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Impact of Nutritional Status on Fixed-dose Chloroquine and Sulfadoxine/Pyrimethamine Combination Treatment of Malaria in Ugandan Children

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Abstract: The importance of nutritional status on the given dose, drug concentrations and treatment outcome were explored during treatment with fixed-dose chloroquine plus sulfadoxine/pyrimethamine (CQ+SP) in uncomplicated falciparum malaria. A total of 83 children were treated. Younger children (6-24 months) were given half-strength (HS) and older children (2-5 years) full-strength (FS) CQ+SP as recommended. The concentrations of CQ and sulfadoxine (S) were determined by HPLC in 100 μL of capillary blood on filter paper. Multiple logistic regressions were used to determine associations with outcomes. Stunting (height-for-age <-2 Z-scores) was more common (27.7%) compared to underweight (wt-for-age <-2 Z-scores, 19.3%) and wasting (wt-for-ht <-2 Z-scores, 9.6%). Between the dose groups stunting was significantly common among the younger children than the older children (51.6% vs. 13.5%, respectively, p = 0.005), with mean given doses of CQ and S (mg kg^{-1}) lower in the HS than FS dose groups (p<0.001). Day 1 concentrations of S were also higher in the FS compared to the HS dose group. Nearly all children with day 1 S and day 3 CQ concentrations above the population mean cured. Significant explanatory covariates for cure were day 1 S concentration (p = 0.004), day 3 CQ concentration (p = 0.037) and stunting (p = 0.046). During the fixed-dose CQ+SP combination older children got higher than the recommended doses which resulted in higher blood concentrations of CQ and S with significantly better cure rates. Stunting resulted in higher given doses which may have contributed to better cure rates.

Key words: Malaria, treatment, nutritional status, chloroquine, sulfadoxine, fixed-dose combination

INTRODUCTION

Important outcome determinants in malaria treatment include host, drug and parasites factors. During malaria infection, young age and high baseline temperature and parasitaemia have been associated with early treatment failure and increased probability of complications (Hamer *et al*., 2003; Sowunmi *et al*., 2005; Staedke *et al*., 2004). Lack of naturally acquired immunity (premunition) to malaria (Hviid, 2005), immunosuppression from other underlying diseases (particularly HIV/AIDS) or malnutrition have also been shown to increase the frequency and severity of malaria infection besides causing poor treatment outcomes (Caulfield *et al*., 2004; Djimde *et al*., 2003; French *et al*., 2001; Friedman *et al*., 2005). Interindividual variations in drug concentrations also influence response to antimalarials (Hellgren *et al*., 1989; Rombo *et al*., 1987). While, the emergence of *P. falciparum* strains resistant to chloroquine (CQ) and sulfadoxine/pyrimethamine (SP) resulted in antimalarial drug policy changes across Sub-Saharan Africa (Wellems and Plowe, 2001; White, 2004).

Childhood malaria is known to be most severe in pre-school age, categorized as "the under-fives" and often treated as one homogeneous group. In this age group, the disease can cause malnutrition with consequent changes in growth indices (Kikafunda *et al*., 1998; Nyakeriga *et al*., 2005) and possibly influencing susceptibility to malaria and treatment outcome (Caulfield *et al*., 2004; Friedman *et al*., 2004). Age has been used to approximate

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drug dosages, but in the presence of nutritional deficiencies, anthropometrics variability may occur with important consequences for treatment outcome (Burden *et al*., 2005).

In an efficacy study, comparing amodiaquine plus sulfadoxine/pyrimethamine (AQ+SP) to fixed-dose chloroquine plus sulfadoxine/pyrimethamine (CQ+SP) combinations in Ugandan children, 6 months to 5 years, with uncomplicated falciparum malaria, we found that the AQ+SP group had better outcomes (2.6% failure) than the CQ+SP group (29.1% failure). In the CQ+SP group significantly more treatment failures were found among the youngest children (6-24 months of age) given only the half strength dose compared to the older children (2-5 years of age) given the full strength dose (Obua *et al*., 2006). With these observations, we further evaluated effects of nutritional status and the fixed-dose regimen on the clinical outcome.

