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Efficacy and safety of intermittent preventive treatment in schoolchildren with sulfadoxine/pyrimethamine (SP) and SP plus piperaquine in Democratic Republic of the Congo: a randomised controlled trial

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ABSTRACT

In endemic areas, malaria and its adverse effects in schoolchildren may be prevented by intermittent preventive treatment (IPTsc). However, the most appropriate drug regimen for IPTsc remains to be identified. A randomised controlled trial was conducted in Kinshasa, DRC. Enrolled schoolchildren were assigned to a passive control arm ($n = 212$), sulfadoxine/pyrimethamine (SP) ($n = 202$) or SP plus piperaquine (SP/PQ) ($n = 202$). The primary endpoint was haemoglobin (Hb) change. Secondary endpoints were anaemia, parasitaemia prevalence and clinical malaria incidence. Data were analysed by modified intention-to-treat (mITT) and per-protocol. A linear mixed mode was used due to repeated measurements. Of 616 enrolled children, 410 (66.6%) were eligible for mITT analysis. The control arm was used as reference. After 12 months, the Hb level increased by 0.20 g/dL (95% CI –0.61 to 0.47; $P = 0.168$) and 0.39 g/dL (0.12–0.66; $P < 0.01$) in the SP and SP/PQ arms, respectively. SP treatment reduced anaemia, malaria parasitaemia and clinical malaria by 10% (0–20%; $P = 0.06$), 19% (2–33%; $P = 0.042$) and 25% (–32 to 57%; $P = 0.37$), respectively. The corresponding values for SP/PQ were 28% (19–37%; $P < 0.001$), 40% (26–52%; $P < 0.001$) and 58% (17–79%; $P < 0.01$). No deaths or severe adverse events (SAEs) were observed. SP/PQ offered substantial protection against anaemia, malaria parasitaemia and clinical malaria and showed no SAEs. SP/PQ, a combination of two long-acting non-artemisinin-based antimalarials, may be a valuable option for IPTsc in Africa.

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1. Introduction

In malaria-endemic areas where subjects are permanently exposed to infectious mosquito bites, severe disease develops mainly in infants and young children [1]. In children aged ≥5 years and school-age children, malaria infection is mainly characterised by asymptomatic recurrent parasitaemia [2].

Asymptomatic *Plasmodium* infections induce inflammation that is associated with iron deficiency anaemia, which in turn is associated with cognitive impairment in schoolchildren [3,4]. In low-income countries, more than one-half of the school-age population suffers from anaemia; in Sub Saharan Africa, ca. 85 million school-aged children are affected. Anaemia reduces their cognitive potential, retards growth and predisposes them to other diseases [5]. Moreover, severe anaemia is one of the leading causes of death due to malarial disease in childhood in intense and stable malaria transmission areas [6]. Also, malaria accounts for ca. 13–50% of all annual school absenteeism and impairs the educational achievement of children [6]. However, whilst there is growing awareness of the importance of reducing the burden of malaria in schoolchildren and increasing political support for school-based malaria control [6], there is still limited evidence on malaria preventive strategies to guide policy formulation [7,8]. Sleeping under a bednet is a possible strategy to fight malaria in this specific group; however studies have also shown that schoolchildren were less likely to sleep under a bednet [9]. Screening and treatment, although promising, raise questions regarding the appropriate diagnostic test for tracking malaria infection in asymptomatic schoolchildren and the feasibility of such a preventive strategy at a national level [10,11]. Another intervention under investigation is intermittent preventive treatment (IPT). However, evidence of the benefits of IPT in school-aged children (IPTsc) living in malaria-endemic areas is limited and the most appropriate drug regimen for IPTsc remains controversial [12]. A

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handful of studies conducted across African settings have demonstrated different protective efficacies against malaria parasitaemia, clinical malaria and anaemia [7,13–18]. This disparity leads to the conclusion that more evaluations of IPTsc need to be conducted and that drugs with a long half-life should be prioritised for investigation. This trial investigated the protective efficacy and safety of two IPTsc regimens compared with passive case detection against malaria in primary school children living in a malaria-endemic area.

2. Methods

2.1. Study design

This was an open-label, randomised controlled trial enrolling asymptomatic schoolchildren and investigating the efficacy of IPTsc with sulfadoxine/pyrimethamine (SP) or SP combined with piperaquine (PQ) on anaemia and malaria morbidity in Congolese schoolchildren. The trial was composed of three treatment arms: SP monotherapy; SP combined with PQ (SP/PQ); and no antimalarial treatment (control). The study was conducted in Mokali health area, a semi-rural area of Kinshasa, Democratic Republic of the Congo (DRC). Malaria transmission is intense and perennial in this region, with two seasonal peaks (March–May and November–December) [19,20].

Participants were recruited at the primary schools Boyambi and Likabo situated nearest to the regional health centre. The expected number of schoolchildren was 650 per school at the beginning of the year, with an absenteeism rate of 40% and a school dropout rate of 20% reported by school directors. The trial design and protocol are described in detail elsewhere [21]. Briefly, asymptomatic schoolchildren of both sexes were enrolled in November 2012 and were followed-up until November 2013. IPTsc with SP or SP/PQ was given at baseline (November 2012), at Month 4 (March 2013) and at Month 7 (June 2013). SP was administered as a single treatment dose and PQ was given as two doses (32 mg/kg) at a 24-h interval. Owing to the high endemicity of soil-transmitted helminths and schistosomiasis in the study area and taking into account the possible impact of these infections on anaemia, all participants were treated with albendazole (400 mg) and praziquantel (40 mg/kg) at enrolment and at Month 12, according to World Health Organization (WHO) guidelines [22]. The primary endpoint was the change in mean haemoglobin (Hb) concentration at 12 months of follow-up. Secondary study endpoints were change in anaemia prevalence at 4, 7 and 12 months of follow-up, prevalence of asymptomatic malaria at baseline and at Months 4, 7 and 12, and incidence of clinical malaria during 4 months after enrolment; owing to budget constraints, the follow-up period for clinical malaria incidence was 4 months.

