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Sulfadoxine–pyrimethamine resistance and intermittent preventive treatment during pregnancy: a retrospective analysis of birth weight data in the Democratic Republic of Congo (DRC)

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Abstract

OBJECTIVE To assess the effect of intermittent preventive treatment with sulfadoxine–pyrimethamine (IPTp-SP) on birth weight in sites with varying degrees of drug resistance.

METHODS Birth weight data from three regions in Democratic Republic of Congo with varying degrees of sulfadoxine–pyrimethamine (SP) resistance (1.6% in Mikalayi, 21.7% in Kisangani and 60.6% in Rutshuru) were analysed retrospectively by means of a logistic model that included the number of SP doses taken by the mother and other potentials confounding factors.

RESULTS The IPTp-SP reduced the risk of low birth weight (LBW) in Kisangani (adjusted OR, 0.15; IC95%, 0.05–0.46) and in Mikalayi (adjusted OR, 0.12; IC95%, 0.01–0.89). In both sites, the average birth weight was higher for mothers having received two rather than one or no SP doses ($P < 0.001$). In Rutshuru, IPTp-SP had an effect in primigravidae but not in multigravidae. However, after adjustment for other LBW risk factors, there was no difference in the proportion of LBW (adjusted OR 0.92; IC95%, 0.37–2.25) between women having taken at least 2 SP doses and those with only one dose or none.

CONCLUSION IPT-SP remains an effective strategy in Kisangani and Mikalayi where the therapeutic failure to SP in children with clinical malaria was 21.7% and 1.6%, respectively, while IPTp-SP effect seems lower in Rutshuru where the therapeutic failure to SP was 60.6%. The threshold value of SP resistance at which IPTp-SP fails to have a significant impact on birth weight and LBW is unknown. Considering that no alternative is currently available, additional studies on the efficacy of IPTp-SP in the areas of high SP resistance such as Rutshuru are needed so that the threshold at which this intervention fails to provide any benefit is determined with some precision.

keywords malaria, intermittent preventive treatment, sulfadoxine–pyrimethamine, pregnancy, birth weight, Democratic Republic of Congo

Introduction

Pregnant women are highly vulnerable to malaria infection (Brabin 1983; Greenwood *et al.* 2005; WHO 2006; Rogerson *et al.* 2007; Menendez *et al.* 2008; Lagerberg 2008). Among the 50 millions at risk each year in endemic countries, more than half live in sub-Saharan Africa (Steketee *et al.* 2001; Desai *et al.* 2007; Menéndez *et al.* 2007). Malaria causes maternal anaemia and low birth weight (LBW), the latter caused by placental malaria that compromises the maternal – foetal exchanges (Steketee *et al.* 2001; Steketee 2003; WHO 2004, 2008a,b; Mutabingwa *et al.* 2005). It is estimated that maternal malaria causes more than 35% of preventable LBW, an important risk factor for infant mortality (McCormick 1985; Newman *et al.* 2003; Steketee 2003; Van Geertruyden *et al.* 2004; Sirima *et al.* 2006).

Intermittent preventive treatment during pregnancy with sulfadoxine–pyrimethamine (IPTp-SP) and insecticide-treated bed net (ITN) can reduce maternal anaemia and LBW by about 40% (WHO 2005a,b). Unfortunately, IPTp-SP coverage in Africa, and more specifically in the

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Democratic Republic of Congo (DRC), is still low, that is between 5% and 18% (WHO and UNICEF 2003; Ministère du Plan et Macro International 2008; WHO 2008a,b).

While countries are trying to increase IPTp-SP coverage, *Plasmodium falciparum (Pf)* has become increasingly resistant to sulfadoxine–pyrimethamine (SP) (White 2005; Briand *et al.* 2007; Vallely *et al.* 2007). In DRC, SP treatment failure by day 28 varied between 2% and 60%, which prompted the change of the first-line treatment from SP to an Artemisinin-based combination therapies, that is amodiaquine-artesunate, in March 2005 (Odio 2005).

