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Individual efficacy of intermittent preventive treatment with sulfadoxine–pyrimethamine in primi- and secundigravidae in rural Burkina Faso: impact on parasitaemia, anaemia and birth weight

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Summary

OBJECTIVE To assess the efficacy at individual level of intermittent preventive treatment with sulfadoxine–pyrimethamine (IPTp-SP) in primi- and secundigravidae in rural Burkina Faso.

METHODS Data of 1441 women enrolled in a health centre randomized trial and delivering a live-singleton between September 2004 and October 2006 were analysed at individual level. Prevalence of peripheral and placental parasitaemia, anaemia (PCV <33%), low-birth weight (<2500 g; LBW), mean packed cell volume (PCV) and birth weight were compared in relation to the number of directly observed SP doses.

RESULTS Two or more doses of SP significantly reduced the risk of placental parasitaemia [adjusted odds ratio (AOR) = 0.04, 95%CI = 0.003–0.60, $P = 0.023$] and anaemia at delivery (AOR = 0.31, 95%CI = 0.18–0.52, $P < 0.001$). IPTp was associated with reduced risk of LBW in primigravidae (AOR = 0.11, 95%CI = 0.07–0.17, $P < 0.001$) but not secundigravidae (AOR = 0.70, 95%CI = 0.26–1.91, $P = 0.452$). For each increment in number of SP doses mean PCV increased by 1.0% (95%CI = 0.4–1.7, $P = 0.005$) at 32 weeks gestation, by 1.2% (95%CI = 0.2–2.2, $P = 0.025$) at delivery and mean birth weight by 220 g (95%CI = 134–306 $P < 0.001$) in primigravidae and by 102 g (95%CI = 55–148, $P = 0.001$) in secundigravidae.

CONCLUSION The risk of malaria infection was significantly reduced by IPTp with SP in primi- and secundigravidae in rural Burkina Faso. The impact on clinical outcomes is lower and mainly limited to primigravidae for LBW. Incomplete uptake of IPTp-SP and limited effect in low risk groups together may substantially dilute the measurable impact of effective interventions. This needs to be taken into account when evaluating interventions at community level.

keywords malaria, pregnancy, birth weight, intermittent preventive treatment, sulfadoxine–pyrimethamine, Burkina Faso

Introduction

Intermittent preventive treatment for pregnant women (IPTp) is a key component of malaria control in pregnancy recommended by WHO (2004) for areas with stable *Plasmodium falciparum* transmission. Every year, about 10 000 maternal and 75 000–200 000 infant deaths are estimated to be associated with pregnancy-malaria (Guyatt & Snow 2001; Steketee *et al.* 2001), making malaria prevention in this risk group a global health priority (WHO 2003, 2004). Only sulfadoxine–pyrimethamine (SP), given twice at scheduled antenatal visits after quickening, is currently recommended for IPTp in Africa (WHO 2004). The goal is a coverage of 80% of pregnant women in endemic areas receiving at least two doses of IPTp-SP (WHO 2005).

The main adverse effects of malaria infection in pregnancy are maternal anaemia and low-birth weight (LBW), both related to the sequestration of *P. falciparum* in the placenta and more frequent and severe in primigravidae

(PG) (Brabin 1983). IPTp-SP effectively reduces severe anaemia, peripheral and placental malaria and LBW in PG and secundigravidae (SG) (Schultz *et al.* 1994; Parise *et al.* 1998; Verhoeff *et al.* 1998; Shulman *et al.* 1999), but not in multigravidae (Mbaye *et al.* 2006). However, in recent program evaluations, the impact on maternal anaemia and birth weight was lower than expected despite a significant reduction of malaria infections (Sirima *et al.* 2006; Hommerich *et al.* 2007; Ramharter *et al.* 2007). This may be explained by the inadequate coverage of women receiving the required two doses, possibly due to late antenatal clinical attendance and to weaknesses within the health system (Van Eijk *et al.* 2004b; Hill & Kazembe 2006).

In Burkina Faso, the majority of pregnant women attend antenatal clinics at least once, but only one-fifth during the first trimester (Ministère de la Santé 2006a). Malaria prevention in pregnancy was based on weekly chloroquine (CQ) until the introduction of IPTp-SP in 2006.

Between 2004 and 2006, the impact of a village-based promotional campaign to enhance antenatal clinic (ANC) attendance and IPTp-SP uptake was evaluated in a community-based trial where health centres (HC) were randomised to one of three arms, i.e. IPTp-SP with health promotion, IPTp-SP without promotion and weekly CQ. Despite a significant increase in IPTp-SP coverage, haematological and birth weight outcomes did not differ between IPTp-SP arms with and without promotion (Gies *et al.* 2008). Therefore we analysed the impact of IPTp-SP at individual level.