This study was approved by the Ethical Committees of the University of Kinshasa (Kinshasa, DRC) and the University of Antwerp (Antwerp, Belgium). This trial was registered, before recruitment of the first subject, at ClinicalTrials.gov (http://www.clinicaltrials.gov; NCT01722539). Special permission was obtained from the DRC Ministry of Health. A series of meetings were also held in the participating schools to explain the nature and purpose of the trial. Written informed consent was obtained from each parent or legal guardian of all children prior to enrolment. Oral consent was also obtained from children aged ≥12 years.

For the present study, SP was supplied by the IDA Foundation (Amsterdam, The Netherlands) as scored tablets containing 500 mg sulfadoxine and 25 mg pyrimethamine. PQ 320 mg tablets were manufactured and provided by Sigma Tau (Rome, Italy).

Albendazole and praziquantel were used as anthelmintic and trematodicide agents, respectively. These two drugs were supplied by the IDA foundation.

2.2. Study procedures

2.2.1. Baseline, enrolment and treatment allocation

Between 10 and 24 November 2012, children whose parents provided written informed consent for their participation and who fulfilled the following inclusion criteria were enrolled in the trial: (i) male and female primary schoolchildren (primary school year grades 1–5); (ii) permanent resident of the area; (iii) no malaria-related symptoms; (iv) no disability; (v) no chronic illness; (vi) no known allergy to study drugs; (vii) no clinical signs of decompensated anaemia; (viii) no known illness or conditions, such as haematological, cardiac, renal or hepatic diseases; (ix) body weight <14 kg; and (x) no major chronic infectious diseases [human immunodeficiency virus (HIV), tuberculosis, etc.].

A standardised assessment of symptoms and a focused physical examination, including measurement of weight and temperature, were conducted. A blood sample was collected for detection of *Plasmodium* infection and for estimation of Hb concentration. Each child was randomly assigned (1:1:1 ratio) to one of the three treatment arms (SP, SP/PQ and control) according to a predetermined randomisation list of blocks of eight generated by an independent statistician. Sealed envelopes labelled with the school unique ID code and containing the list with the treatment allocation per ID number were provided and were opened at the moment the children were recruited. Study treatments and possible co-medications were given according to the study treatment allocation and the participant's health status.

2.2.2. Follow-up visits at months 4, 7 and 12

Enrolled children were followed-up for 12 months. Cross-sectional surveys were performed in both schools in March, June and November 2013. Because primary schools close by early July (for 2 months), the second follow-up visit, originally planned for July, took place in June. Additional fingerprick blood samples were obtained at all visits from all available enrolled children to assess Hb concentration with a portable photometer (Hemo Control®; EKF Diagnostics, Barleben, Germany). Anaemia was defined as a Hb concentration of <11, <11.5 and <12 g/dL, respectively, for schoolchildren aged <5 years, 5–11.9 years and 12–14.9 years. Anaemia was defined as severe anaemia (Hb <7 g/dL), moderate anaemia (Hb 7–9.9 g/dL) and mild anaemia (Hb 10–11.4 g/dL) [23]. Giemsa-stained thick blood smears were used for microscopy. Blood slides were examined using light microscopy at 1000× magnification.

A total of 100 microscopic fields were examined in the thick blood smear before concluding that a blood slide was negative. All slides were read by experienced microscopists. The parasite density per microlitre of blood was calculated using the following formula: (no. of trophozoites × 8000)/no. of leucocytes. Data on past symptoms were obtained through a questionnaire administered to the children. Stool samples were taken at baseline and after 12 months of follow-up and were examined by the Kato–Katz technique. During the 4 months of follow-up after the first IPT treatment, any child experiencing clinical malaria or other illnesses was directed to the regional hospital of Biyela, where all symptoms were recorded, a blood sample was collected for laboratory analysis including malaria diagnosis (microscopy), and the child was treated according to the national guidelines. The principal investigator was always informed that a child was admitted to the hospital and he had access to the child's medical file. Information was reported in a case report form.

2.2.3. Statistical analysis

Based upon a previous study, we considered an effect size of 0.56 g/dL mean Hb [7]. Assuming a significance level set at 5%, an intra-individual variance of 1, and allowing for an absenteeism rate of 40% and a dropout rate of 20%, a minimum sample size of 600

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provided a 99% power to detect the targeted effect size considered as clinically relevant.

The impact on Hb levels was assessed using linear mixed-model analysis [mixed between–within subjects analysis of variance (ANOVA)]. Measures for comparison of treatment arms were expressed as prevalence, mean difference and protective effect (PE), which was calculated as PE = 1 – (rate ratio of malaria parasitaemia, clinical malaria or anaemia) × 100%. Kaplan–Meier analysis was used to estimate the time to the first episode of clinical malaria. The 95% confidence intervals (CIs) were calculated, and a *P*-value of <0.05 was considered statistically significant. Data were analysed per-protocol (PP) excluding children with missing data and those who were not treated according to the randomisation, and as modified intention-to-treat (mITT) in which eligible randomised schoolchildren participated in at least two study interventions and were present at the post-treatment survey. Statistical analysis was performed using the statistical program SPSS v.22 (IBM Corp., Armonk, NY).

3. Results

3.1. Study subjects and follow-up

A total of 616 children aged 4–13 years were enrolled in the trial, of which 410 (66.6%) were examined in the post-intervention survey at 12 months (Table 1; Fig. 1). The number of children lost to follow-up was similar in the SP/PQ, SP and control [72/202 (35.6%), 65/202 (32.2%) and 69/212 (32.5%), respectively]. The main reasons included change of school, outmigration and dropout of school. Participants lost to follow-up had similar baseline characteristics to children included in the mITT and PP analyses (Table 1). The Little's test suggested a missing completely at random (MCAR) mechanism ($P = 1.0$). Fig. 1 shows the trial profile. A total of 410 children were included in the mITT analysis, whereas 389 children were included in the PP analysis (Table 1). The characteristics of children at enrolment are fully described elsewhere [24].