MATERIALS AND METHODS

Study site and participants: This is a sub-analysis of results from the efficacy study of a fixed-dose CQ+SP compared to AQ+SP in children with acute *P. falciparum* malaria, performed at Walukuba Health Centre, Jinja District, Uganda, from July-November 2004 (Obua *et al*., 2006). The main primary end-point was the per protocol day 14 outcomes. Among children treated with CQ+SP, the overall failure rate was 29.1, with 48.4% in the HS group and 18.2% in the FS group. Blood samples and anthropometrics data collected form these children were analysed. Out of the 84 children who had completed the study, samples from 83 children could be evaluated, with 31 children in the HS dose group (6-24 months) and 52 children in the FS group (2-5 years). One was excluded from analysis due to missing height measurement.

Baseline assessment and anthropometrics: Baseline characteristics included haemoglobin concentration (Hb), asexual parasitaemia (per µl of blood) and pre-dose blood samples for the determination of pre-treatment drug concentrations. Anthropometrics measurements: body weight in kilograms (kg); the recumbent length for children 6-24 months of age, standing height for children > 24 months of age and mid-upper arm circumference (MAC) in centimetres (cm) were obtained. Age and sex were recorded. Since, there is no documented reference data for growth and nutritional status for Uganda, we used internationally accepted reference data for children (UNICEF, 2003). The anthropometrics indices were calculated using the ANTHRO software (ANTHRO Version 1.02, CDC/WHO, 1995). The assessments of the anthropometrics were reported as Z-scores with gender considerations. For purposes of uniformity, the children were classified as stunted, underweight, or wasted when the indices ht-for-age, wt-for-age and wt-for-ht, respectively were <-2 Z-scores (or below 2nd percentile). All children within +/- 2 Z-scores were considered normal, as recommended in the International Reference Standard (IRS) (UNICEF, 2003).

Dose schedules: The CQ+SP (Homapak), manufactured by a local pharmaceutical company (KPI Ltd, Kampala, Uganda), has packaging with age-specific dosing schedules. "Half-Strength" (HS) dose is for the younger children (6 months to 2 years) and the "Full-Strength" (FS) dose for the older children (2 to 5 years). The recommended dosing of CQ and SP in Homapak (NMCP-Uganda, 2002) is given in Table 1.

Blood drug concentration determinations: Whole blood for determination of chloroquine and sulfadoxine concentrations were obtained from finger pricks on days 0 (pre-treatment), 1, 2, 3, 7 and 14. Capillary blood samples (100 µL) were stored on filter paper at room temperature for 3-6 months until analysis. HPLC methods for determination of CQ (Minzi *et al*., 2003) and S (Bergqvist *et al*., 1987) were used to determine the concentrations in the samples. The limit of quantification for CQ was 48 nmol L^{-1}, while that for S was 14.5 µmol L^{-1}. The inter-assay coefficient of variation was 2.9% for CQ and 4.4% for S. From the sampling-time points, only trough concentrations could be determined in this study. Thus, the highest attained concentrations of CQ and S and the days they occurred (as median) were used for analysis.

Statistical analysis and calculations: Data collected were entered and cleaned using Excel spreadsheet, before being merged and analysed using the SPSS version 10 (SPSS Inc., Chicago IL). Treatment outcome was dichotomised into cure (Adequate Clinical and Parasitological Response) and failure (combining Early Treatment Failure, Late Clinical Failure and Late Parasitological Failure). The nutritional indices were also dichotomised into below -Z-scores and above -2 Z-scores. Logistic regressions were performed to assess associations between the dichotomised treatment outcomes and various covariates. Due to dependencies among covariates, models with single covariates were mainly used to test associations, but also backward conditional analyses for multiple models were used to identify important covariates. t-tests were performed to compare variables between the dose groups, while,

Table 1: Dosing schedules of fixed-dose CQ+SP

Age group	Package label[a]	Day 1	Day 2	Day 3
6 months-2 years	Half Strength	SP 250/12.5 + CQ 75 (base)	CQ 75 (base)	CQ 75 (base)
> 2years-5years	Full Strength	SP 500/25 + CQ 150 (base)	CQ 150 (base)	CQ 150 (base)

[a]Each blister pack contains one SP and three CQ tablets with tablet strength given in mg

differences between categorical variables were assessed using the Pearson Chi-Square test. Statistical significance was assumed for p = 0.05. Residual plots were used to check distributional assumptions.

