PLASMODIUM FALCIPARUM HYPERPARASITAEMIA IN CHILDREN RISK FACTORS, TREATMENT OUTCOMES, AND GAMETOCYTAEMIA FOLLOWING TREATMENT

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Summary:

The risk factors associated with hyperparasitemia at presentation and after treatment with different antimalarial drug regimens were evaluated in 1,048 children enrolled prospectively in seven antimalarial drug trials between July 1996 and September 2003 in a hyperendemic area of southwestern Nigeria. The outcomes of treatment of hyperparasitaemia, and gametocyte carriage following treatment were also evaluated. The children were assigned to one of seven treatment groups : chloroquine (CQ) only; pyrimethamine-sulfadoxine (PS) only; amodiaquine (AQ) only; CQ plus chlorpheniramine (CQCP); PS combined with CQ or AQ (COM); PS combined with probenecid (PPS); and halofantrine (HF). Hyperparasitaemia was found in 100 (9.5 %) of the 1,048 children at enrolment (day 0). Following oral therapy, 1.2 % of all patients (i.e. 13 patients) became hyperparasitaemic, which developed in all patients by day 1 of follow-up. In a multiple regression model, age ≤ 5 years, and a core temperature (oral or rectal) $\geq 39.5^\circ\text{C}$ were found to be independent risk factors for hyperparasitaemia at enrolment. Following therapy, the cure rate on day 14 was significantly lower in those treated with CQ compared to other treatment groups. Severe resistance (R111) response to treatment occurred significantly more frequently in those with hyperparasitaemia at enrolment than in those without, and was seen in five and one child with hyperparasitaemia who were treated with CQ and CQCP, respectively. Gametocyte carriage was insignificantly lower at enrolment and at all times following treatment in children with hyperparasitaemia than in age- and gender- matched children without hyperparasitaemia who received the same treatment. The results are discussed in the light of management of uncomplicated hyperparasitaemia in children in endemic settings.

KEY WORDS : malaria, hyperparasitaemia, risk factors, gametocytaemia, children, Nigeria.

Résumé : HYPERPARASITÉMIE À *PLASMODIUM FALCIPARUM* CHEZ DES ENFANTS : FACTEURS DE RISQUE ET GAMÉTOCYTÉMIE AVANT ET APRÈS TRAITEMENT

Les facteurs de risque associés à l'hyperparasitémie à *Plasmodium falciparum* à l'admission et après le traitement avec sept protocoles antipaludéens différents par voie orale ont été évalués chez 1 048 enfants lors d'une étude prospective, menée entre juillet 1996 et septembre 2003 au Sud-Ouest du Nigéria, dans une zone hyperendémique. Les résultats du traitement (hyperparasitémie et durée de la persistance des gamétocytes dans le sang) ont été évalués. Les groupes traités étaient : chloroquine (CQ); pyriméthamine-sulfadoxine (PS); amodiaquine (AQ); chloroquine plus chlorpheniramine (CQCP); pyriméthamine-sulfadoxine plus chloroquine ou amodiaquine (COM); pyriméthamine-sulfadoxine plus probenecid (PPS); halofantrine (HF). L'hyperparasitémie a été retrouvée chez 100 enfants lors de l'admission (9,5 %). Après 24 heures de traitement, 1,2 % des enfants ($n = 13$) sont devenus hyperparasités. Avec un programme de régression multiple, nous avons montré qu'un âge ≤ 5 ans et une température centrale $\geq 39,5^\circ\text{C}$ sont des facteurs de risque indépendants pour l'hyperparasitémie à l'admission. Après deux semaines de traitement, le pourcentage de guérison est significativement plus bas dans le groupe CQ. Une résistance sévère à ce traitement (R111) apparaît plus fréquemment chez ceux qui sont hyperparasités à l'admission. Le nombre de gamétocytes circulants était plus bas à l'admission et pendant le traitement chez les enfants hyperparasitiques que chez ceux du même âge et de même sexe avec le même traitement, mais sans hyperparasitémie. Les résultats sont discutés dans le but d'améliorer le traitement des accès palustres non compliqués avec hyperparasitémie dans les zones d'endémie.

MOTS CLÉS : paludisme, hyperparasitémie, facteur de risque, gamétocytémie, enfants, Nigéria.