3.2. Impact of intermittent preventive treatment in schoolchildren (IPTsc) on haemoglobin and anaemia

Over 12 months, there was a significant seasonal variation in Hb levels in all treatment arms (all $P < 0.001$) and a significant interaction ($P < 0.001$) between time and the impact of the interventions, indicating that the impact on Hb differed over time between treatments arms (Table 2). Compared with the control arm, the Hb levels were 0.20 g/dL (95% CI –0.61 to 0.47 g/dL; $P = 0.168$) and 0.39 g/dL (95% CI 0.12–0.66 g/dL; $P = 0.002$) higher in the SP- and SP/PQ-treated children, respectively. Accordingly, the proportion of children with anaemia was lower in the SP arm (29.9%; $P = 0.048$) and the SP/PQ arm (24.6%; $P = 0.0046$) than in control arm (41.3%) (Table 3).

The SP/PQ arm had higher Hb levels compared with the control arm at all time points. Overall, compared with the SP arm, the Hb level was 0.18 g/dL (95% CI –0.09 to 0.45 g/dL) higher in the SP/PQ group ($P = 0.243$). SP/PQ differed from SP at 4 months and 7 months of follow-up ($P = 0.009$ and $P = 0.039$, respectively) (Table 2). The overall PE of SP on anaemia was 10% (95% CI 0–20%; $P = 0.06$) and the corresponding PE of SP/PQ was 28% (95%CI 19–37%; $P = 0.00012$) (Fig. 2). The number of children needed to treat to prevent one case of anaemia was 16 and 6 for SP and SP/PQ, respectively.

3.3. Impact of intermittent preventive treatment in schoolchildren (IPTsc) on malaria parasitaemia

At baseline, the prevalence of malaria parasitaemia was <21% in all arms (Table 1). At the end of the follow-up, the proportion of children with malaria parasitaemia was lower in the SP/PQ arm (9.2%, 95% CI 6.2–13.6%) than in the control arm (23.1%, 95% CI 15.6–29.2%) ($P = 0.0029$) (Table 3). The prevalence of malaria parasitaemia in SP-treated children (13.1%) was also lower ($P = 0.043$) than that observed in the control arm (Table 3). However, the difference between the SP/PQ and SP did not reach significance ($P = 0.338$).

The PE on parasitaemia, over 12 months, was 19% (95% CI 2–33%; $P = 0.042$) and 40% (95% CI 26–52%; $P = 0.0001$), respectively, for the SP and SP/PQ arms (Fig. 3). Given these results, the calculated number of children needed to treat to prevent one case of malaria parasitaemia was 16 with SP and 8 with SP/PQ.

3.4. Impact of intermittent preventive treatment in schoolchildren (IPTsc) on clinical malaria

From November 2012 to March 2013, a total of 136 participants visited the Biyela regional hospital, of which 59 had a confirmed malaria infection (28, 20 and 11, respectively, in the control, SP and SP/PQ arms). No cases of severe malaria, as defined

Table 1
Baseline characteristics of children in the intermittent preventive treatment in schoolchildren (IPTsc) trial in Kinshasa, Democratic Republic of the Congo.

Characteristic	All enrolled children ($n = 616$)			Included in the mITT analysis ($n = 410$)			Included in the PP analysis ($n = 389$)		
	SP	SP/PQ	Control	SP	SP/PQ	Control	SP	SP/PQ	Control
No. (%) of children (grades 1–5)	202 (32.8)	202 (32.8)	212 (34.4)	137 (33.4)	130 (31.7)	143 (34.9)	134 (34.4)	125 (32.1)	130 (33.4)
Male sex [*n* (%)]	106 (52.5)	102 (50.5)	110 (51.9)	75 (54.7)	64 (49.2)	73 (51.0)	74 (55.2)	64 (51.2)	71 (54.6)
Weight (kg) (mean ± S.D.)	24.49 ± 0.40	24.84 ± 0.69	24.81 ± 0.39	24.54 ± 0.49	24.65 ± 0.47	24.72 ± 0.45	24.53 ± 0.51	24.66 ± 0.47	24.62 ± 0.48
Age (years) [median (IQR)]	8 (6.8–9)	8 (6.5–9)	8 (7–9)	8 (7–9)	8 (6.5–9)	8 (7.5–9.5)	8 (7.5–9.5)	8 (6.5–9)	8 (7–9.5)
History of transfusion [*n* (%)]	24 (11.9)	27 (13.4)	20 (9.4)	16 (11.7)	18 (13.8)	13 (9.1)	16 (11.9)	17 (13.6)	13 (10.0)
No. (%) with parasitic infections									
Schistosoma mansoni	8 (4.0)	9 (4.5)	12 (5.7)	3 (2.2)	9 (6.9)	7 (4.9)	3 (2.2)	9 (7.2)	7 (5.4)
STHs	49 (24.3)	51 (25.2)	50 (23.6)	36 (26.3)	32 (24.6)	32 (22.4)	36 (26.9)	32 (25.6)	29 (22.3)
Other characteristics									
Bednet ownership	38 (18.8)	39 (19.3)	41 (19.3)	24 (17.5)	25 (19.2)	29 (20.3)	22 (16.4)	24 (19.2)	24 (18.5)
Bednet use	27 (13.4)	25 (12.4)	29 (13.7)	17 (12.4)	19 (14.6)	17 (11.9)	15 (11.2)	18 (14.4)	19 (14.6)
Study endpoints at baseline									
Hb (g/dL) (mean ± S.D.)	11.54 ± 1.24	11.50 ± 1.25	11.58 ± 1.24	11.78 ± 1.15	11.53 ± 1.24	11.60 ± 1.26	11.79 ± 1.16	11.51 ± 1.25	11.59 ± 1.29
Anaemia [*n* (%)][a]	87 (43.1)	82 (40.6)	88 (41.5)	52 (38.0)	54 (41.5)	57 (39.9)	52 (38.8)	54 (43.2)	55 (42.3)
Malaria parasitaemia [*n* (%)]	42 (20.8)	32 (15.8)	41 (19.3)	27 (19.7)	20 (15.4)	31 (21.7)	27 (20.1)	20 (16.0)	29 (22.3)

mITT, modified intention-to-treat; PP, per-protocol; SP, sulfadoxine/pyrimethamine; SP/PQ, sulfadoxine/pyrimethamine plus piperaquine; S.D., standard deviation; IQR, interquartile range; STH, soil-transmitted helminth; Hb, haemoglobin.