Methods

Study site and population

The study was conducted between 2004 and 2006 in Boromo Health District (BHD), western Burkina Faso, where malaria is holoendemic with highly seasonal transmission during and shortly after the rains (June–December). In 2003, treatment failure with SP in children was 8.2% in a comparable area in Burkina Faso (Tinto *et al.* 2007).

The design of the main study has been described in detail elsewhere (Gies *et al.* 2008). Briefly, 12 peripheral HCs were selected for a community-based trial on IPTp-SP effectiveness and the additional benefit of a promotional campaign. In eight of them IPTp-SP was introduced at ANC while the remaining HCs offered weekly CQ according to the national policy at that time. Within the catchment areas of four HCs specially targeted promotional activities to enhance ANC attendance and SP uptake were conducted (Gies *et al.* 2009).

Data collection

All pregnant women were identified by women field assistants through monthly rounds in the villages and PG and SG were enrolled. Information on sociodemographical characteristics and on the current pregnancy was collected at enrolment and at follow-up visits (32 weeks of gestation and delivery) using structured questionnaires. Intake of SP tablets was supervised by ANC providers and recorded on study questionnaires. A blood sample for parasitaemia and packed cell volume (PCV) was drawn by finger-prick around 32 weeks of gestation and at delivery. Whenever possible a smear was prepared from a swabbed piece from the maternal side of the placenta. Newborns were weighed to the nearest 25 g as soon as possible after birth using a hanging scale; weights obtained 1–8 days after delivery were corrected for physiological changes (Gies *et al.* 2008).

Laboratory investigations

Thick blood films and methanol-fixed placental smears were stained with 10% Giemsa and examined by two independent technicians. For peripheral blood, parasite density was determined by counting asexual forms of the parasite per 200 white blood cells (WBC) assuming 8000 WBC/μl. Parasite density for placental smears was expressed as the percentage of infected red blood cells (RBC) over the total number of RBC after counting at least 1000 RBC. Heparinised capillary tubes containing whole blood were centrifuged within 48 h after collection and PCV read. For each sample, two capillaries were filled from the same finger prick to allow for losses due to transport.

Main variables and definitions

Main outcome variables are malaria infection, anaemia and birth weight. Malaria infection: asexual *P. falciparum* parasites of any density, in a thick film (peripheral parasitaemia) or a placental smear (placental parasitaemia). Anaemia: PCV <33%; moderate to severe anaemia: <30%; severe anaemia: <24%; LBW: <2500 g. Explanatory variables and possible confounders include number of SP doses (0, 1, ≥2), parity, maternal age (≤19, >19), season, socio-economic status (SES), bed net use, distance from HC (≤5 km; >5 km), and sex of newborn. Season compares the high (July–December) and low malaria transmission period (January–June). SES, graded as most poor, poor, less poor and least poor, is derived from household assets using principal component analysis (Filmer & Pritchett 2001; Schellenberg *et al.* 2003). As information about bed net use the previous night could not be reliably collected, bed net ownership assessed at enrolment was used.

Data analysis

Access 2003 was used for double data entry and validation and EpiInfo 2000 (version 3.2.2; Centers for Disease Control and Prevention, Atlanta, GA, USA) and STATA (Intercooled version 10; Stata Corp., College Station, TX, USA) software packages were used for the analysis. All analyses take into account the cluster randomized design of the initial survey using linearised variance estimations with HC as the primary sampling unit (svy setup in STATA). Linear regression models were used to compare mean values of birth weight and PCV while logistic regression models to compare prevalence of malaria infection, anaemia and LBW, and to determine odds ratios. The criterion for statistical significance was set at alpha = 0.05.

The effect of the frequency of IPTp on parasitaemia, anaemia and LBW was examined in multivariable logistic regression models. Parity, maternal age, SES, bed net ownership, season and distance were identified as potential confounders of the association between number of SP doses and parasitaemia or anaemia. Education and place of delivery were not associated with parasitaemia or anaemia. As PG are known to deliver lighter babies than SG, the analysis of LBW was stratified by parity. Potential confounders of the association of number of SP doses and LBW were maternal age, SES, bed net ownership, season, distance and gender of the newborn. Linear regression was used to assess the adjusted effect of IPTp-SP doses on mean PCV and on mean birth weight. All analyses were restricted to normal deliveries of live singletons in the catchment areas of the eight HCs that introduced IPTp-SP in April 2004. Blood samples taken after delivery are excluded from analyses of anaemia and parasitaemia at delivery. Pregnancies of more than 4 months duration when the study started (defined by a delivery date prior to September 1st 2004) were excluded *a priori* from the analysis (Figure 1).