In highly malaria endemic areas, data on SP treatment efficacy are usually collected in symptomatic children under 5 years but the results obtained are not necessarily applicable to IPTp-SP; indeed, this intervention can be reasonably effective even in areas where SP efficacy in children has declined to 50% (WHO 2008a,b). Nevertheless, it is important to continue collecting information on IPTp-SP in regions where resistance to SP is moderate to high (ter Kuile *et al.* 2007). We collected retrospective data on birth weight and IPTp-SP in three sites in DRC where SP efficacy was either high (in two sites) or low (one site).

Methods

The study was carried out in three maternity clinics in areas where information on SP efficacy in 6- to 59-month-old children was available. The *in vivo* tests were conducted between 2002 and 2004 in Mikalayi in the south–west of the country, within 33 km of the city of Kananga; in Umoja, in the suburbs of Kisangani; and in Kiwandja, about 70 km from Goma in the Rutshuru health district (Odio 2005) (Figure 1). SP treatment failure at day 28 post-treatment was low in Mikalayi (1.6%), moderate in Kisangani (21.7%) and high in Rutshuru (60.6%) (Figure 1). These estimations are similar to those produced by other studies conducted in the same areas (Kazadi *et al.* 2003; Alker *et al.* 2008).

All women (i) who gave birth in 2007 in the study maternity clinics (ii) attended the antenatal care (ANC) at least once during pregnancy and (iii) whose ANC card was available for analysis were included in this study. Each maternity unit kept the ANC cards for all pregnant women from their catchment area. Hospital records and ANC cards were fully reviewed and the information transcribed. The primary outcome was the birth weight analysed both as a continuous or categorical (LBW: <2500 g) variable. Newborns were weighed by a standard procedure in the three maternity using mechanical baby scales with a precision of 10 g. The tendency of rounding the birth weight probably occurred in all three sites and should not significantly affect the results. Women were categorised according to the number of IPTp-SP doses received, into either two or more doses *vs.* one or none.

Mothers' demographic and anthropometric variables were also collected, that is age, weight, height and the body mass index (BMI) as well as the number of visits to the ANC and previous pregnancy outcomes. The estimated gestational age of the newborn, estimated by last menstrual period, was obtained but not included in the analysis.

The descriptive analysis used proportions for categorical variables, means with standard deviation or median with interquartile range for continuous variables. Contingency

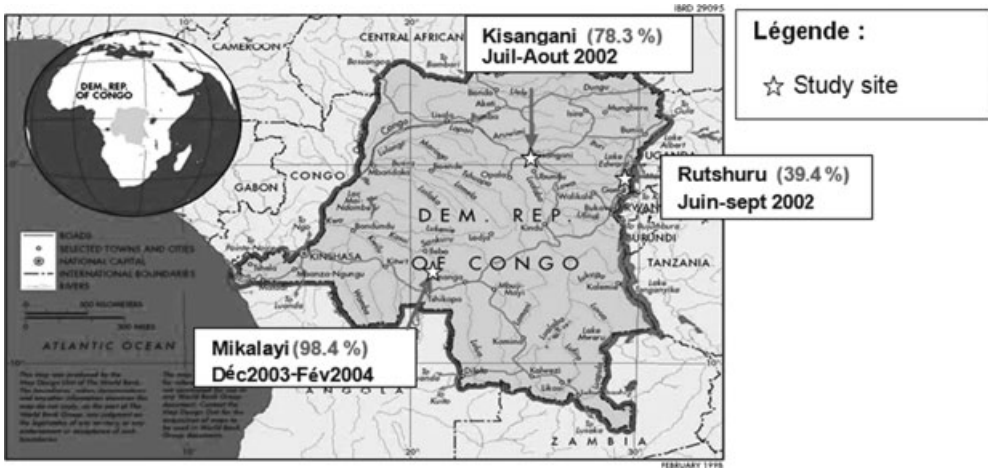

Figure 1 Results of *in vivo* efficacy assessment of sulfadoxine–pyrimethamine in symptomatic malaria carried out on 6–59 months children (proportion of adequate clinical and parasitological response at day 28) (Odio 2005).