Ethical clearance: The Institutional Review Board of Makerere University - Uganda and the Regional Ethical Review Board at Karolinska Institutet in Stockholm approved the study design. Permission to conduct the study in Uganda was given by the Uganda National Council for Science and Technology (UNCST).

RESULTS

Baseline characteristics: Stunting was the most frequent nutritional/growth status abnormality, constituting 27.7% of the study population, followed by underweight 19.3%, with only 9.6% found wasted. Ten percent of children had concurrent stunting and underweight. The proportion of stunting in the HS group was nearly 4 times that in the FS group (51.6 vs. 13.5%, p = 0.005). No significant differences were found in the proportion of wt-for-age (underweight, 22.6% vs. 17.3%) and wt-for-ht (wasted, 6.5% vs. 11.5%) between the HS and FS dose groups, respectively. The baseline characteristics for the whole study population and in the HS and FS dose groups are shown in Table 2.

Given dose and drug concentrations between dose groups: Of the 83 children, 11.6% had pre-treatment concentrations of both CQ and S, 20.9% had CQ only and 4.7% had S only. The day 0 median pre-treatment concentration was 132 nmol L^{-1} (range 49-1270 nmol L^{-1}) for CQ and 79 μmol L^{-1} (range 15-164 μmol L^{-1}) for S, with no difference between the HS and FS dose groups. No difference in cure rates between the children with and those without pre-treatment drug concentrations (p=0.801) was found. The highest concentrations for CQ were observed on day 3 (median), while that for S was on day 1 (median). Within the whole population, the mean CQ and S given doses with corresponding mean concentrations are given in Table 3.

The CQ given dose, S given dose and day 1 S concentration were significantly higher in the FS compared with the HS group (Table 3). There was no difference in the mean day 3 concentrations of CQ between the dose groups.

Evaluation of effects of given dose and attained concentrations on treatment outcomes between and within dose groups: Using logistic regressions analysis for the individual variables (CQ given dose, day 3 CQ concentration, S given dose and day 1 S concentration) in the whole study population, the given doses of CQ and S and the day 1 S concentration were individually significantly associated with cure or failure, with CQ given dose at p = 0.007 (OR = 1.136, 95% CI 1.036 -1.246), S given dose at p = 0.007 (OR = 1.22, 95% CI 1.032-1.219) and the day 1 S concentration at p=0.001 (OR = 1.010, 95% CI 1.004-1.017). In the HS dose group, neither the given doses nor attained concentrations were significantly associated with treatment outcomes. In the FS dose group, the day 1 S concentration was significantly associated with the treatment outcome (p = 0.012, OR 1.011, 95% CI 1.002-1.020), while day 3 CQ concentration had borderline association with treatment outcome (p = 0.07). Nearly all children with day 1 S concentrations above the population mean (319 μmol L^{-1}) and day 3 CQ concentrations above population mean (1922 nmol L^{-1}) were cured (Fig. 1 and 2).

Anthropometrics influence on treatment outcomes: In the whole study population, the difference in cure rates between the stunted (18/23, 78%) and non-stunted (41/60, 68%) was not significant (p = 0.429, Table 4). Comparison between the dose groups showed that the odds for cure among the stunted in the FS compared to the HS dose groups was not different (p = 0.272). Significantly higher odds for cure was found among the non-stunted in the FS compared to the HS dose groups (odds 36/9 vs. 5/10, p = 0.003, OR = 8.00, 95% CI 2.18-29.31).

Logistic regressions were performed to determine which of the three anthropometrics indices (stunting, wasting and underweight) separately, could best differentiate between cure and failure. No association was found for any of the parameters in the whole group or in any of the 2 dose groups.