Ethical considerations

Local health authorities and community leaders were informed about the study objectives and procedures for data collection. All study participants gave informed consent after explanation of the procedures in the local language. Women found to be parasitaemic or anaemic at 32 weeks or at delivery were offered antimalarial treatment (quinine) and extra haematinics according to national guidelines. The study was approved by the Burkina Faso Ministry of Health and the Ethical Committee at the Institute of Tropical Medicine, Antwerp.

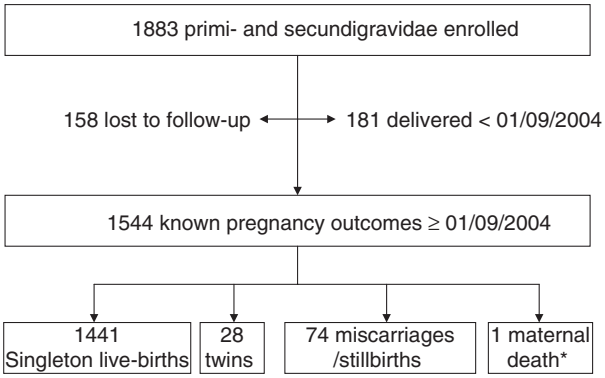

Figure 1 Enrolment of study participants and delivery outcomes (IPTp-SP study arms only). *From meningitis.

Results

Study participants

A total of 1883 women were enrolled of whom 1544 (82%) were followed until the end of pregnancy (Figure 1). Women lost to follow-up (8.4%; 158) and women not included into the analysis (9.6%; 181) did not differ in parity and age from women included. Most women (93.3%) delivered live singletons, 28 (1.8%) gave birth to twins, and 74 (4.8%) experienced a miscarriage or stillbirth. The general characteristics of the study participants are presented in Table 1. Bed nets were available in one of three households (35.5%), most of them not treated with insecticide (85%). No or incomplete IPTp (<2 doses) was associated with younger age, parity (more often PG), no bed net ownership and distance to the HC (>5 km).

Antenatal clinic attendance was high with 95.3% of women visiting the ANC at least once and a median number of three visits per woman (range: 0–6). At 32 weeks of gestation, the majority (90%; 1070/1177) had received at least one dose of SP. At delivery, 37 (2.4%) women had received three or more doses of SP, 871 (56.4%) two doses, 531 (34.4%) one dose and 105 (6.8%) no SP at all.

Number of IPTp-SP doses and peripheral/placental parasitaemia

Information on malaria infection is available for 1174 (81%) women at around 32 weeks of gestation and for 922 (64%) at delivery. Overall, about one of five (32 weeks: 20.0%; delivery: 18.3%) blood films showed evidence of malarial infection, all *P. falciparum*. The prevalence of placental malaria was 19.2% (170/886), most of it

Table 1 Baseline characteristics of primi- and secundigravidae with singleton live-births, Boromo, Burkina Faso, 2004–2006

Characteristic*, % (*n*)	0 doses SP (*n* = 81)	1 dose SP (*n* = 483)	≥2 doses SP (*n* = 877)
Age ≤ 19 years †	65.4 (53)	59.1 (285)	48.9 (429)
Primigravida†	60.5 (49)	59.2 (286)	52.9 (464)
Any formal education	14.8 (12)	19.5 (94)	23.8 (208)
Single‡	9.9 (8)	5.0 (24)	4.7 (41)
Husband farmer or breeder	93.7 (74)	92.7 (446)	90.3 (791)
Socio-economic status †			
Most poor	27.3 (21)	19.4 (93)	17.4 (151)
Poor	31.2 (24)	28.6 (137)	21.2 (184)
Less poor	26.0 (20)	27.4 (131)	25.8 (224)
Least poor	15.6 (12)	24.6 (118)	35.8 (311)
Bednet ownership †	33.3 (27)	30.0 (144)	38.8 (340)
Distance to HC >5 km †	76.5 (62)	39.8 (192)	23.0 (202)
Delivery in HC †	17.3 (14)	56.3 (272)	72.5 (636)
Delivery in high transmission season †	47.4 (37)	60.0 (289)	43.4 (381)
Male sex of baby	50.6 (41)	51.0 (246)	50.0 (435)
Trimester of 1st ANC (if ANC >0)	*n* = 22	*n* = 479	*n* = 877
1st trimester	18.2 (4)	5.4 (26)	13.0 (114)
2nd trimester	72.7 (16)	47.4 (227)	75.8 (665)
3rd trimester	9.1 (2)	47.2 (226)	11.2 (98)
Median (IQR) GA at 1st IPTp-SP dose (in weeks)	–	22 (19–25)	20 (17–23)