[a] Anaemia was defined as a Hb concentration of <11, <11.5 and <12 g/dL, respectively, for schoolchildren aged <5 years, 5–11.9 years and 12–14.9 years.

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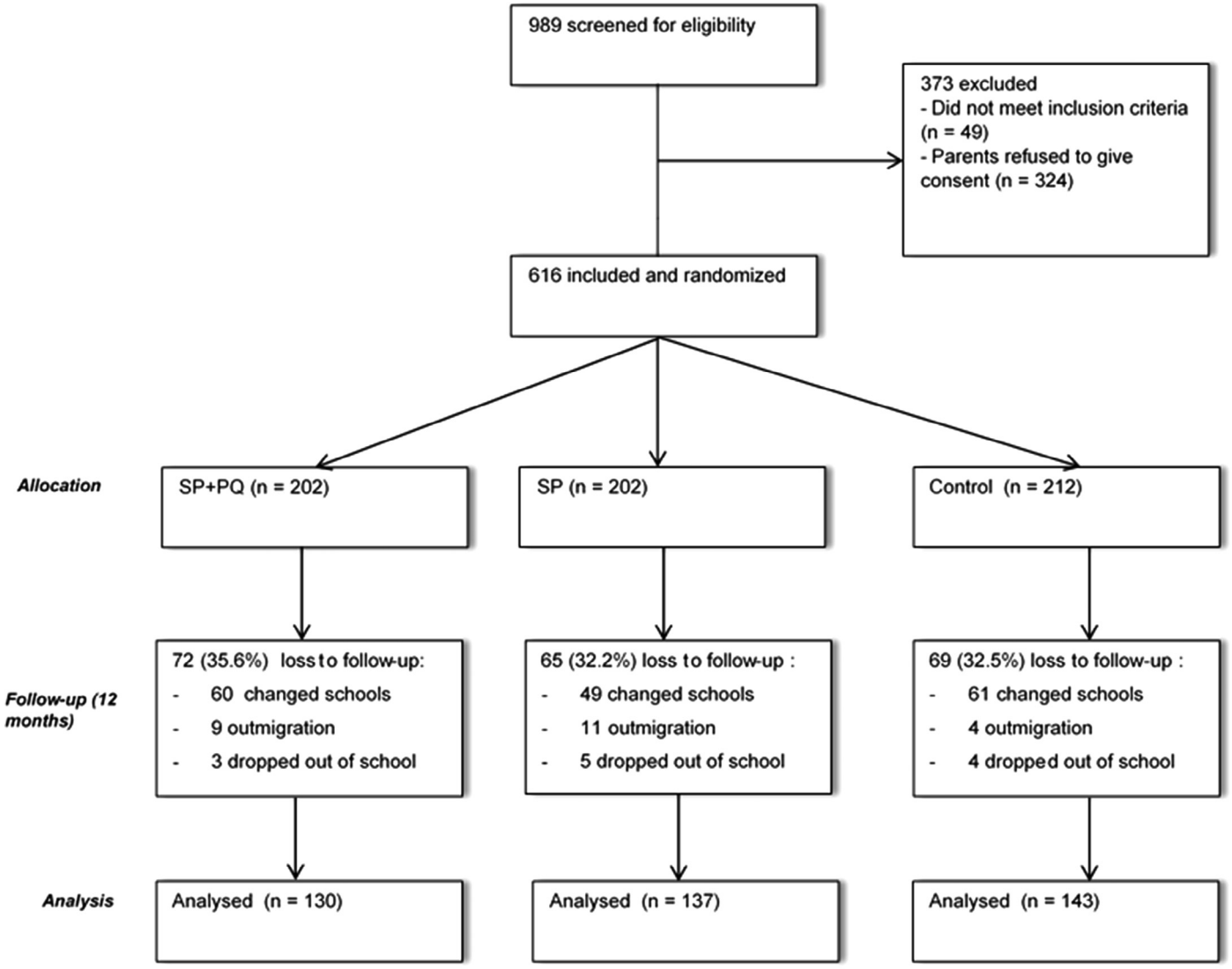

Fig. 1. Flow diagram of participants in the intermittent preventive treatment in schoolchildren (IPTsc) trial in Kinshasa, Democratic Republic of the Congo. SP, sulfadoxine/pyrimethamine; SP/PQ, sulfadoxine/pyrimethamine plus piperaquine.

by the WHO, were observed. The mean time to onset of clinical malaria was 26 days (95% CI 20.5–31.5 days), 29 days (95% CI 25.2–34.7 days) and 47 days (95% CI 34.9–59.8 days) in the control, SP and SP/PQ arms, respectively ($P = 0.001$) (Fig. 4). Thus, the time difference (TD) was significantly greater in the SP/PQ arm than in the control arm (TD, 21.3 days, 95% CI 8.4–34.1 days; $P = 0.001$) and the SP arm (TD, 17.3 days, 95% CI 3.8–30.9 days; $P = 0.002$). The TD did not differ between the SP and control arms (TD, 3.95 days, 95% CI –14.5 to 6.63 days; $P = 0.64$). The protective effect was 25% (95% CI –32 to 57%; $P = 0.37$) and 58% (95% CI 17–79%; $P = 0.0013$) for the SP and SP/PQ arms, respectively (Fig. 5). The calculated number needed to treat in order to prevent one episode of clinical malaria was 40 and 100, respectively, for the SP/PQ and SP treatments.