Multiple logistic models for explanatory covariates: Multiple logistic regressions were performed for the whole study population by modelling treatment outcome with all available relevant covariates (S given dose, day 3 CQ concentration, day 1 S concentration, sex, wt-for-age Z-scores, wt-for-ht Z-scores, ht-for-age Z-scores, Hb day 0, parasitaemia day 0 and temperature day 0) but excluding

Table 2: Baseline characteristics for the whole study population and in the dose groups

	Whole group N = 83		Half-strength (HS) n=31		Full-strength (FS) n = 52		Significance (95%CI of difference between
Anthropometrics	Mean	SD	Mean	SD	Mean	SD	HS and FS)
Age (months)	31.4	14.7	16.7	4.7	40.2	11.1	-
Weight (Kg)	12.0	2.7	9.5	1.4	13.5	2.2	-
Height (cm)	87.5	12.3	75.2	6.5	94.8	8.6	-
MAC[a] (cm)	14.9	1.6	13.8	1.6	15.5	1.3	-
Ht-for-Age Z-scores	-0.91	1.62-	-1.55	1.55	-0.53	1.55	
Stunting %	27.7	-	51.6	-	13.5	-	0.005 (0.32-1.73)
Wt-for-Age Z-scores	-1.01	1.12	-1.14	1.05	-0.94	1.16	
Underweight %	19.3	-	22.6	-	17.3	-	0.435
Wt-for-Ht Z-scores	-0.52	1.28	-0.21	1.27	-0.70	1.27	
Wasting %	9.6	-	6.5	-	11.5	-	0.093
Day 0 Hb (g 100mL^{-1})	9.65	1.69	9.30	1.46	9.85	1.79	0.148
Day 0 Parasitaemia (#×10^3 µL^{-1})	59.4	57.7	64.2	55.2	56.5	59.6	0.564
Day 0 Temperature (°C)	38.0	0.9	38.2	0.9	37.9	1.0	0.098
Sex Proportion (% males)	59.0		54.8		61.5		0.549

[a]Mid-arm circumference (MAC). *Statistical comparisons done only for variables that are not expected to differ within and between the dose groups. Anthropometrics indices presented as standard deviations (Z-scores) from reference mean

Table 3: Given dose and drug concentrations in the whole group and between half strength and full strength dose groups

Treatment	Whole group n = 83	Half strength n = 31	Full strength n = 52	T-test of FS-HS difference p values (95%CI)
CQ Given dose (mg kg^{-1}) Mean (SD)	31 (7)	24 (4)	34 (6)	<0.001 (7.6-12.6)
Day 3 Conc. (nmol L^{-1}) Mean (SD)	1922 (1092)	1681 (1157)	2095 (1026)	0.149 (-153.3-981.2)
S Given dose (mg kg^{-1}) Mean (SD)	34 (8)	27 (4)	38 (7)	<0.001 (8.4-14.0)
Day 1 Conc. (µmol L^{-1}) Mean (SD)	319 (121)	258 (84)	354 (126)	0.001 (40.4-150.9)

Table 4: Treatment outcomes within the dose groups by stunting status

		Treatment outcomes		
Dose groups		Failure (%)	Cure (%)	Within-group $\times^2$ p value
Whole group	Non-Stunted n = 60	19 (32)	41 (68)	0.429
	Stunted n = 23	5 (22)	18 (78)	
HS	Non-Stunted n = 15	10 (67)	5 (33)[a]	0.076
	Stunted n = 16	5 (31)	11 (69)	
FS	Non-Stunted n = 45	9 (20)	36 (80)[a]	0.331
	Stunted n = 7	0 (0)	7 (100)	

[a]Higher odds for cure was found among the non-stunted in the FS compared to the HS dose groups (odds 36/9 vs. 5/10, p = 0.003, OR = 8.00, 95%CI 2.18 - 29.31)

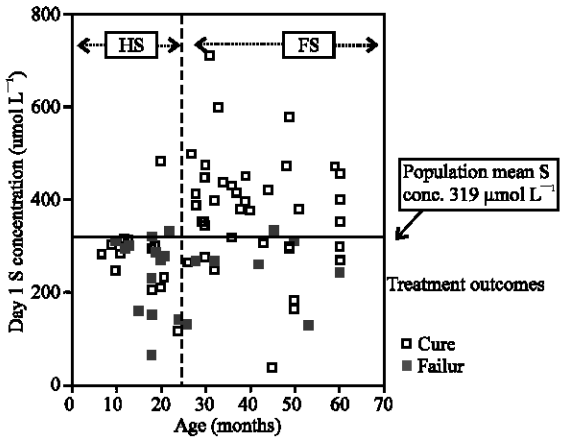

Fig. 1: Sulfadoxine (S) day 1 concentration by age in the half-strength (HS) and the full-strength (FS) dose groups showing treatment cure and failure

