case of placental malaria (NNT = 1/0.24 = 4.2) *vs.* three (CI 3–11) for multigravidae (NNT = 1/0.29 = 3.4).

In the low transmission area, three of 156 women who used at least one dose of IPTp had placental malaria *vs.* one of 19 women who did not use IPTp. This gives an ARR of 3% (0.05–0.02 × 100). Therefore, in the low transmission area, 33 (CI 20–50) pregnant women need to be treated with at least a single dose of IPTp to prevent one case of placental malaria (NNT = 1/0.03 = 33.3). One of 69 primigravidae in the same transmission area had placental malaria, whereas there was none among those who did not use IPTp at all. For multigravidae in this transmission area, two of 87 who used IPTp had placental malaria *vs.* one of 15 of who did not use IPTp. The ARR in primigravidae in this area was less

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than 0 and for multigravidae, 4% (0.067–0.023 × 100). Therefore, 25 (CI 14–50) multigravidae need to be treated in the low transmission area with at least a single dose of IPTp to prevent one case of placental malaria (NNT = 1/0.04 = 25).

IPTp and maternal anaemia

A total of 223/350 (63.7%) study women had their haemoglobin concentration measured before delivery. The prevalence of maternal anaemia in the high transmission area was 60.4% (81/134; CI 51.6–68.8) and 43.8% (39/89; CI 33.3–54.7) in the low transmission area. Living in an area of high malaria transmission was associated with a significantly higher risk of maternal anaemia than living in low endemic area (adjusted OR 1.8; CI 1.0–3.2; $P = 0.036$) (Table 4). The prevalence of maternal anaemia in the high transmission area among women who used at least one dose of IPTp was 61% (76/125), similar to the 56% (5/9) among those who did not use IPTp (adjusted OR 1.2; CI 0.3–4.8; $P = 0.755$) (Table 3a). In the low transmission area, prevalence of anaemia was 46.2% (36/78) among women who used at least one dose of IPTp *vs.* 27.3% (3/11) among those who did not (adjusted OR 2.6; CI 0.6–10.7; $P = 0.191$) (Table 3b). Among other explanatory variables, placental malaria, gravidity, history of malaria infection during pregnancy, HIV status, anthelminthic and use of iron and folate supplementation at least a month during pregnancy period had no statistically significant effect on maternal anaemia (Table 4).

IPTp and low birthweight

The prevalence of LBW in the high transmission area was 6.3% (11/175; CI 3.2–11.0) *vs.* 4% (7/175; CI 1.6–8.1) in low transmission area (adjusted OR 1.7; CI 0.6–4.5; $P = 0.293$) (Table 5). The prevalence of LBW in the high transmission area among women who used at least one dose of IPTp was 5.5% (9/163) *vs.* 16.7% (2/12) for those who did not (adjusted OR 0.3; CI 0.1–1.5; $P = 0.146$) (Table 3a). The prevalence of LBW in the low transmission area among women who used at least one dose of IPTp was 3.8% (6/156) *vs.* 5.3% (1/19) for

Table 4 Strength of association between maternal anaemia and other factors

	Anaemia					
Variable	Yes 120 (%)	No 103 (%)	Crude RR (95% CI)	*P*	Adjusted RR* (95% CI)	*P*†
Placental malaria						
Infected	20 (16.7)	10 (9.7)	1.9 (0.8–4.2)	0.133	1.5 (0.6–3.4)	0.362
Not infected	100 (83.3)	93 (90.3)				
Gravidity						
Primigravidae	42 (35.0)	44 (42.7)	0.7 (0.4–1.2)	0.238	0.7 (0.4–1.3)	0.261
Multigravidae	78 (65.0)	59 (57.3)				
Transmission						
High	81 (67.5)	53 (51.5)	2.0 (1.1–3.4)	0.015	1.8 (1.0–3.2)	0.036
Low	39 (32.5)	50 (48.5)				
History of malaria						
Yes	24 (20.0)	19 (18.4)	1.1 (0.6–2.1)	0.769	1.1 (0.6–2.2)	0.737
No	96 (80.0)	84 (81.6)				
HIV status‡						
Positive	4 (3.4)	4 (3.9)	0.9 (0.2–3.5)	0.835	0.9 (0.2–3.9)	0.912
Negative	115 (96.6)	99 (96.1)				
Iron and folates§						
Yes	105 (88.2)	91 (89.2)	0.8 (0.4–2.1)	0.819	0.8 (0.3–1.8)	0.552
No	14 (11.8)	11 (10.8)				
Anthelminthic						
Yes	108 (90.0)	89 (86.4)	0.3 (0.4–1.2)	0.406	1.1 (0.5–2.6)	0.804
No	12 (10.0)	14 (13.6)				

*Adjusted for placental malaria and transmission intensity.
†Estimated from the logistic regression model.
‡One woman had no HIV result.
§Missing iron and folate use information in two women.