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tables were analysed using the chi-square test. Means were compared by *t*-test or one-way ANOVA followed by multiple comparisons (Bonferroni). When data were not normally distributed, the Kruskal–Wallis test was used for the median.

An analysis of birth weight as well as of LBW by the number of SP doses taken by the mothers, stratified by site and gravidity range was done. OR's homogeneity was tested by the Breslow and Day (1994) test. A logistic regression model of LBW including the number of SP doses, main outcome studied, and other potential confounding factors (parity, BMI, gestational age and number of ANC visits) selected by backward method was constructed. Interactions between site and number of SP doses were introduced into the model and tested with the likelihood ratio test. The Hosmer and Lesmeshow (2000) test was used to improve model goodness of fit. All statistical analyses were performed using STATA/IC 10.0 for Windows (StataCorp LP).

This study was approved by the authorities of the national, provincial and local Ministry of Health. The protocol was approved by the ethics commission and deontology of the Provincial Council of the Medical Board of the Oriental Province.

Results

In total, 1393 women who had delivered in the three health facilities in 2007 were included in the study: 138 in Kisangani, 582 in Mikalayi and 673 in Rutshuru. Women in Kisangani were significantly younger than in the other two sites, though after Bonferroni correction, the difference remained significant only between Kisangani and Mikalayi (Table 1). In Kisangani the BMI, the parity and the number of living children were significantly lower than in the other two sites, while the proportion of women under 18, primigravidae and low BMI was higher. Mean birth weight was lower in primigravidae; the proportion of LBW was higher in mothers who had taken just one SP dose or none (Table 2).

Among the women included in the study, the percentage of those having received two IPTp-SP doses was relatively

Table 1 Demographic and anthropometric characteristics of women by health facility

Characteristics	All	Rutshuru	Mikalayi	Kisangani	*P*
Age (year) *n*	1367	666	563	138	
Mean (DS)	26.0 (6.7)	25.8 (6.5)	26.7 (7.0)	24.5 (6.9)	0.002*
<18 freq (%)	93 (6.8)	39 (5.9)	34 (6.1)	20 (14.5)	0.005**
18–39 freq (%)	1220 (89.2)	602 (90.4)	504 (89.5)	114 (82.6)	
>39 freq (%)	54 (4.0)	25 (3.7)	25 (4.4)	4 (2.9)	
Gravidity *n*	1390	671	582	137	
Median (P_{75}–P_{25})	3 (5–1)	3 (5–1)	3 (5–1)	2 (3–0)	<0.001***
0 freq (%)	250 (18.0)	110 (16.4)	100 (17.2)	40 (29.2)	<0.001*
1–5 freq (%)	892 (64.2)	442 (65.9)	361 (62.0)	89 (65.0)	
>5 freq (%)	248 (17.8)	119 (17.7)	121 (20.8)	8 (5.8)	
Living Infant *n*	1371	670	564	137	
Median (P_{75}–P_{25})	2 (4–1)	2 (4–1)	2 (4–1)	2 (3–0)	0.006**
Height (Cm) *n*	1019	441	446	132	
Mean (DS)	156.6 (7.6)	156.9 (6.4)	154.9 (7.5)	161.8 (9.0)	<0.001*
<150 freq (%)	129 (12.7)	48 (10.9)	76 (17.0)	5 (3.8)	<0.001*
≥150 freq (%)	890 (87.3)	393 (89.1)	370 (83.0)	127 (96.2)	
Weight (kg) *n*	1061	468	461	132	
Mean (±DS)	58.1 (7.3)	59.2 (7.9)	57.0 (6.7)	57.7 (6.5)	<0.001*
BMI (kg/m^2) *n*	873	319	423	131	
Mean (DS)	23.7 (2.9)	24.2 (2.7)	23.8 (2.9)	22.1 (2.4)	<0.001*
<21 freq (%)	115 (13.2)	31 (9.7)	52 (12.3)	32 (24.4)	<0.001*
≥21 freq (%)	758 (86.8)	288 (90.3)	371 (87.7)	99 (75.6)	
Number of ANC *n*	1286	673	486	127	
Median (P_{75}–P_{25})	3 (4–2)	3 (3–2)	4 (4–3)	3 (3–2)	<0.001***
≥4 freq (%)	415 (32.3)	86 (12.8)	304 (62.5)	25 (19.7)	<0.001*
3 freq (%)	484 (37.6)	294 (43.7)	140 (28.8)	50 (39.4)	
2 freq (%)	315 (24.5)	240 (35.6)	32 (6.6)	43 (33.8)	
1 freq (%)	72 (5.6)	53 (7.9)	10 (2.1)	9 (7.1)	