HC, health centre; ANC, antenatal clinic; IPTp, intermittent preventive treatment in pregnancy; SP, sulfadoxine–pyrimethamine; IQR, interquartile range; GA, gestational age.
*Varying denominators due to missing values for age (*n* = 1), school (*n* = 2), income (*n* = 6), bednet (*n* = 3), husband's profession (*n* = 5), SES (*n* = 15), GA 1st ANC (*n* = 3).
†Significant differences between groups ($P < 0.05$).
‡Never married, divorced or widowed.

observed during the rainy season (90.6%) and in PG (67.1%).

The use of IPTp-SP was associated with a significantly lower risk of peripheral and placental infection (Figure 2). At 32 weeks, one IPTp-SP dose reduced the risk of infection by 62% ($P < 0.001$) and two doses by 90% ($P < 0.001$) as compared to no IPTp-SP (Table 2). Similarly, at delivery, compared to no IPTp-SP, one IPTp-SP dose reduced the risk of peripheral infection by 77% ($P = 0.059$) and of placental infection by 86% ($P = 0.110$), while with two IPTp-SP doses, the risk of peripheral infection was reduced by 94% ($P = 0.004$) and that of placental infection by 96% ($P = 0.023$). The latter was significant despite the small number of women with no previous SP intake who had a placenta sample taken (9/81). Two IPTp-SP doses were significantly better than one IPTp-SP dose for infection at 32 weeks (AOR 0.26, 95%CI 0.14–0.49, $P = 0.001$), at delivery (AOR 0.27, 95%CI 0.21–0.35, $P < 0.001$) and for placental malaria (AOR 0.30, 95%CI 0.22–0.40, $P < 0.001$).

Number of IPTp-SP doses and haematological status (PCV and anaemia)

Packed cell volume was measured at 32 weeks of gestation in 1124 (78%) women and at delivery in 792 (55%) women. Mean PCV at 32 weeks was 32.4% (95%CI 31.9–32.8) and increased towards the end of pregnancy with 34.8% (95%CI 33.8–35.8) at delivery (Figure 3). With each dose of IPT-SP (≥2 doses grouped together), the adjusted mean PCV increased by 1.0% (95%CI 0.4–1.7, $P = 0.005$) at 32 weeks and by 1.2% (95%CI 0.2–2.2, $P = 0.025$) at delivery.

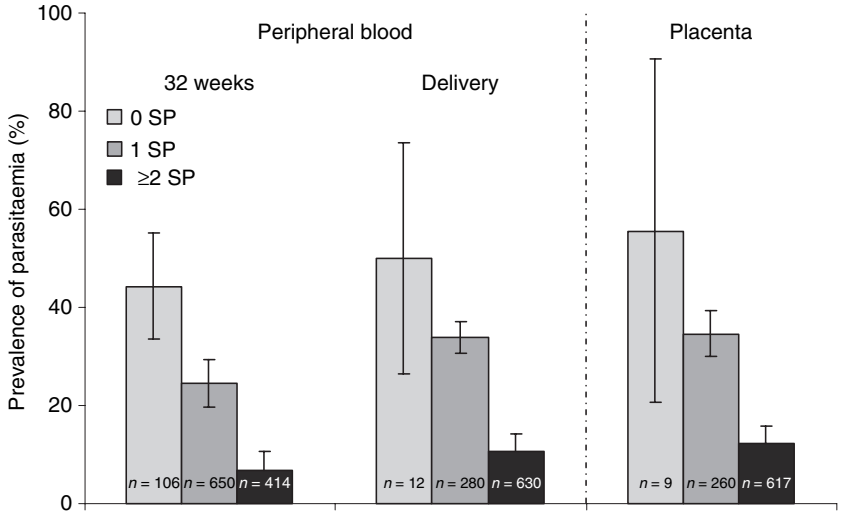

Figure 2 Prevalence of malarial infection in primi-and secundigravidae by frequency of SP doses, Boromo, Burkina Faso, 2004–2006. Error bars represent 95% confidence intervals.