INTRODUCTION

Plasmodium falciparum infections may result in rapid multiplication of asexual parasites and massive increases in circulating peripheral parasites particularly in the relatively non-immune or, less

frequently, in the semi-immune. These massive increases may reach or surpass a threshold referred to as hyperparasitaemia. Hyperparasitaemia, defined as 5 % or more parasitized erythrocytes or a parasitaemia greater than 250,000/ μL blood, is considered one of the several features of severe malaria (WHO, 1990, 2000 a). Hyperparasitaemia not accompanied by other features of severe malaria (uncomplicated hyperparasitaemia) often pose management problems in patients resident in endemic areas. Apart from a general recommendation of parenteral antimalarials (WHO, 2000 b), there are no other clear-cut guidelines for the management of uncomplicated hyperparasitaemia in children resident in such areas. However, it has been suggested that

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uncomplicated hyperparasitaemia in children in these endemic areas be treated with oral antimalarial drugs providing the drug is rapidly absorbed and the parasites are fully sensitive to the antimalarial drug(s) chosen (Sowunmi *et al.*, 1992, 1996, 2000 a). Such a suggestion needs review in view of the increasing resistance in *P. falciparum* to many antimalarials drugs and the lack of facilities to monitor drug sensitivity of *P. falciparum* *in vitro* and *in vivo* in many endemic areas.

There is little information on, for example, the risk factors associated with uncomplicated hyperparasitaemia or the time-course of gametocytaemias following oral antimalarial treatment of uncomplicated hyperparasitaemias in African children. Such information is necessary in view of the increasing resistance in *P. falciparum* to chloroquine (CQ) and other commonly available antimalarials and the increasing morbidity and mortality associated with drug resistance (Trape *et al.*, 1998; Trape, 2001). In addition, it may improve the overall management of these cases. The present study was designed to address these issues. The main aims of the study were : to evaluate the risk factors associated with hyperparasitaemia in a group of children presenting with acute, symptomatic, apparently uncomplicated, *P. falciparum* malaria in an endemic area; to assess the outcomes of oral antimalarial treatment of uncomplicated hyperparasitaemia; and to follow the temporal changes in gametocytaemias in children with hyperparasitaemias who were treated with oral antimalarial drugs.

PATIENTS AND METHODS

PATIENTS

The study took place between July 1996 and September 2003 in patients presenting at the University College Hospital in Ibadan, a hyper-endemic area for malaria in southwestern Nigeria (Salako *et al.*, 1990). Ethical clearance was provided by the local ethics committee. During the period, a series of antimalarial drug studies were conducted to evaluate the efficacy and safety of different treatment regimens. All antimalarial drugs were given orally. The details of the studies have been described before (Sowunmi *et al.*, 1998 a, b, c, 2000 a; Sowunmi, 2002, 2003; Sowunmi & Fateye, 2003). Briefly, children with symptoms compatible with acute falciparum malaria who fulfilled the following criteria were enlisted in the study : age below 12 years, pure *P. falciparum* parasitaemia greater than 2000 asexual forms/ μ L blood, negative urine tests for antimalarial drugs (Dill-Glazko and lignin tests), absence of concomitant illness, no evidence of severe malaria (WHO, 2000 a) and written

informed consent given by parents or guardians. After enrolment and start of treatment (day 0), follow-up with clinical and parasitological evaluation was at days 1-7, and then on days 14, and when necessary, on days 21 and 28, for example, in patients who received pyrimethamine-sulfadoxine (PS) [Fansidar®, Hoffmann La Roche] combined with chloroquine [Nivaquine®, May & Baker Plc, Nigeria] or amodiaquine [Camoquine®, Parke Davis, Senegal]. Clinical evaluation consisted of a general clinical examination including measurement of weight, core temperature and physical examination.

ASSESSMENT OF PARASITAEMIA

Thick and thin blood films prepared from a finger prick were Giemsa-stained and were examined by light microscopy under an oil-immersion objective, at $\times 1,000$ magnification, by two independent assessors. Parasitaemia in thick films was estimated by counting asexual parasites relative to 1,000 leukocytes, or 500 asexual forms, whichever occurred first. From this figure, the parasite density was calculated assuming an average leukocyte count of 6,000/ μ L of blood (Shaper & Lewis, 1971; Ezeilo, 1971; Sowunmi *et al.*, 1995). Gametocytes were also counted in thick films against 1,000 leukocytes assuming an average leukocyte count of 6000/ μ L of blood at enrolment (day 0) and on days 7 and 14. Fractional gametocyte density (FGD) at enrolment was defined as gametocyte count divided by total asexual and sexual count (Price *et al.*, 1999). Haematocrit was done at enrolment in 124 of the patients treated with PS or CQPS, AQPS or PPS.