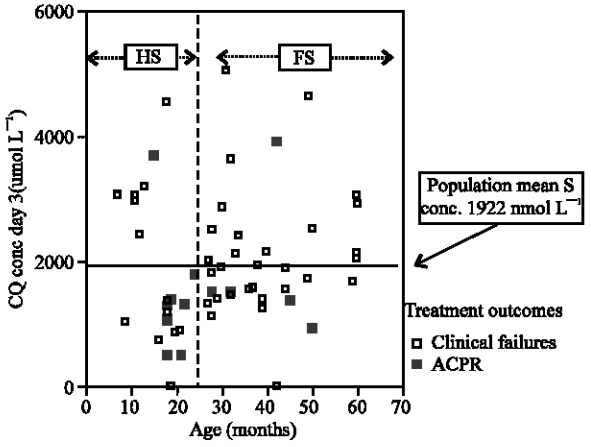

Fig. 2: Chloroquine (CQ) day 3 concentrations by age in the half-strength (HS) and the full-strength (FS) dose groups showing treatment cure and failure

those that are age related (MAC) or used for deriving the anthropometrics indices (age, weight, height). CQ given dose was also excluded due to colinearity with S given dose. The day 1 S concentration was found to be the only

significant explanatory variable (p = 0.045, OR = 1.023; 95% CI 1.001-1.046). Finally, by performing backward conditional logistic regression, after starting with the full model as above, only day 1 S concentration (p = 0.004, OR = 1.024, 95% CI 1.008 -1.041), day 3 CQ concentration (p = 0.037, OR = 1.001, 95% CI 1.000-1.002) and ht-for-age Z-scores (p = 0.046, OR = 0.556, 95% CI 0.312 - 0.990) were kept in the model as the significant explanatory covariates for treatment outcomes.

DISCUSSION

Stunting was the most frequent presentation of malnutrition among the children. The proportions of stunting, underweight and wasting found in this study was similar to those found in children attending the mother and child health (MCH) clinics and surveys within the region (Matee *et al*., 1997; Kikafunda *et al*., 1998; Nyakeriga *et al*., 2004). The difference in stunting status between the older (FS) and the younger (HS) groups was significant in this study. However, the fact that the rates of underweight and wasting were similar in both groups indicates that poor nutritional status was perhaps not the only factor responsible for the high rate of stunting in the younger children (HS group).

The dosing assumption with the fixed-dose CQ+SP formulation was that children receiving the higher dose group were on average twice the weight of those in the lower dose group (NMCP-Uganda, 2002). The two dose groups would in theory receive approximately equal amounts (mg kg^{-1} body weight) of the drugs. But the actual doses in terms of mg kg^{-1} received during treatment were higher, with higher concentrations and better cure rates in the FS dose group. The importance of given dose has previously been reported by Kofoed *et al*. (2002) in Guinea-Bisau and Sexton *et al*. (1988) in Rwanda. When double doses (50 mg kg^{-1}) or the usual doses (25 mg kg^{-1}) of CQ were given to children with uncomplicated falciparum malaria, the children treated with double doses had higher drug concentrations and better cure rates. In terms of tolerability we had previously reported that no adverse reactions were reported among the children that got the higher dose (Obua *et al*., 2006).

Overall, in this study, stunting was associated with better cure rates. This observation was surprising, as it goes against the common understanding of the role of malnutrition in malaria, where it is associated with poor treatment outcomes (French *et al*., 2001; Kikafunda *et al*., 1998). Thus, possibility that stunting may be important for the outcome of *P. falciparum* malaria treatment with fixed-dose formulations needs further evaluation, as stunted children form nearly one-third of the under-fives (Kikafunda *et al*., 1998; Nyakeriga *et al*., 2004).