Table 2 Efficacy of IPTp-SP on peripheral and placental parasitaemia in primi- and secundigravidae, Boromo, Burkina Faso, 2004–2006

	Peripheral parasitaemia						Placental parasitaemia		
	32 weeks (n = 1156)			Delivery (n = 915)			(n = 878)		
	AOR†	(95%CI)	P-value	AOR‡	(95%CI)	P-value	AOR§	(95%CI)	P-value
Frequency of IPTp-SP									
≥2 doses	0.10	(0.04–0.24)	<0.001	0.06	(0.01–0.33)	0.004	0.04	(0.003–0.60)	0.023
1 dose	0.39	(0.27–0.55)	<0.001	0.23	(0.05–1.07)	0.059	0.14	(0.01–1.67)	0.110
0 doses	1	(Ref)		1	(Ref)		1	(Ref)	

Multivariable analysis using survey logistic regression adjusted for age, parity, socio-economic status, bed net ownership, season and distance.
AOR, adjusted odds ratio; CI, confidence interval; IPTp-SP, intermittent preventive treatment with sulfadoxine-pyrimethamine.
†≥Two doses *vs.* one dose: AOR 0.26 95%CI 0.14–0.49, P = 0.001.
‡≥Two doses *vs.* one dose: AOR 0.27 95%CI 0.21–0.35, P < 0.001.
§≥Two doses *vs.* one dose: AOR 0.30 95%CI 0.22–0.40, P < 0.001.

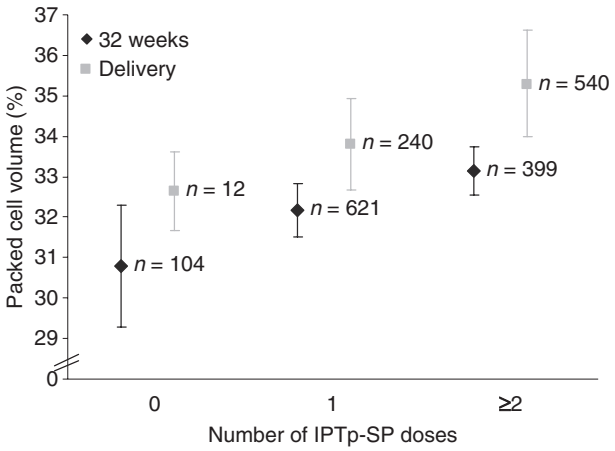

Figure 3 Mean PCV values of primi- and secundigravidae by number of previous SP doses during pregnancy and at delivery, Boromo, Burkina Faso, 2004–2006. Error bars represent 95% confidence intervals.

Overall, almost half of the women (48.8%) were anaemic (PCV <33%) around 32 weeks of gestation and 30.9% at delivery. Moderate to severe anaemia (PCV <30%) was found in 25.4% at 32 weeks and in 16.3% at delivery. The prevalence of anaemia at any cut-off point decreases with increasing number of IPTp-SP doses (Figure 4). One or more IPTp-SP doses reduced the risk of anaemia both at 32 weeks and at delivery (Table 3) though statistical significance is not reached for all categories.

Number of IPTp-SP doses and birth weight

Among singleton live-births, mean birth weight increased with increasing number of SP doses from 2563 g (95%CI

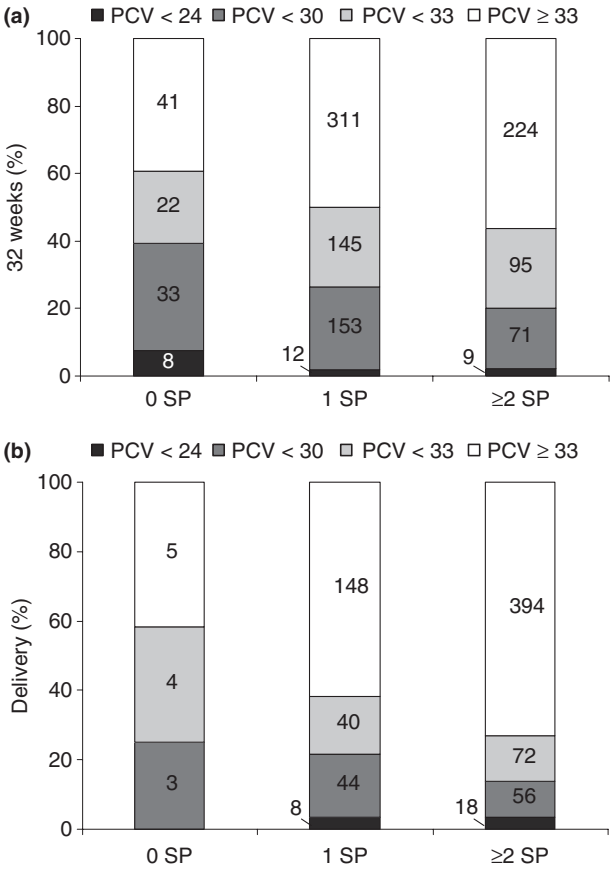

Figure 4 Proportional distribution of PCV by number of IPTp doses during pregnancy (a) and at delivery (b) in primi- and secundigravidae, Boromo, Burkina Faso, 2004–2006. Numbers in bars represent number of women in corresponding category.