EVALUATION OF RESPONSE TO DRUG TREATMENT

Response to drug treatment was assessed using World Health Organization (WHO) criteria (WHO, 1973) as follows : S = sensitive, clearance of parasitaemia without recurrence; RI (mild resistance) = parasitaemia disappears but reappears within 7 to 14 days; RII (moderate resistance) = decrease of parasitaemia but no complete clearance from peripheral blood; RIII (severe resistance) = no pronounced decrease or increase in parasitaemia at 48 hours after treatment. In those with sensitive or RI response, parasite clearance time (PCT) was defined as the time elapsing from drug administration until there was no patent parasitaemia for at least 72 h. Asexual parasite reduction ratio [PRR] (White, 1997) was defined as the ratio of day 0/day 2 parasitaemia.

RE-TREATMENT OF TREATMENT FAILURES

All patients with RII and RIII responses were re-treated with intramuscular artemether (9.6 mg/kg, over five days). Patients with RI response were re-treated with oral mefloquine 25 mg/kg single dose and followed

up for another 14-28 days. Patients were retreated whenever they became symptomatic or when they show profound clinical (hyperpyrexia, oral fluid intolerance) or parasitological deterioration.

STATISTICAL ANALYSIS

Data were analysed using version 6 of the Epi-Info software (Anon., 1994), and the statistical program SPSS for Windows version 10.01 (SPSS, 1999). Proportions were compared by calculating χ^2 with Yates' correction or Fisher exact test. Normally distributed, continuous data were compared by Student's t-tests and analysis of variance (ANOVA). Data not conforming to a normal distribution were compared by the Mann-Whitney U-test and the Kruskal-Wallis test (or by Wilcoxon rank sum test). A multiple logistic regression model was used to test the association between hyperparasitaemia (yes or no at presentation or during follow up) and factors that were significant at univariate analysis : age ≤ 5 years, and presence of fever (oral or rectal temperature) $\geq 39.5^\circ\text{C}$. Because the study was conducted over a period of seven years, time was included as a covariate in the analysis. P-values of ≤ 0.05 were taken to indicate significant differences.

RESULTS

The demographic characteristics of the children enrolled in the study are summarized in Table I. At enrolment, 303, 173, 104, 203, 143, 78 and

44 of the 1,048 children were allotted to, and were subsequently treated with chloroquine (CQ) only; pyrimethamine-sulfadoxine (PS) only; amodiaquine (AQ) only; CQ plus chlorpheniramine (CQCP); PS combined with CQ or AQ (COM); PS combined with probenecid (PPS); and halofantrine (HF) [Halfan®, GlaxoSmithkline], respectively. Hyperparasitaemia was found in 100 (9.5 %) of the 1,048 children at enrolment.

RISK FACTORS FOR HYPERPARASITAEMIA AT ENROLMENT

Factors associated with hyperparasitaemia at enrolment are presented in Table II. Age ≤ 5 years, and oral or rectal temperature $\geq 39.5^\circ\text{C}$ were independent risk factors for uncomplicated hyperparasitaemia at enrolment.

Variables	Value [mean $\pm$ sd (range)]
Age (years)	5.5 $\pm$ 2.5 (0.5-11.9)
M : F	493 : 555
Weight (kg)	15.1 $\pm$ 4.8 (6.6-27)
Presenting body temperature ($^\circ\text{C}$)	38.6 $\pm$ 1.2 (36.4-40.8)
Duration of illness (d)	3.0 $\pm$ 1.5 (1-14)
Asexual parasite density (per μL)	
Geometric mean	30,129
Range	2,090-2,341,000
No. > 250000	100

Table I. – Summary of demographic and other characteristics of the 1,048 children enrolled in the study.

	Total no.	No. of children with hyperparasitaemia	Crude OR (95 % CI)	P. value	Adjusted OR (95 % CI)	P. value
Age (years)						
≤ 5	533	62	1.65		1.61	
> 5	515	38	1 (1.06-2.6)	0.025	1 (1.05-2.47)	0.026
Gender						
male	493	45	1.1		–	
female	555	55	1 (0.58-1.4)	0.7 $^\alpha$	–	–
Duration of illness (d)						
≥ 3	696	66	0.98		–	
< 3	352	34	1. (0.62-1.56)	0.9	–	–
Fever*						
$\geq 39.5^\circ\text{C}$	214	31	1.88		1.84	
$< 39.5^\circ\text{C}$	834	69	1 (1.15-3.01)	0.008 $^\alpha$	1 (1.17-2.89)	0.009
Gametocytes						
Yes	124	11	0.91		–	
No	924	89	1 (0.43-1.78)	0.9 $^\alpha$	–	–

OR, odds ratio,

α , χ^2 with Yate's correction,

CI, confidence interval.