3.5. Safety outcomes

No deaths or serious or severe adverse events (SAEs) were observed. The most frequent adverse events encountered were abdominal pain, dizziness, headache, fever, vomiting and weakness. The frequency of any adverse effect was significantly higher

Table 2
Impact of interventions on haemoglobin (Hb) level in the intermittent preventive treatment in schoolchildren (IPTsc) trial in Kinshasa, Democratic Republic of the Congo.

	After 1st dose (Month 4)		After 2nd dose (Month 7)		After 3rd dose (Month 12)		Whole study period	
	Mean Hb level (g/dL) (95% CI)	*P*-value	Mean Hb level (g/dL) (95% CI)	*P*-value	Mean Hb level (g/dL) (95% CI)	*P*-value	Mean Hb level (g/dL) (95% CI)	*P*-value
MD SP vs. control	0.12 (–0.20, 0.46)	0.449	0.18 (–0.20, 0.52)	0.219	0.23 (–0.32, 0.51)	0.084	0.20 (–0.61, 0.47)	0.168
MD SP/PQ vs. SP	0.46 (0.11, 0.81)	0.009*	0.41 (0.02, 0.82)	0.039*	0.17 (–0.12, 0.45)	0.257	0.18 (–0.09, 0.45)	0.243
MD SP/PQ vs. control	0.59 (0.26, 0.92)	0.001*	0.61 (0.21, 1.01)	0.003*	0.41 (0.12, 0.70)	0.006*	0.39 (0.12, 0.66)	0.002*

CI, confidence interval; Hb, haemoglobin; MD, mean difference; SP, sulfadoxine/pyrimethamine; SP/PQ, sulfadoxine/pyrimethamine plus piperaquine.
* Statistically significant.

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Table 3
Prevalence of anaemia and malaria parasitaemia over 12 months of follow-up in the intermittent preventive treatment in schoolchildren (IPTsc) trial in Kinshasa, Democratic Republic of the Congo.

	Treatment arm						*P*-value		
	Control arm		SP arm		SP/PQ arm		SP vs. control	SP/PQ vs. control	SP/PQ vs. SP
	n/*N*	% (95% CI)	*n*/*N*	% (95% CI)	*n*/*N*	% (95% CI)			
Anaemia									
Baseline	85/212	40.1 (33.4–47.0)	83/202	41.1 (34.2–48.2)	87/202	43.1 (36.3–50.4)	0.842	0.551	0.92
Month 4	129/199	64.8 (57.7–71.4)	130/198	65.7 (58.6–72.2)	92/196	46.9 (39.2–53.9)	0.916	0.00038*	0.00017*
Month 7	119/190	62.6 (55.3–69.5)	96/182	52.7 (45.4–60.0)	86/181	47.5 (39.9–54.5)	0.317	0.018*	0.345
Month 12 (mITT analysis)	59/143	41.3 (33.1–49.8)	41/137	29.9 (22.4–38.3)	32/130	24.6 (16.5–31.1)	0.048*	0.0046*	0.34
Month 12 (PP analysis)	54/130	41.5 (33.9–51.1)	40/134	29.9 (21.9–37.3)	30/125	24.0 (16.4–31.2)	0.047*	0.0033*	0.33
Parasitaemia									
Month 4	75/199	37.7 (31.3–44.9)	63/198	31.8 (25.7–38.9)	46/196	23.5 (17.7–29.7)	0.291	0.0031*	0.07
Month 7	61/190	32.1 (25.2–38.4)	52/182	28.6 (22.0–35.2)	38/181	21.0 (15.2–26.9)	0.499	0.019*	0.114
Month 12 (mITT analysis)	33/143	23.1 (15.6–29.2)	18/137	13.1 (7.5–18.7)	12/130	9.2 (6.2–13.6)	0.043*	0.0029*	0.338
Month 12 (PP analysis)	31/130	23.8 (15.9–30.1)	18/134	13.4 (7.6–18.8)	11/125	8.8 (6.1–13.2)	0.039*	0.0013*	0.324

SP, sulfadoxine/pyrimethamine; SP/PQ, sulfadoxine/pyrimethamine plus piperaquine; *n*, number of cases; *N*, total number of children; CI, confidence interval; mITT, modified intention-to-treat; PP, per-protocol.
* Statistically significant.

in SP/PQ-treated children compared with controls ($P = 0.0069$), and dizziness was associated with SP/PQ treatment ($P = 0.0025$) (Table 4). When excluding dizziness, the frequency of any adverse effect did not differ between treatment arms (data not shown).

4. Discussion

This study demonstrated that the combination of SP and PQ (SP/PQ) increased the Hb concentration by 0.39 g/dL and reduced the overall risk of anaemia, malaria parasitaemia and clinical malaria by 28%, 40% and 58%, respectively. SP reduced the overall risk of malaria parasitaemia and anaemia by 19% and 10%, respectively, at Month 12. However, no effect of SP on malaria parasitaemia and anaemia was observed at Months 4 and 7. Moreover, SP did not show any efficacy on clinical malaria at Month 4, and no significant Hb change was observed. These results suggest that SP was effective only at Month 12, a period coinciding with relatively low transmission compared with Months 4 and 7. This is in agreement with other studies where a high rate of SP failure coincided with high transmission periods [25]. A marked effect of season on Hb level, frequency of anaemia and malaria parasitaemia was observed in all arms at Months 4 and 7 of follow-up. These two surveys coincided with the peak transmission observed in March and June. Hospital data from Kinshasa reported a high incidence of malaria especially in children aged 2–15 years during the months of March, June and December (unpublished data).

The poor effect of SP alone as a means to prevent malaria and its adverse outcomes in schoolchildren has been reported elsewhere [17] and this is the due to the increasing resistance to SP across Africa [26]. However, SP is still effective to prevent malaria and its adverse effects in pregnancy in Kinshasa [27], where the prevalence of the relevant mutation (*pfdhps*540^{E}) was found to be <10% [28]. Despite increasing resistance to SP, this drug has several advantages, including its low cost, single administration and proven safety.