Table 3 Efficacy of IPTp-SP on anaemia during pregnancy and at delivery by number of SP doses, Boromo, Burkina Faso, 2004–2006

	32 weeks (n = 1110)			Delivery (n = 787)		
	PCV <33% AOR (95%CI)	PCV <30% AOR (95%CI)	PVC <24% AOR (95%CI)	PCV <33% AOR (95%CI)	PCV <30% AOR (95%CI)	PVC <24%* AOR (95%CI)
Frequency of IPTp-SP						
≥2 doses	0.50 (0.24–1.05)	**0.37** (0.22–0.61)	**0.24** (0.08–0.78)	**0.31** (0.18–0.52)	0.46 (0.09–2.37)	1.07 (0.35–3.34)
1 dose	0.60 (0.35–1.02)	**0.51** (0.36–0.72)	**0.17** (0.06–0.53)	**0.47** (0.28–0.81)	0.76 (0.18–3.28)	1 (Ref.)
0 doses	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	–

Multivariable analysis using survey logistic regression adjusted for age, parity, socio-economic status, bed net ownership, season and distance. Significant odds ratios are presented in bold.
PCV, packed cell volume; AOR, adjusted odds ratio; CI, confidence interval; IPTp-SP, intermittent preventive treatment with sulfadoxine-pyrimethamine.
*Reference group set at 1 dose of SP because no woman with 0 doses and complete data had a PCV <24%.
≥Two doses *vs.* one dose at any cut-off point: not significant.

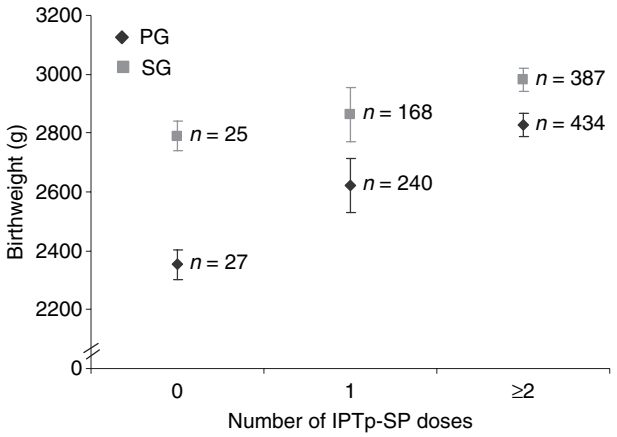

Figure 5 Mean birth weight of live-born singletons by number of SP doses received during pregnancy for primigravidae (PG) and secundigravidae (SG), Boromo, Burkina Faso, 2004–2006. Error bars represent 95% confidence intervals.

2420–2706) with 0 doses, to 2723 g (95%CI 2656–2789) with one dose and 2899 g (95%CI 2871–2928) with two or more doses (P < 0.001). PG (2740 g, 95%CI 2711–2769) had significantly lighter babies than SG (2938 g, 95%CI 2875–3001, P < 0.001) (Figure 5). One IPTp-SP dose compared to 0 doses was associated with an adjusted mean increase in birth weight of 336 g (95% CI 188–484, P < 0.001) in PG and 75 g (95%CI 4–145, P = 0.039) in SG (adjusted for age, SES, bed net, gender of the baby, season and distance). Two or more doses of SP compared to one dose increased birth weight by 194 g (95%CI 80–308, P = 0.003) in PG and by 109 g (95%CI 41–177, P = 0.005) in SG.