Table II. – Risk factors for *P. falciparum* hyperparasitaemia at enrolment.

HYPERPARASITAEMIA DURING FOLLOW UP

Following oral therapy, 1.2 % of all patients (i.e. 13 of the 1,048 patients) became hyperparasitaemic, which developed in all patients by day 1 of follow-up. The 13 patients were treated with CQ (10 patients) PS (one patient) or COM (two patients), and following treatment, all but two had sensitive response. The two children in the COM group who became hyperparasitaemic on day 1 specifically received PS combined with CQ. The two children with resistance response (1 RI, 1RII) were treated with CQ. Compared with other treatment groups, there was a significant difference in the proportion of children treated with CQ who became hyperparasitaemic on day 1 following treatment ($P = 0.01$).

TREATMENT OUTCOMES OF HYPERPARASITAEMIA

The clinical and parasitological characteristics of the 100 children who had hyperparasitaemia at enrolment and were treated with oral antimalarial drugs are summarized in Table III. Despite enrolment at different periods, these characteristics were similar (primarily because the criteria for enrolment into all studies were similar). No child with hyperparasitaemia was treated with AQ alone.

The responses of the asexual hyperparasitaemia to drug treatment are shown in Table IV. The cure rate following treatment with CQ was significantly lower than the other treatment groups.

	CQ (n = 33)	CQCP (n = 25)	PS (n = 25)	COM (n = 11)	PPS* (n = 5)	HF* (n = 1)	P. value
Age (years)							
Mean $\pm$ sd	4.3 $\pm$ 2.3	5.1 $\pm$ 2.3	4.6 $\pm$ 2.8	4.9 $\pm$ 2.2	7.5 $\pm$ 1.5	5.0	0.6
Range	1.5-9	0.7-10.5	0.5-10.5	3-8.1	6.3-10	-	
M : F	12 : 21	13 : 12	12 : 13	6 : 5	3 : 2	1 : 0	-
Duration of illness (d)							0.5
Mean	2.8 $\pm$ 1.2	3.2 $\pm$ 1.3	3.5 $\pm$ 2.5	3.0 $\pm$ 0.7	3.0 $\pm$ 0.0	3.0	
Range	1-6	1-6	1-14	2-4	3-3	-	
Parasitaemia (μ L)							
Geometric mean	438,649	467,090	398,318	387,090	750,304	-**	0.4
Range	253,091-1,500,000	253,600-2,341,000	253,091-1,254,000	250,145-716,000	414,750-1,388,000		

PS, pyrimethamine-sulfadoxine; CQ, chloroquine; CQCP, chloroquine plus chlorpheniramine;

COM, pyrimethamine-sulfadoxine combined with chloroquine or amodiaquine;

PPS pyrimethamine-sulfadoxine combined with probenecid; HF, halofantrine.

* Excluded from multiple comparison because of relatively small number of patients.

** Parasitaemia at enrolment was 438,660 per μ L.

Table III. – Clinical and parasitological characteristics of 100 children with *P. falciparum* hyperparasitaemia who were treated with oral antimalarial drugs.

	CQ (n = 33)	CQCP (n = 25)	PS (n = 25)	COM (n = 11)	PPS* (n = 5)	HF* (n = 1)	P. value
FCT (d)							
Mean $\pm$ sd	2.0 $\pm$ 0.9	2.3 $\pm$ 1.0	2.2 $\pm$ 1.2	1.6 $\pm$ 0.5	2.2 $\pm$ 1.3	1.0	0.5
Range	1-4	1-4	1-4	1-2	1-4	-	
PRR							
Median ($\times 10^4$)	3.6	1.0	37.1	13.1	30.2	-	0.3
Interquartile range ($\times 10^4$)	0.006-72.2	0.03-44.6	27.3-77.6	0.09-45.1			
PCT (d)							
Mean	2.8 $\pm$ 1.1	3.2 $\pm$ 0.8	2.8 $\pm$ 1.3	2.6 $\pm$ 0.5	2.6 $\pm$ 0.9	3.0	0.4
Range	2-6	2-5	2-6	2-3	2-4	-	
S (no. of patients)	18	22	22	11	5	1	
RI	8	1	3	0	0	0	
RII	2	1	0	0	0	0	
RIII	5	1	0	0	0	0	
Cure rate (%)	54.5	88	88	100	100	-	0.001