*One-way ANOVA, **Pearson's χ^2, ***Kruskal–Wallis test.

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Table 2 Birth weight and low birth weight (LBW) frequencies by health facility, gravidity and sulfadoxine–pyrimethamine (SP) doses taken by mothers

		Birth weight (g)		LBW	
	n	Mean (SD)	*P*	Freq (%)	*P*
All	1381	3078.3 (509.0)		126 (9.1)	
Sites					
Rutshuru	670	3027.0 (443.7)	<0.001*	55 (8.2)	0.012**
Mikalayi	574	3183.1 (536.4)		49 (8.5)	
Kisangani	137	2889.8 (594.7)		22 (16.1)	
Gravidity					
Primigravidae	247	2861.5 (482.7)	<0.001***	38 (15.4)	<0.001**
Multigravidae	1131	3125.8 (503.1)		88 (7.8)	
SP doses					
≤1 SP dose	590	3070.2 (547.8)	0.938*	67 (11.4)	0.004**
≥2 SP doses	694	3072.3 (448.2)		47 (6.8)	

*One-way ANOVA, **Pearson's χ^2, ***t-test.

high in Rutshuru (73.7%, 496/673) and Kisangani (63.5%, 87/137), while it was extremely low in Mikalayi (23.8% 115/484) ($P < 0.001$). When analysing the mean birth weight by the number of IPTp-SP doses taken, no difference could be found in Rutshuru, while in the other two sites, there was a statistically significant difference between babies born to mothers having taken the two doses as compared to one or none, the latter having the lowest birth weight (Table 3). Similarly, both in Mikalayi and Kisangani, the risk of LBW was significantly lower in women having taken two IPTp-SP doses (Mikalayi: OR = 0.17; IC95%, 0.02–0.67-, $P = 0.006$ and Kisangani: OR = 0.16; IC95%, 0.05–0.48, $P \leq 0.001$), while there was no difference in Rutshuru. This was confirmed after adjusting for other risk factors for LBW, for example first pregnancy and low BMI, which were also associated with LBW, in some sites significantly (Table 4). However, after stratification by gravidity, even in Rutshuru, the mean birth weight was higher (2833.8 g *vs.* 2520.7, $P = 0.010$) and the risk of LBW lower (OR = 0.26; IC95%, 0.07–1.19) for primigravidae who received at least two SP doses compared with those who received only one or none (Table 3), while after adjustment for other risk factors for LBW the difference did not remained statistically significant (Table 4).