Overall the prevalence of LBW (<2500 g) was 36.5% (19/52) without any IPTp-SP, 24.5% (100/408) with one dose and 12.8% (104/812) with two or more doses of SP. The proportion of LBW-babies was higher among PG (22.8% *vs.* 11.0%, P < 0.001), adolescents (21.7% *vs.* 12.9%, P < 0.001), female newborns (22.7% *vs.* 12.2%, P = 0.005), during the high transmission season (20.3% *vs.* 15.0%, P = 0.048) and without any bed net (18.7% *vs.* 15.6%, P = 0.043). In multivariable analysis, both one (AOR 0.24, 95%CI 0.14–0.40, P < 0.001) and two or more doses of IPTp-SP (AOR 0.11, 95%CI 0.07–0.17, P < 0.001) significantly reduced the risk of LBW in PG compared to no IPTp-SP but not in SG (Table 4). However, for the latter the reference group with LBW and 0 SP was small (4/25). When comparing two or more IPTp-SP doses with only one dose, the risk of LBW was similarly reduced in PG (AOR 0.47, P = 0.050) and SG (AOR 0.51, P = 0.045).

Discussion

In rural Burkina Faso, two or more doses of IPTp-SP significantly reduced the prevalence of peripheral and placental parasitaemia, anaemia and LBW in PG and SG. For malaria infection, peripheral and placental alike, only 10% of the mothers were positive after ≥2 SP doses; anaemia prevalence at delivery was reduced by one-half (27% *vs.* 58%) and LBW by two-thirds (13% *vs.* 37%). These results are consistent with efficacy trials of IPTp-SP (Parise *et al.* 1998; Shulman *et al.* 1999; Kayentao *et al.* 2005; Gill *et al.* 2007; Ouedraogo *et al.* 2008) and observational studies (Verhoeff *et al.* 1998; Van Eijk *et al.* 2004a; Sirima *et al.* 2006; Hommerich *et al.* 2007) and support the recent policy change from weekly CQ to IPTp-SP in Burkina Faso (Ministère de la Santé 2006b). Nevertheless, the results of the community-based trial did not show any difference between the IPTp-SP arms with and without

Table 4 Efficacy of IPTp-SP on LBW by number of doses stratified by parity, Boromo, Burkina Faso, 2004–2006

	Primigravidae (n = 694)			Secundigravidae (n = 562)		
	AOR	(95%CI)	P-value	AOR	(95%CI)	P-value
Frequency of IPTp-SP						
≥2 doses	0.11†	(0.07–0.17)	<0.001	0.70‡	(0.26–1.91)	0.452
1 dose	0.24	(0.14–0.40)	<0.001	1.37	(0.49–3.82)	0.514
0 doses	1	(Ref.)		1	(Ref.)	

Multivariable analysis using survey logistic regression adjusted for age, socioeconomical status, bed net ownership, gender of baby, season of delivery and distance.
IPTp-SP, intermittent preventive treatment with sulfadoxine-pyrimethamine; LBW, low-birth weight (<2500 g); AOR, adjusted odds ratio; CI, confidence interval.
†≥Two doses *vs.* one dose: AOR 0.47 95%CI: 0.22–1.00, P = 0.050.
‡≥Two doses *vs.* one dose: AOR 0.51 95%CI: 0.27–0.98, P = 0.045.

promotion, and this despite a difference in coverage of 70% and 49% respectively (Gies *et al.* 2008). The high efficacy observed at individual level indicates that IPTp-SP is able to prevent malaria infection and its consequences during pregnancy but that the critical threshold that has to be achieved to obtain community effectiveness yet needs to be defined and might be higher than the 80% coverage recommended by WHO (WHO 2005). The contrast between the individual and community IPTp-SP impact observed in this study may be a key to understand the lack of correlation between parasitological and morbidity outcomes frequently observed in malaria prevention trials in pregnancy (Menendez *et al.* 2008).

Placental parasitaemia is the most specific indicator of malaria in pregnancy and often used as a proxy-indicator for malaria control though, from a programmatic point of view, impact indicators for birth outcomes (severe maternal anaemia, LBW, perinatal mortality) may be more meaningful. In this study, even a single dose of SP clearly reduced peripheral and placental parasitaemia and the overall dose-dependent effect is comparable with earlier studies on IPTp-SP (Parise *et al.* 1998; Rogerson *et al.* 2000; Van Eijk *et al.* 2004a). However, during the high transmission season a high proportion of women with ≥2 doses of SP had a malaria positive placental smear (23%; 66/285), most likely due to high re-infection rates between the last dose of SP and delivery (Kayentao *et al.* 2005; Sirima *et al.* 2006). This suggests that the effect of IPTp-SP may not solely depend on the total number of doses but also on the timing of SP administration in relation to the duration of pregnancy and the malaria transmission season (Van Eijk *et al.* 2004a). One dose of SP given close to delivery during the high transmission period might be sufficient to reduce parasitaemia but not anaemia and LBW and, in this study, it explains the lack of difference between study arms with 70% and 49% IPTp coverage.