PRR, parasite reduction ratio; FCT, fever clearance time; PCT, parasite clearance time; PS, pyrimethamine-sulfadoxine; CQ, chloroquine;

CQCP, chloroquine plus chlorpheniramine, COM, pyrimethamine-sulfadoxine combined with chloroquine or amodiaquine;

PPS pyrimethamine-sulfadoxine combined with probenecid; HF, halofantrine;

RI = parasitaemia disappears but reappears within 7 to 14 days; RII = decrease of parasitaemia but no complete clearance from peripheral blood; RIII = no pronounced decrease or increase in parasitaemia at 48 hours after treatment. S = sensitive response.

* Excluded from multiple comparison because of relatively small number of patients.

Table IV. – Therapeutic responses of 100 children with acute *P. falciparum* malaria who had hyperparasitaemia at enrolment.

COMPARISON OF OUTCOMES OF TREATMENT OF NON HYPERPARASITAEMIA AND HYPERPARASITAEMIA

Sixteen of 948 children without hyperparasitaemia had RIII response to treatment compared to six of 100 children with hyperparasitaemia. The difference between these proportions was significant ($\chi^2 = 6.22$, $P = 0.001$). Four children (three treated with CQ and one with PS) aged ≤ 3 years who had hyperparasitaemia progressed to cerebral malaria, while two of the 948 children without hyperparasitaemia had the same outcome. The difference between these two proportions was significant ($P = 0.001$, by Fisher exact test). The two children without hyperparasitaemia who progressed to cerebral malaria were treated with CQ. Adverse reactions reported following drug treatment were similar in children with hyperparasitaemia and in age- and gender- matched children without hyperparasitaemia who were treated with the same drugs (data not shown). For example, in those treated with CQ, pruritus occurred in five (of 33) and four (of 33) children with and without hyperparasitaemia, respectively.

GAMETOCYTE CARRIAGE AND GAMETOCYTAEMIA IN CHILDREN WITH HYPERPARASITAEMIA

In order to evaluate gametocyte carriage and gametocytaemia in those who were hyperparasitaemic at presentation, children with hyperparasitaemia were matched with those without hyperparasitaemia for time of presentation, age, gender, and drug treatment.

At enrolment gametocyte carriage was similar in children with hyperparasitaemia and in age- and gender-matched children without hyperparasitaemia who received the same drug treatment (6 of 100 *vs* 11 of 100 children, $\chi^2 = 1.03$, $P = 0.3$). Similarly following treatment, gametocyte carriage was similar on day 7 (16 of 100 *vs* 27 of 100 children, $\chi^2 = 2.9$, $P = 0.08$) and on day 14 (9 of 100 *vs* 17 of 100 children, $\chi^2 = 2.2$, $P = 0.14$).

At enrolment gametocytaemia was similar in children with hyperparasitaemia and in age- and gender-matched children without hyperparasitaemia who received the same drug treatment (geometric mean 12, range 6-24/uL *vs* 14 range 6-72, $P = 0.5$). Similarly following treatment, gametocytaemia was similar on day 7 (geometric mean 71, range 6-1320/uL *vs* 66, range 6-828, $P = 0.4$) and on day 14 (geometric mean 57, range 12-480/uL *vs* 70 range 12-360, $P = 0.7$).

Fractional gametocyte density was insignificantly lower in children with hyperparasitaemia compared with those without hyperparasitaemia (median 0.003, range 0.001- 0.005 *vs* 0.048, range 0.0015-2.3 %, $P = 0.24$).

RE-TREATMENT OF TREATMENT FAILURES

All treatment failures responded to re-treatment with intramuscular artemether or oral mefloquine with clearance of fever and parasitaemia within 72 h of commencing re-treatment and with no recurrence of parasitaemia during additional 14-28 days of follow-up.

DISCUSSION

Uncomplicated hyperparasitaemia is not uncommon in African children presenting with acute, symptomatic, *P. falciparum* malaria (Salako *et al.*, 1990; Sowunmi *et al.*, 1992, 1996, 2000 a). Prevalence rates in endemic and non endemic areas in Africa probably vary widely; in southwest Nigeria, the rate is approximately 10-12 % (Sowunmi, unpublished data). The 10 % prevalence recorded in the present study was similar to that previously reported from the same area in the early 1990's (Salako *et al.*, 1990).