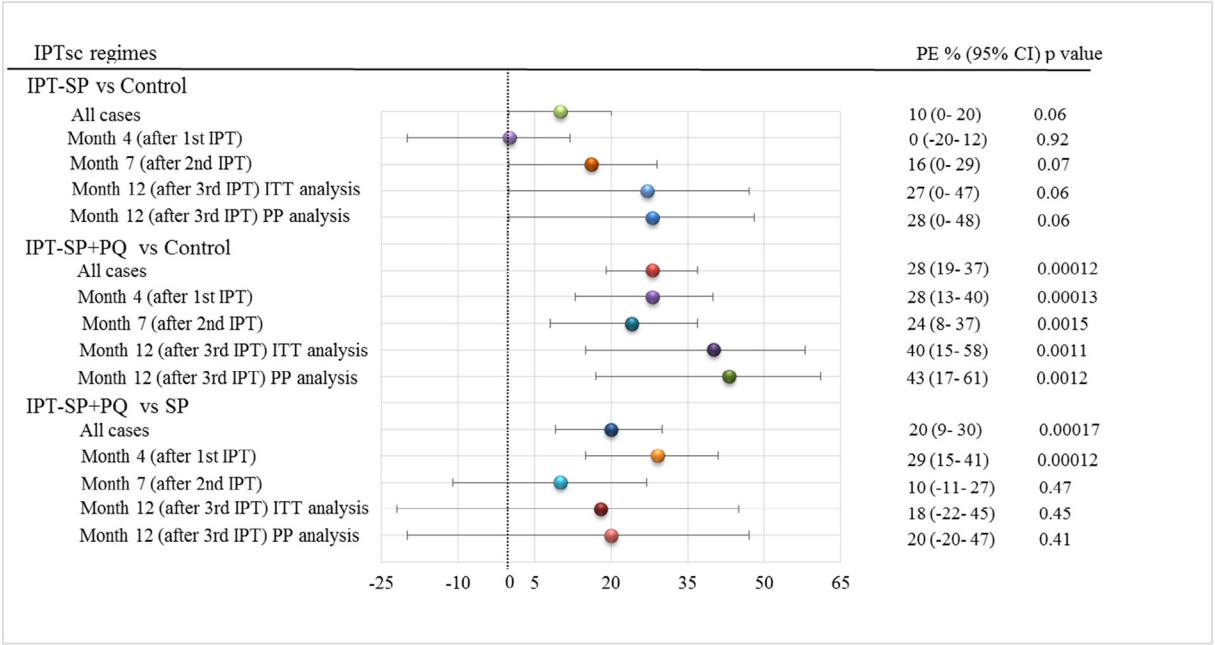

Fig. 2. Protective effect (PE) of intermittent preventive treatment in schoolchildren (IPTsc) on anaemia over 12 months of follow-up in Kinshasa, Democratic Republic of the Congo. SP, sulfadoxine/pyrimethamine; SP/PQ, sulfadoxine/pyrimethamine plus piperaquine; mITT, modified intention-to-treat; PP, per-protocol; CI, confidence interval.

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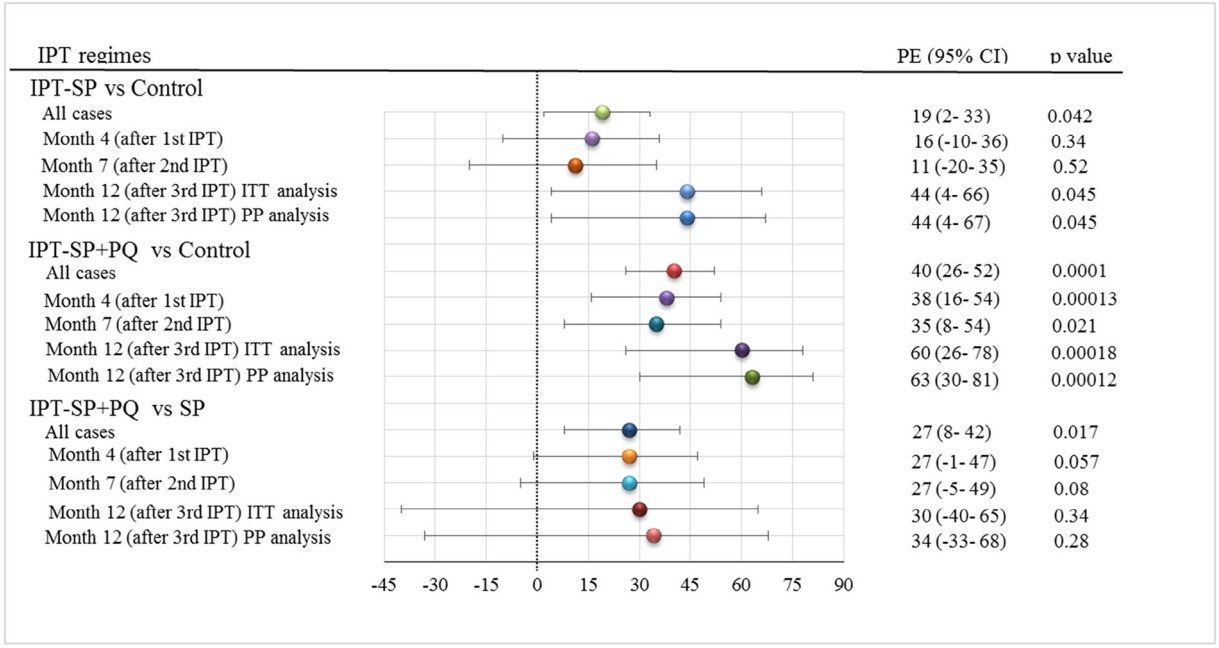

Fig. 3. Protective effect (PE) of intermittent preventive treatment in schoolchildren (IPTsc) on malaria parasitaemia over 12 months of follow-up in Kinshasa, Democratic Republic of the Congo. SP, sulfadoxine/pyrimethamine; SP/PQ, sulfadoxine/pyrimethamine plus piperaquine; mITT, modified intention-to-treat; PP, per-protocol; CI, confidence interval.