The contribution of *P.falciparum* infection to anaemia in pregnant women is one of the reasons for preventing malaria during pregnancy (Guyatt & Snow 2001) although, because anaemia has multiple causes, changes in prevalence should be interpreted with caution. In this study, mean PCV increased linearly with each dose of SP, with a corresponding reduction of the anaemia prevalence, though statistical significance was not reached with all anaemia categories. Anaemia at 32 weeks may be a better point of evaluation compared to anaemia at the time of delivery. Evidence that IPTp-SP reduces maternal anaemia is mainly derived from a few studies in Kenya (Parise *et al.* 1998; Shulman *et al.* 1999) who assessed third trimester anaemia and where prevalence of severe anaemia (Hb <8 g/dl) in low-parity women was much higher (about 25%) than in our study population and similar settings (<5%) (Kayentao *et al.* 2005; Sirima *et al.* 2006; Ouedraogo *et al.* 2008). Recent studies evaluating IPTp-SP in the context of insecticide-treated nets (ITNs) reported a much lower prevalence of severe anaemia and only limited impact of the additional use of IPTp-SP (Mbaye *et al.* 2006; Menendez *et al.* 2008). Seasonal influences and host characteristics such as parity are additional factors influencing the measurement of anaemia. Considering that malaria probably contributes to anaemia mostly during the high transmission season and particularly in PG and SG, despite its clinical relevance for maternal outcomes, evaluating and monitoring maternal anaemia may only insufficiently reflect the effectiveness of malaria control interventions.

When comparing two or more doses with no IPTp-SP, both the reduction in LBW prevalence and the gain in mean birth weight observed in this study were much greater in PG than in SG; in the former even a single IPTp-SP dose significantly reduced LBW. Most studies reporting on the effect of IPTp-SP on LBW have been done on PG and SG

(Challis *et al.* 2004; Kayentao *et al.* 2005); of those including women of all parities (Verhoeff *et al.* 1998; Van Eijk *et al.* 2004a; Sirima *et al.* 2006) only Sirima *et al.* report data for PG and SG separately. Their results confirm that, despite similar infection rates, the effect of IPTp-SP on LBW was greater in PG than in SG (Sirima *et al.* 2006). Some authors suggest that parity specific patterns of malaria infection during pregnancy are being modified in the context of high coverage with ITNs (Njagi *et al.* 2003; Mbaye *et al.* 2006; Menendez *et al.* 2008). In this study, where bed net use (most of these not insecticide-treated) was extremely low, the limited effect of IPTp-SP on birth weight in SG may have been sufficient to dilute the overall effectiveness of IPTp-SP and to level out differences between study arms (Gies *et al.* 2008).

There are some limitations to this analysis, in the first instance the comparability of treatment groups. Incomplete dosing of SP resulted from non-attendance or insufficient attendance of antenatal clinics and/or inadvertent omission of SP administration at ANC. Only a small proportion of women did not receive IPTp-SP (5.6%) and these were younger, poorer, less educated, and lived in remote villages with a more difficult access to ANC. Therefore, they probably were *a priori* at an increased risk of experiencing an adverse pregnancy outcome. Furthermore, they were more likely to deliver at home so that a substantial number of information at delivery from this group is missing. Such characteristics apply to a lesser extent also to women who took just one IPTp-SP dose. However, adjusting for differences between groups did not significantly modify the results, though additional non-identified confounders may remain. Complete uptake of SP is closely related to regular ANC attendance (Gies *et al.* 2009) which is likely to influence pregnancy outcomes independently of malaria. However, in the CQ control arm of the main study, no significant effect of regular ANC attendance on prevalence of anaemia and LBW was observed (S. Gies, unpublished data). All study participants were from rural areas and there is no indication that the risk of exposure to malaria changed with distance from a health centre. Thus, even if some underlying confounding remains and the dose-dependent effect might be overestimated, we are confident that the efficacy of IPTp-SP in this study is a true finding.

In summary, IPTp-SP efficiently reduced peripheral and placental parasitaemia in PG and SG in rural Burkina Faso. Mean PCV and birth weight increased with increasing number of doses of SP and prevalence of anaemia and LBW was reduced. The significantly higher contribution of malaria to LBW in PG is illustrated by the larger effect observed in this specific group. Incomplete uptake of IPTp-SP, particularly in high risk groups, and limited effect in low risk groups together may substantially dilute the measurable impact of effective interventions. This needs to be taken into account when evaluating malaria control interventions at community level.

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