The risk factors associated with uncomplicated hyperparasitaemia at presentation are not frequently documented. In falciparum infections, younger age (≤ 3 years) has been associated with hyperparasitaemia and increased risk of progression to cerebral malaria (Sowunmi *et al.*, 2000 a). In the present study, age ≤ 5 years and oral or rectal temperature $\geq 39.5^\circ\text{C}$ were independent risk factors associated with hyperparasitaemia at presentation. In falciparum infections in young children, the general trend is for parasitaemia to increase with time, and more specifically, to be accompanied by increases in body temperature. However, in severe infections there may be hypothermia. In practice many children with lower oral or rectal temperatures than our model found may be hyperparasitaemic. This would be so because many parents or guardians have ready access to over the counter remedies including antipyretics before presentation. This 'blunting' of presenting oral or rectal temperature may mislead the attending health care provider and distract attention from the possible presence of hyperparasitaemia.

The responses of apparently uncomplicated hyperparasitaemia to oral therapy are less frequently reported, probably because of the dangers associated with oral therapy in a condition that may rapidly progress to a fatal outcome, and probably also because of increasing resistance in *P. falciparum* to antimalarial drugs leading to reluctance to try oral therapy. Providing the parasites are fully sensitive to the oral drugs chosen, responses to drug therapy appears to be independent of parasite load. Thus in a comparative study, therapeutic responses of those with and without hyperparasitaemia were similar in children from an endemic

area in West Africa (Sowunmi *et al.*, 2000 a). In addition, in drug sensitive infections, the disposition of parasitaemia appears to follow a first order kinetics (Sowunmi *et al.*, 2000 a, b). In our cohort of children, CQ was the least effective drug in children with hyperparasitaemia and clearly represented a significant decline in the sensitivity of *P. falciparum* to this drug. Thus with prevailing degree of CQ resistance, this drug may not be ideal for the treatment of malaria irrespective of parasite load. The significantly higher proportions of children without hyperparasitaemia who subsequently developed it following treatment with CQ or PS compared with the other treatment groups suggest slow onset of antimalarial action or reduced sensitivity to these drugs and a risk for development of post-treatment hyperparasitaemia.

The similar frequencies of pruritus (and other adverse drug reactions following treatment in those with and in those without hyperparasitaemia who were treated with the same drugs [data not shown]) suggest that hyperparasitaemia does not predispose to undue adverse drug reactions following treatment (Sowunmi *et al.*, 2000 a).

Relatively low asexual parasitaemia and absence of fever are some of the risk factors associated with gametocyte carriage in falciparum infections (Price *et al.*, 1999; Akim *et al.*, 2000; von Seidlein *et al.*, 2001). The lower gametocyte carriage and gametocytaemia following treatment of the children with hyperparasitaemia indicate that oral therapy of this condition is not associated with undue generation of gametocytes. However, it is not known whether gametocytes arising from patients who had hyperparasitaemia are more infectious to the mosquito than those arising from patients without hyperparasitaemia who were treated with the same drugs.

Hyperparasitaemia is a potentially life threatening condition, and with or without other features of severe malaria requires close clinical and parasitological monitoring. Its occurrence in children from this endemic area without other overt features of severe falciparum malaria suggests the presence of some degree of immunity, although these children are, in general, considered relatively non-immune compared with adults from the same endemic area, and are prone to multiple infections (Happi *et al.*, 2003). Should oral CQ or PS continued to be used for a potentially life threatening situation in view of increasing resistance of *P. falciparum* to these drugs in Africa? We feel otherwise. A recent study suggests that AQ, a drug more effective than CQ in both CQ-sensitive and resistant- *P. falciparum* infections, rapidly clears hyperparasitaemia (Ndounga & Basco, 2003). In the small number of children treated with a combination of PS plus AQ in our study population, neither clearance nor parasite reduction ratio was

significantly faster or higher, respectively than those of other treatments. In view of the fact that artemisinin and its derivatives clear parasitaemia more rapidly than most of the currently available antimalarials (Hien & White, 1993), these drugs combined with, for example, AQ may be tried for the management of uncomplicated hyperparasitaemia in children from Africa. This suggestion is predicated on the fact that AQ is a relatively safe drug (Olliaro *et al.*, 1996), and may be a suitable partner combination drug with the artemisinin derivatives, for example, artesunate for use in Africa (Adjuik *et al.*, 2002). Studies to assess the efficacy of such combinations in uncomplicated and complicated hyperparasitaemias are under way in our study area.

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