Although, only children without history of antimalarial drug intake prior to treatment were recruited, nearly one-third had detectable drug levels in their pre-treatment blood samples. Quashie *et al*. (2005) previously showed that pre-dose levels of CQ influenced the treatment outcomes. The pre-dose levels of CQ and S found in this study were probably too low to contribute any significant additional effects. Higher concentrations of both CQ (day 3) and S (day 1) were however associated with the better cure rates. In the present study the sampling schedules did not allow for a true determination of peak concentrations of S or CQ. The scarce number of samples also did not permit for an accurate calculation of the AUC. Thus, although we could establish that attained drug concentrations of both CQ and S are important for the therapeutic response, the interesting question whether it is the peak concentration or the AUC that is the most important could not be answered.

The significant higher odds for cure that was found among the non-stunted in the older FS compared to the HS dose groups was indeed a reflection of the age-group fixed-dosing. From a dosing point of view, no differences were expected within the younger and older children. However, there was almost a 2-fold difference in the given dose between the two dose groups and nearly all children who failed treatment had CQ and S concentrations below the population mean. Thus, it appears that in any of the dose-groups, lower anthropometric indices resulted in higher given doses. With this in mind, it is important to note that the fixed-dose schedules for the administration of co-formulated artemether-lumefantrine combination (Coartem) in Uganda indicates that children between 4 months-3 years or weight range of 5-14 kg, are all given the same fixed dosage for uncomplicated malaria (NMCP-Uganda, 2006). There might therefore be a three-fold difference in the given dose (mg kg^{-1}) between the age/weight extremes. This will, perhaps in accordance with the present study, result in treatment failure in those the lowest given dose. We suggest that in order to accommodate variations in the anthropometrics, concentration-outcome studies be done in order to design appropriate optimal graded age-dose intervals.

CONCLUSION

In the treatment of uncomplicated falciparum malaria with fixed-dose CQ+SP combination, older children got higher than the recommended doses which resulted in higher blood concentrations of CQ and S with significantly better cure rates. There were no significant differences in treatment outcome as a result of different

nutritional status, but stunting contributed to higher given dose resulting in better cure rates. However, the importance of stunting as a covariate for treatment outcome needs further evaluation.

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REFERENCES

Bergqvist, Y., E. Hjelm and L. Rombo, 1987. Sulfadoxine assay using capillary blood samples dried on filter paper-suitable for monitoring of blood concentrations in the field. Ther Drug Monit, 9: 203-207.

Burden, S.T., E Stoppard, J. Shaffer, A. Makin and C. Todd, 2005. Can we use mid upper arm anthropometry to detect malnutrition in medical inpatients? A validation study. J. Hum. Nutr. Diet, 18: 287-294.

Caulfield, L.E., S.A. Richard and R.E. Black, 2004. Undernutrition as an underlying cause of malaria morbidity and mortality in children less than five years old. Am. J. Trop. Med. Hyg., 71 (2): 55-63.

Djimde, A.A., O.K. Doumbo and O. Traore *et al*., 2003. Clearance of drug-resistant parasites as a model for protective immunity in Plasmodium falciparum malaria. Am. J. Trop. Med. Hyg., 69: 558-563.

French, N., J. Nakayingi, E. Lugada, C. Watera, J.A.G. Whitworth and C.F. Gilks, 2001. Increasing rates of malaria fever with deteriorating immune status in HIV-1-infected Ugandan adults. AIDS, 15: 899-906.

Friedman, J.F., A. Kwena and L.B. Mirel *et al*., 2005. Malaria and nutritional status among pre-school children: Results from cross-sectional surveys in western Kenya. Am. J. Trop. Med. Hyg., 73: 698-704.

Hamer, D.H., W.B. MacLeod and E. Addo-Yobo *et al*., 2003. Age, temperature and parasitaemia predict chloroquine treatment failure and anaemia in children with uncomplicated Plasmodium falciparum malaria. Trans. R. Soc. Trop. Med. Hyg., 97: 422-428.

Hellgren, U., C.M. Kihamia, L.F. Mahikwano, A. Björkman, Ö. Eriksson and L. Rombo, 1989. Response of Plasmodium falciparum to chloroquine treatment: relation to whole blood concentrations of chloroquine and desethylchloroquine. Bull. WHO, 67: 197-202.