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Table 5 Strength of association between low birthweight and other risk factors

Risk factor	Low birthweight: Yes 18 (%)	Low birthweight: No 332 (%)	Crude RR (95% CI)	*P*	Adjusted RR* (95% CI)	*P*†
Placental malaria						
Infected	3 (16.7)	30 (9.0)	2.0 (0.6–7.4)	0.290	2.1 (0.6–7.5)	0.279
Not infected	15 (83.3)	302 (91.0)				
Gravidity						
Primigravida	7 (38.9)	124 (37.3)	1.1 (0.4–2.8)	0.895	1.1 (0.4–3.1)	0.809
Multigravida	11 (61.1)	208 (62.7)				
Transmission						
High	11 (61.1)	164 (49.4)	1.6 (0.6–4.3)	0.337	1.7 (0.6–4.5)	0.293
Low	7 (38.9)	168 (50.6)				
History of malaria						
Yes	6 (33.3)	62 (18.7)	2.2 (0.8–6.0)	0.134	2.2 (0.8–6.1)	0.130
No	12 (66.7)	270 (81.3)				

*Adjusted for history of malaria.
†Estimated from the logistic regression model.

those who did not (adjusted OR 0.7; CI 0.1–6.4; $P = 0.757$) (Table 3b). Among other explanatory variables, placental malaria, gravidity, history of malaria infection during pregnancy, HIV status, anthelminthic and use of iron and folate supplementation at least a month during pregnancy period had no statistically significant effect on the risk of LBW (Table 5).

Discussion

To our knowledge, the present study is the first to evaluate the effectiveness of IPTp in relation to placental malaria in areas with different malaria transmission intensities and high parasite resistance to SP. The evaluation takes into account other malaria preventive measures such as ITNs, and other preventive measures against maternal anaemia such as routine anthelminthic, iron and folate supplementation. The study responded to a call from WHO that emphasised the importance of enhanced regular monitoring of IPTp effectiveness (WHO 2012).

Overall 9% prevalence of placental malaria in this study corresponds to 8% prevalence which was observed 9 years ago in Ifakara, another part of the country (Kabanywanyi *et al.* 2008). It shows that malaria in pregnancy is still an important health issue in Tanzania that needs to be addressed by effective preventive measures. Self-reporting of ITNs use by 95% of pregnant women is encouraging considering the reported ITNs efficacy of 23% against placental parasitaemia, 33% against miscarriage/stillbirth and 23% against LBW according to a systematic reviews of randomised trials (Gamble *et al.* 2007). The possibility of overestimating ITNs use in the present study cannot be excluded due to self-reporting as the participant may try to please the interviewer. In the present study, all women with placental malaria reported to have used ITNs, which precludes any effectiveness calculation. Our assessment of IPTp effectiveness applies thus only in condition of full ITN coverage.

Use of IPTp was associated with protection against placental malaria in all study areas. The study findings agree with previous studies and reviewed evidence of IPTp to reduce the risk of placental malaria (Hommerich *et al.* 2007; Kayentao *et al.* 2013). There was no IPTp dose-dependent relationship to reduced risk of placental malaria. The latter is opposite to what was reported by Kayentao *et al.* (2013) in a systematic review that risk of placental infection decreases with increased number of IPTp doses. However, our study was not powered to determine the effect of increasing dose on placental malaria. The time interval between the last IPTp administrated dose and screening for placental malaria may be a stronger determinant for detecting parasitaemia rather than the cumulative number of doses a woman received during her pregnancy. This is essential to consider, particularly in high transmission areas, where the daily likelihood for a woman to have infectious mosquito bites is higher.

Due to the observed significant risk of having placental malaria when living in a high transmission area, the value for money of IPTp was much higher in areas of high transmission intensity, with only one-eighth of the number of women treated with at least one dose of IPTp required to avert on case of placental malaria compared to the low transmission area. Because of the known

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higher risk of placental malaria in primigravidae, we attempted to estimate the NNT in this group *vs.* the multigravida ones in both areas, but the small sample size and uneven representation of the exposure groups, both being potential biases of the study, did not allow meaningful results. In view of the importance to determine NNT in other malaria interventions in pregnancy such as ITN use, 18 and 50 pregnant women are the NNT with ITN to prevent at least one placental malaria case and an LBW case, respectively, as observed in a randomised trial of ITN in high malaria transmission area in Kenya (ter Kuile *et al.* 2003). The NNT should be more regularly used as criterion to prioritise interventions, especially so in moderate to low transmission areas. This estimation is essential in an era of declining malaria.

The primary aim of malaria preventive measures in pregnancy is to prevent deleterious effects of malaria in woman and the baby. The usual concept is that IPTp reduces maternal parasitaemia and hence maternal anaemia, placental malaria and LBW. IPTp effectiveness was challenged by Harrington *et al.* (2011) who conducted a study in Muheza, Tanzania, an area known to have high SP resistance, where IPTp neither lowered the risk of placental malaria nor had reduced maternal anaemia or LBW. A further challenging finding was reported by Gutman *et al.* (2013) in Malawi, which showed that IPTp did not reduce the frequency of placental malaria but was associated with improved birth outcomes. We found that IPTp did reduce placental malaria, but had no effect on maternal anaemia. For LBW, there was still a beneficial but insignificant effect, probably due to the low rate in both study areas. Women who delivered at home may have had an adverse outcome, but our study had the limitation of recruiting at delivery. However, inconsistences of IPTp effectiveness on improving maternal anaemia and LBW have also been reported in a systematic review by McClure *et al.* (2013). It is likely that malaria is only one of the important contributors of maternal anaemia and LBW in developing countries. Hence it will be essential in the coming years to monitor the changes in maternal malaria morbidity and the dynamic of LBW rates in areas of declining malaria transmission to better understand the roles of malaria, malnutrition, other infections and social-economic factors on maternal and baby outcomes.

Conclusion

The study shows that IPTp was associated with a lower rate of placental malaria, but this effect did not translate into protection against maternal anaemia and low birthweight. The NNT may suggest IPTp as an appropriate malaria control intervention, at least in areas with high level of malaria transmission. IPTp benefit is questionable in areas of low transmission. The NNT should be regularly evaluated in different level of malaria transmission and parasite resistance, different geographic settings and on both mother and infant outcomes to best maximise benefit at reasonable costs.

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