Discussion

When analysing the mean birth weight or the risk of LBW in women who attended ANC and delivered in the three health facilities, it appears that two doses of SP had a significant impact in two sites, while in the remaining site, the impact was found only in primigravidae. Nevertheless, in this site, the difference did not reach statistical significance after adjustment for other known LBW risk factors. It is tempting to ascribe this to an attenuation of effect of IPTp-SP in Rutshuru because of the high SP resistance reported a few years earlier (Odio 2005; Alker *et al.* 2008). LBW or rather its risk in primigravidae compared with multigravidae has already been proposed as an indicator for monitoring the malaria burden and the effectiveness of control interventions in this highly vulnerable group (Brabin *et al.* 1999). The observed reduction of the risk in LBW and the increase in the mean birth weight associated with two IPTp-SP doses is comparable with those reported from other sub-Saharan African countries (Newman *et al.* 2003; WHO 2004, 2008a,b, Vallely *et al.* 2007). In addition, the substantial reduction in the risk of LBW observed in Mikalayi and Kisangani, where SP resistance was 2% and 22%, respectively, is in line with the conclusions of a recent review of randomised trials reporting that with SP resistance up to 26% (no study done in places with higher SP resistance was found) the two-dose regimen of IPTp-SP provides substantial benefit, though more frequent dosing is required in HIV-positive pregnant women (ter Kuile *et al.* 2007). Similarly, another review on published and unpublished studies relating SP treatment efficacy in children and pregnant women with uncomplicated malaria and IPTp-SP noticed the lack of information in regions where SP resistance exceeds 50% (WHO 2008a,b). Therefore, the results reported in this study contribute to fill the knowledge gap as SP resistance in Rutshuru was around 60% and two IPTp-SP doses did not have a clear benefit on the birth weight as in the other two sites. However, the limitations inherent to this type of study, that is using data collected through the routine health information system, and the small number of sites should be considered.

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Table 3 Newborn's weight by number of IPTp-SP doses stratified by gravidity by each site

Doses of sulfadoxine–pyrimethamine (SP)	All				Primigravidae				Multigravidae			
	n	Mean	(DS)	*P*	*n*	Mean	(DS)	*P*	*n*	Mean	(DS)	*P*
Birth weight (g)												
All	1284	3071.3	(496.3)	0.938*	233	2853.5	489.6	0.027*	1048	3119.9	485.4	0.918*
≤1	590	3070.2	(547.8)		83	2758.0	576.6		506	3121.5	443.9	
≥2	694	3072.3	(448.2)		150	2906.3	427.1		542	3118.4	526.7	
Rutshuru	670	3027.0	(443.7)	0.714*	109	2790.7	440.5	0.010*	559	3073.1	430.4	0.667*
≤1	177	3037.5	(492.0)		15	2520.7	499.1		162	3085.4	464.5	
≥2	493	3023.3	(425.5)		94	2833.8	417.3		397	3068.1	416.2	
Mikalayi	477	3185.7	(510.5)	<0.001*	84	2986.3	(515.6)	0.024*	393	3228.3	499.9	0.002*
≤1	363	3141.5	(515.5)		56	2896.9	(522.0)		307	3186.1	502.5	
≥2	114	3326.3	(469.4)		28	3165.0	(460.9)		86	3378.8	462.7	
Kisangani	137	2889.8	(594.7)	<0.001*	40	2745.8	(512.0)	0.005*	96	2948.6	621.5	0.001*
≤1	50	2667.8	(753.4)		12	2406.7	(699.2)		37	2743.5	769.2	
≥2	87	3017.4	(436.6)		28	2891.1	(326.3)		59	3077.3	470.9	
Doses of SP	*n*	%	OR	*P*	*n*	%	OR	*P*	*n*	%	OR	*P*
Low birth weight (<2500 g)												
All	1284	8.88		0.004**	233	15.9		<0.001**	1048	7.4		0.106**
≤1	590	11.36	1		83	27.7	1		506	8.7	1	
≥2	694	6.77	0.57 (0.38–0.85)		150	9.3	0.27(0.12–00.59)		542	6.1	0.68(0.41–1.12)	
Rutshuru	670	8.21		0.639**	109	14.7		0.044***	559	6.7		0.912**
≤1	177	9.04	1		15	33.3	1		162	6.8	1	
≥2	493	7.91	0.86 (0.48–1.70)		94	11.7	0.26(0.07–1.19)		397	7.1	1.04(0.49–2.38)	
Mikalayi	477	7.76		0.006**	84	14.3		0.054***	393	6.1		0.025**
≤1	363	9.64	1		56	19.6	1		307	7.8	1	
≥2	114	1.75	0.17 (0.02–0.67)		28	3.6	0.15(0.00–1.17)		86	1.2	0.14(0.00–0.88)	
Kisangani	137	16.06		<0.001**	40	22.5		0.001***	96	13.5		0.014**
≤1	50	32.00	1		12	58.3	1		37	24.3	1	
≥2	87	6.90	0.16 (0.05–0.48)		28	7.1	0.05(0.00–0.43)		59	6.8	0.22(0.05–0.91)	