Hviid, L., 2005. Naturally acquired immunity to Plasmodium falciparum malaria in Africa. Acta Trop., 95: 270-275.

Kikafunda, J.K., A.F. Walker, D. Collett and J.K. Tumwine, 1998. Risk factors for early childhood malnutrition in Uganda. Pediatrics 102: E45.

Kofoed, P.E., F. Lopez, P. Johansson, A. Sandstrom, K. Hedegaard, P. Aaby and L. Rombo, 2002. Treatment of children with Plasmodium falciparum malaria with chloroquine in Guinea-Bissau. Am. J. Trop. Med. Hyg., 67: 28-31.

Matee, M.I.N., A.E. Msengi and E. Simon *et al*., 1997. Nutritional status of under fives attending maternal and child health clinics in Dar es Salaam, Tanzania. East Afr. Med. J., 74: 368-371.

Minzi, O.M.S., M. Rais, J.O. Svensson, L.L. Gustafsson and O. Ericsson, 2003. High-performance liquid chromatographic method for the determination of amodiaquine, chloroquine and their metabolites in biological samples. J. Chromatogr. B., 783: 473-480.

National Malaria Control Program-Uganda, 2002. Implementation Guidelines for the Home Based Management of Fever Strategy. 1st Edn. Ministry of Health, Kampala, Uganda.

National Malaria Control Program-Uganda, 2006. Antimalaria policy change to ACTs 2005. Ministry of Health, Kampala, Uganda.

Nyakeriga, A.M., M. Troye-Blomberg, A.K. Chemtai, K. Marsh and T.N. Williams, 2004. Malaria and nutritional status in children living on the coast of Kenya. Am. J. Clin. Nutr., 80: 1604-1610.

Obua, C., L.L. Gustafsson, C. Aguttu, W.W. Anok-bonggo, J.W. Ogwal-Okeng and J. Chiria, U. Hellgren, 2006. Improved efficacy with amodiaquine instead of chloroquine in sulfadoxine/pyrimethamine combination treatment of falciparum malaria in Uganda: Experience with fixed-dose formulation. Acta Trop., 100: 142-150.

Quashie, N.B., B.D. Akanmori, B.Q. Goka, D. Ofori-Adjei and J.A. Kurtzhals, 2005. Pretreatment blood concentrations of chloroquine in patients with malaria infection: Relation to response to treatment. J. Trop. Pediatr., 51: 149-153.

Rombo, L., Y. Bergqvist and U. Hellgren, 1987. Chloroquine and desethylchloroquine concentrations during regular long term malaria prophylaxis. Bull. WHO, 65: 879-8 83.

Sexton, J.D., P. Deloron, L. Bugilimfura, A. Ntilivamunda and M. Neill, 1988. Parasitologic and clinical efficacy of 25 and 50 mg kg^{-1} of chloroquine for treatment of Plasmodium falciparum malaria in Rwandan children. Am. J. Trop. Med. Hyg., 38: 237-243.

Sowunmi, A., B.A. Fateye, A.A. Adedeji, F.A. Fehintola, G.O. Gbotosho, T.C. Happi, E. Tambo and A.M. Oduola, 2005. Predictors of the failure of treatment with chloroquine in children with acute, uncomplicated, Plasmodium falciparum malaria, in an area with high and increasing incidences of chloroquine resistance. Ann. Trop. Med. Parasitol., 99: 535-544.

Staedke, S.G., H. Sendagire, S. Lamola, M.R. Kamya, G. Dorsey and P.J. Rosenthal, 2004. Relationship between age, molecular markers and response to sulphadoxine-pyrimethamine treatment in Kampala, Uganda. Trop. Med. Int. Health, 9: 624-629.

UNICEF, 2003. The State of the World's Chlidren.

Wellems, T.E. and C.V. Plowe, 2001. Chloroquine-resistant malaria. J. Infect. Dis., 184: 770-776.

White, N.J., 2004. Antimalarial drug resistance. J. Clin. Invest., 113: 1084-1092.

World Health Organization, 1995. Physical status: The use and interpretation of anthropometry. Report of a WHO Expert Committee, WHO Technical Report Series No. 854, Geneva.