Despite the low prevalence of mutation, predicting fairly good efficacy of SP in Kinshasa, it appears from the current results that SP alone, administrated every 4 months, should not be considered as an effective drug regimen for malaria prevention in schoolchildren. In contrast, SP combined with PQ demonstrated acceptable protection against clinical malaria, malaria parasitaemia and anaemia. Moreover, SP/PQ was superior for preventing anaemia and malaria parasitaemia with an overall PE (SP/PQ vs. SP) of 20% (95% CI 9–30%) and 27% (95% CI 8–42%), respectively. This could be explained by the additional effect of the long half-life of PQ. The impact of SP/PQ did not differ from that provided by other combinations such as amodiaquine (AQ) + SP [17], AQ + artesunate (AS) [15] or SP+AS [15], and SP/PQ was no better than dihydroartemisinin/piperaquine (DP) given monthly, which showed a PE of 94% (95% CI 93–96%) and

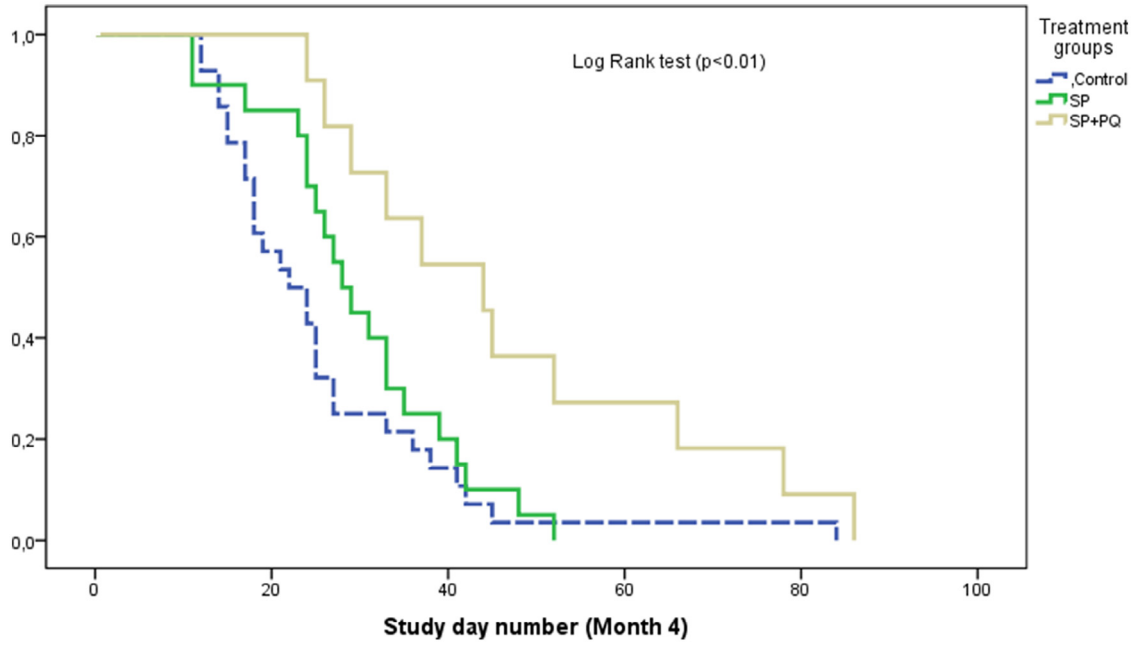

Fig. 4. Kaplan–Meier plot of clinical malaria incidence during 90-day of follow-up in intermittent preventive treatment in schoolchildren (IPTsc) trial in Kinshasa, Democratic Republic of the Congo. SP, sulfadoxine/pyrimethamine; SP/PQ, sulfadoxine/pyrimethamine plus piperaquine. Mean ± standard deviation time to onset of clinical malaria: 26 ± 14.7 days, 29 ± 10.9 days and 47 ± 21.1 days, respectively, in the control, SP and SP/PQ arms [analysis of variance (ANOVA), $P = 0.001$].

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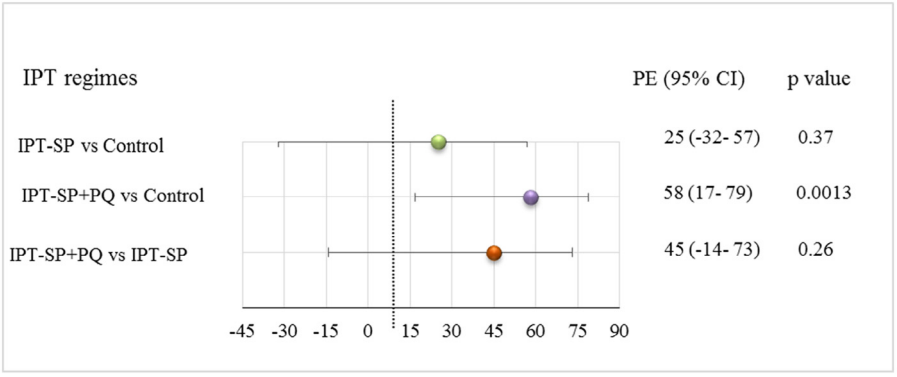

Fig. 5. Protective effect (PE) of intermittent preventive treatment in schoolchildren (IPTsc) on clinical malaria over 4 months of follow-up in Kinshasa, Democratic Republic of the Congo. SP, sulfadoxine/pyrimethamine; SP/PQ, sulfadoxine/pyrimethamine plus piperaquine; CI, confidence interval.

40% (95% CI 29–4%) for malaria parasitaemia and anaemia, respectively [18]. However, a number of issues need to be considered when comparing the efficacy provided by drugs used in other studies, including: the difference in dosing intervals (monthly for DP vs. every 4 months for SP/PQ); the difference in timing of assessing efficacy (42 days after treatment for SP+AQ vs. 4 months for SP/PQ); and the number of doses administrated (only once for SP+AS, AQ+AS and SP+AQ vs. 3 doses for SP/PQ).