*t-test, **Pearson's χ^2, ***Fisher's exact test.

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Table 4 Risk factors for low birth weight (LBW) after adjustment

	Mikalayi (n = 342)		Kisangani (n = 122)		Rutshuru (n = 318)	
Risk factors	OR ($IC_{95\%}$)	P*	OR ($IC_{95\%}$)	P*	OR ($IC_{95\%}$)	P*
Number of sulfadoxine–pyrimethamine doses						
≤1	1	0.038	1	0.001	1	0.853
≥2	0.12 (0.01–0.89)		0.15 (0.05–0.46)		0.92 (0.37–2.25)	
Gravidity						
0	3.64 (1.27–10.38)	0.016	1.68 (0.55–5.10)	0.362	2.39 (0.91–6.28)	0.077
1–5	1		1		1	
>5	1.13 (0.29–4.45)	0.857	**		2.45 (0.87–6.95)	0.091
BMI (kg/m^2)						
<21	2.30 (0.68–7.76)	0.180	1.19 (0.38–3.79)	0.764	5.87 (2.29–15.06)	0.001
≥21	1		1		1	

Not included in the model before stratification because not significant: Number of ANC, Maternal age *Wald χ^2, **No LBW infant recorded in this strata.

The quality of data used may be questioned as they were not collected to investigate a specific research question, but rather to monitor the implementation of the IPTp-SP. Moreover, the women included in the study represent a selected group as they delivered in the health facilities. Observations in this group may not necessarily apply to women who delivered at home. Nevertheless, the fact that other known risk factors such as low BMI or prematurity were found independently associated with LBW in at least one of the sites is reassuring and may indicate that the dataset is of reasonable quality.

The three sites also represent areas of different endemicity, with Rutshuru, the site where two doses of IPTp-SP did not have any impact, being probably the one with the lowest intensity of transmission (Ministère de la Santé 2007; Taylor *et al.* 2011). Therefore, differences could be due to the lower malaria burden in Rutshuru. However, the little information available from this region indicates that this is unlikely. Prevalence of malaria infection was 17.4% in pregnant women attending the maternity hospital of Rutshuru, an area with unstable malaria transmission (Meuris *et al.* 1993) and 21% among delivering mothers in Kinshasa maternity hospitals, in an area of stable transmission (Lukuka *et al.* 2006).

It would have also been interesting to have other facilities in areas with high SP resistance. Data on SP efficacy were collected between 2002 and 2004; those on birth weight and IPTp-SP doses in 2007 – a gap of several years. The national policy on treatment changed in 2005, from SP to amodiaquine-artesunate, which may have had an impact on the prevalence of SP-resistant malaria parasites. This is probably unlikely as often the period between the decision of changing the national antimalarial drug policy and its implementation can be as long as 2–3 years (WHO 2006) and the time necessary to observe a change in the drug-resistance pattern may be even longer (Mita *et al.* 2003).

In conclusion, IPTp-SP seems to remain an effective strategy in areas where SP treatment failure in children with uncomplicated malaria is below 30% (34), while the effect seemed to be much lower where SP resistance was as high as 60%. The threshold value of SP resistance at which IPTp-SP fails to have a significant impact on birth weight and LBW is unknown. Considering that no alternative is currently available, additional studies on the efficacy of IPTp-SP in areas of high resistance such as Rutshuru are needed so that the threshold at which this intervention fails to provide any benefit is determined with some precision.

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