Besides the efficacy of a drug regimen, feasibility should be taken into consideration when assessing an IPTsc strategy. Therefore, combination of SP/PQ presents an acceptable efficacy associated with a feasible scheme, allowing a dosing interval of every 4 months compared with DP administered monthly. The use of short-acting drugs such as artemisinins, given with a short interval between doses, although effective, may be challenging and costly, and the drug pressure in the context of IPTsc may lead to an increase of the selection of mutants resistant to artemisinin. However, owing to the rapid clearance of malaria parasites from the blood provided by artemisinin derivatives, they should be preferably used for curative treatment rather than for malaria prevention where a prophylactic effect is a key feature. Moreover, the magnitude of an expected rebound effect, after the last dose of IPTsc, may be greater in children receiving IPTsc monthly compared with those treated every 4 months. Indeed, compared with monthly dosing, which can be considered as chemoprophylaxis, IPTsc every 4 months allows for a longer unprotected period of time between doses. This period allows the occurrence of a low-grade malaria infection or occasional exposure to malaria parasites maintaining specific malaria immunity, which naturally depends on the half-life of the drugs used [29]. Therefore, a balance may be needed between optimum impact with frequent doses exposing to a greater risk of rebound versus longer spacing between doses, reducing the risk and the magnitude of rebound but with less impact.

There is no evidence of the superiority of IPTsc over bednet use, or vice versa, in protection against malaria-related outcomes in schoolchildren. However, considering that school-age children are less likely to sleep under a bednet [9] and are most likely to sleep under poor household sleeping arrangements, such that school-aged children sleep on the floor and in areas where it is not possible to hang nets [30,31], a situation that may affect the effectiveness of bednets in this age group, IPTsc every 4 months may be an appreciable option. Studies have shown that the combination of bednets and IPT provided a high level of protection against malaria-related outcomes in schoolchildren and those under 5 [13,31,32]. However, this could not be assessed in the current study owing to the low reported coverage of bednets. Therefore, IPTsc using long half-life drugs, integrated with other interventions such as bednet use and iron supplementation, could provide additional benefit.

The present study has a number of limitations. First, the effect on clinical malaria, a secondary endpoint, was evaluated only after a single dose of IPTsc. This did not allow to evaluate the impact of IPTsc in a longitudinal cohort or to assess any seasonal interactions.

Second, the expected high rate of loss to follow-up, reaching 30% in all treatment arms, may indicate a selection bias towards this representativeness of this age group and may increase the chance of missing SAEs. School cohorts tend to have high rates of loss to follow-up, and even a low rate of loss to follow-up may lead to significant bias. However, as the Little's test suggests an MCAR

Table 4
Risk of adverse events in all children over 12 months of follow-up and comparison with the control arm in the intermittent preventive treatment in schoolchildren (IPTsc) trial in Kinshasa, Democratic Republic of the Congo.

	Control arm ($N = 212$)		SP arm ($N = 202$)			SP/PQ arm ($N = 202$)		
	n	% Risk (95% CI)	*n*	% Risk (95% CI)	*P*-value (vs. control)	*n*	% Risk (95% CI)	*P*-value (vs. control)
Any adverse events	111	52.4 (43.9–61.0)	107	53.0 (43.8–61.3)	0.921	133	65.8 (54.9–77.5)	0.0069*
Dizziness	11	9.9 (7.1–13.0)	18	16.8 (12.7–21.0)	0.839	48	36.1 (25.0–43.4)	0.0025*
Abdominal pain	47	42.3 (29.5–55.5)	32	29.9 (19.1–39.7)	0.105	37	27.8 (22.1–33.7)	0.392
Headache	22	19.8 (15.7–29.3)	18	16.8 (12.1–24.7)	0.622	20	15.0 (10.4–22.0)	0.501
Vomiting	9	8.1 (5.3–9.7)	14	13.1 (7.4–19.3)	0.164	12	9.0 (6.3–14.0)	0.574
Nausea	6	5.4 (3.6–6.4)	13	12.1 (9.6–16.3)	0.064	4	3.0 (1.1–7.3)	0.752
Fever	8	7.2 (5.3–9.7)	8	7.5 (5.6–9.2)	0.875	5	3.8 (1.2–8.0)	0.634
Weakness	5	4.5 (3.6–6.4)	5	4.7 (2.3–8.9)	0.808	4	3.0 (1.1–7.3)	0.941
Skin rash	3	2.7 (1.9–3.1)	0	–	–	3	2.3 (0.91–5.5)	0.725
Serious adverse events	0	–	0	–	–	0	–	–

SP, sulfadoxine/pyrimethamine; SP/PQ, sulfadoxine/pyrimethamine plus piperaquine; CI, confidence interval.
* Statistically significant.

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mechanism and as the dropout rate was predictable, randomised across arms and children lost to follow-up were similar to those eligible for the analyses, we believe that the results are representative for schoolchildren. Moreover, the linear mixed model used is robust enough to deal with a high rate of loss to follow-up [33–35]. Third, a longer follow-up period of ≥24 months could give a better picture of the seasonal interaction with treatment efficacy and a possible cumulative effect. Fourth, the lack of information on the impact of IPTsc on school performance or school attendance in this study could not help to fully assess the value of the strategy in this specific group.

5. Conclusion

The drug regimen, efficacy and safety profile of antimalarial used to prevent *Plasmodium falciparum* infection in pregnant women and infants and, to a lesser extent, children under 5, have been widely investigated. This is not the case in older school-aged children. This study revealed that SP/PQ could be a suitable drug regimen to prevent malaria in schoolchildren by virtue of its acceptable efficacy and feasible scheme, allowing a dosing interval of every 4 months. In contrast, SP alone, despite the good efficacy predicted by the low prevalence of *pfdhps*540^{E}, should not be considered as an effective means to prevent malaria and its related adverse effects in schoolchildren living in high transmission area for malaria.

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Competing interests: None declared.

Ethical approval: This study was approved by the Ethical Committee of the University of Kinshasa (Kinshasa, DRC) [registration no. ESP/ CE/045/2012] and the University of Antwerp (Antwerp, Belgium) [registration no. B300201214729].

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