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A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CLINICAL TRIAL OF THE IMPACT OF MALARIA PREVENTION ON THE EDUCATIONAL ATTAINMENT OF SCHOOL CHILDREN

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Abstract. A double-blind, placebo-controlled trial of nine months duration was carried out to investigate the impact of malaria and its prevention on the educational attainment of school children in a malaria-endemic area in southern Sri Lanka where both *Plasmodium falciparum* and *P. vivax* infections are prevalent. A total of 587 children attending grades 1–5 in four schools and resident in the area were randomly allocated to chloroquine (n = 295) and placebo (n = 292) arms. Language and mathematics scores of end-of-term school examinations for 1998 and 1999 and number of days absent and reasons for absenteeism during seven months pre-intervention and nine months of the intervention were recorded. The results indicate that there were no differences in language (95% confidence interval [CI] = 48.44–53.78 in chloroquine group and 50.43–55.81 in placebo group) and mathematics (95% CI = 49.24–54.38 in chloroquine group and 51.12–56.38 in placebo group) scores between the two groups prior to the intervention. During the intervention, the malaria incidence rate decreased by 55% (95% CI = 49–61%) and school absenteeism due to malaria was reduced by 62.5% (95% CI = 57–68%) in children who received chloroquine compared with the placebo group. Post-intervention, children who received chloroquine scored approximately 26% higher in both language (95% CI = 21–31%) and mathematics (95% CI = 23–33%) than children who received placebo. In a multivariate model, educational attainment was significantly associated with taking chloroquine prophylaxis and absenteeism due to malaria ($P < 0.001$ for both) but not due to health causes other than malaria or non-health causes. Language scores were associated with number of malaria attacks ($P = 0.022$). Educational attainment was significantly better among children whose compliance to chloroquine prophylaxis was higher ($P < 0.001$). The data suggest that malarial attacks have an adverse impact on the educational attainment of the school child and prevention of these attacks significantly improves educational attainment of children living in malaria-endemic areas.

INTRODUCTION

Children who survive to school age continue to be vulnerable to malaria and estimates from Africa indicate that 20–50% of school children experience clinical malarial attacks each year.[1] Higher rates have been reported from malaria-endemic areas of Asia.[2] In areas of low unstable malaria transmission, school children may be at a greater risk of severe and fatal consequences of infection because of the slow build up of exposure-driven immunity.[3] However, these risks are balanced by the low, and very often, seasonal exposure to the parasite. Prolonged and repeated illness may result in their being absent from school for significant lengths of time. School attendance can be affected when other members of the family become ill with malaria; girls in particular may be kept at home to help out. Studies in the Democratic Republic of the Congo, Kenya, Senegal, and on the Thailand-Myanmar border indicate that malaria is a cause of 5–8% of all absenteeism, which is equivalent to 50% of all preventable absenteeism.[2,4–8] Thus, malaria may reduce both the opportunity and the ability of a young person to learn.[9]

The impact of parasitic infections on the cognitive function of school children has been investigated. Colbourne,[10] Boivin and others,[11] and Serouri and others[12] have investigated the impact of asymptomatic malaria on cognitive function. In the first study, the teacher rating that was used was not sensitive enough to show small differences. In the second study, it was possible that the small sample size, the high chloroquine resistance (40%), and the battery of tests used confounded their results. Serouri and others have reported that children who were negative for malarial parasites (non-parasitemic group) performed better in fine motor functions but not in cognitive tests than parasitemic children.[12]

The impact of malarial infections on the cognitive performance of children has been studied in a series of studies in a low transmission area of Asia. At school entry, most indices of school performance tested were poorer as the number of malaria infections experienced by the child increased after controlling for confounding factors.[13] School performance of 6–14-year-old children was related to the number of previous clinical attacks of malaria.[14] It has been reported that an acute attack of uncomplicated malaria causes significant short-term impairment of cognitive performance, with the impairment persisting for more than two weeks and being cumulative with repeated attacks of malaria.[15]

Cerebral malaria has been implicated as a host development risk factor within the complex web of poverty in sub-Saharan Africa, which limits children's ability to achieve their full intellectual potential and, thus, extend the human cost of the disease beyond general measures of mortality and morbidity.[16] Studies carried out mainly in areas of high malaria endemicities where cerebral malaria is a frequent complication have reported the cognitive sequelae after brain injuries during malaria.[16–18] In Kenya, school children who had been hospitalized with cerebral malaria were 4.5 times more likely to have mild-to-severe learning difficulties 3–4 years later even though half the children had no neurologic problems at the time of hospitalization.[18]

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We report here the results of a randomized, double-blind, placebo-controlled study in which we investigated the impact of malaria prevention on the educational attainment of the school child. The study was performed in southern Sri Lanka in an area where both *Plasmodium falciparum* and *P. vivax* malaria are endemic, and where many children experience multiple episodes of malarial disease.

MATERIALS AND METHODS

Study area. The study was conducted in the Kataragama and Buttala areas of the Moneragala District in the dry zone of southern Sri Lanka where both *P. vivax* and *P. falciparum* malaria of unstable endemicity are prevalent. Malaria transmission in the area is seasonal and composed of two peaks. The major peak corresponds to the northeast monsoonal rains from November to February. Almost all malarial infections in children are symptomatic and chloroquine resistance is reported in approximately 20–30% of *P. falciparum* infections.[19,20]

Study design. Of 647 children between 6 and 12 years of age enrolled in grades 1–5 in four schools and resident in the area, parents of 596 children consented for their children to be enrolled in the study. However, only 587 children were included in the study because two children had learning disabilities as reported by the class teacher and seven children did not have past examination results (Figure 1). A sample of 234 children in each arm of the trial was required to detect a difference of 7.5 marks out of 100 with 90% power and a two-sided alpha error of 5% assuming that the standard deviation of the scores was 25 marks based on the distribution of baseline marks.

A randomized, double-blind, placebo-controlled clinical trial was conducted from March to November, 1999. Children in each class of each school were randomly assigned to either chloroquine or placebo arms using computer generated random numbers. Of the 587 children enrolled, 295 received chloroquine and 292 received the placebo. At weekly school visits, one chloroquine tablet (150 mg of chloroquine phosphate base) or placebo (5 mg of nicotinamide) was given to each child after a meal under the direct supervision of a research assistant or the teacher. Both tablets were sugar coated. No children were lost to follow-up. However, children received varying amounts of chloroquine and placebo tablets during the intervention period (1–30 tablets) because of various reasons such as being absent, not having breakfast, having a headache, or being on medication for some other condition such as a common cold. The children, parents, and guardians were informed of the possible side effects of the drug such as visual disturbances, depigmentation or loss off hair, or skin reactions and were requested to report such manifestations to the class teacher who in turn was asked to immediately notify the principal investigator.

Anthropometric and hematologic investigations. Anthropometric and hematologic investigations on all subjects were carried out at the beginning and at the end of the study. Two milliliters of venous blood were collected for estimation of hemoglobin levels by Sahli's method and examination of a Giemsa-stained peripheral blood smear for malarial parasites. A thin blood smear was used to determine parasitemia.[21]

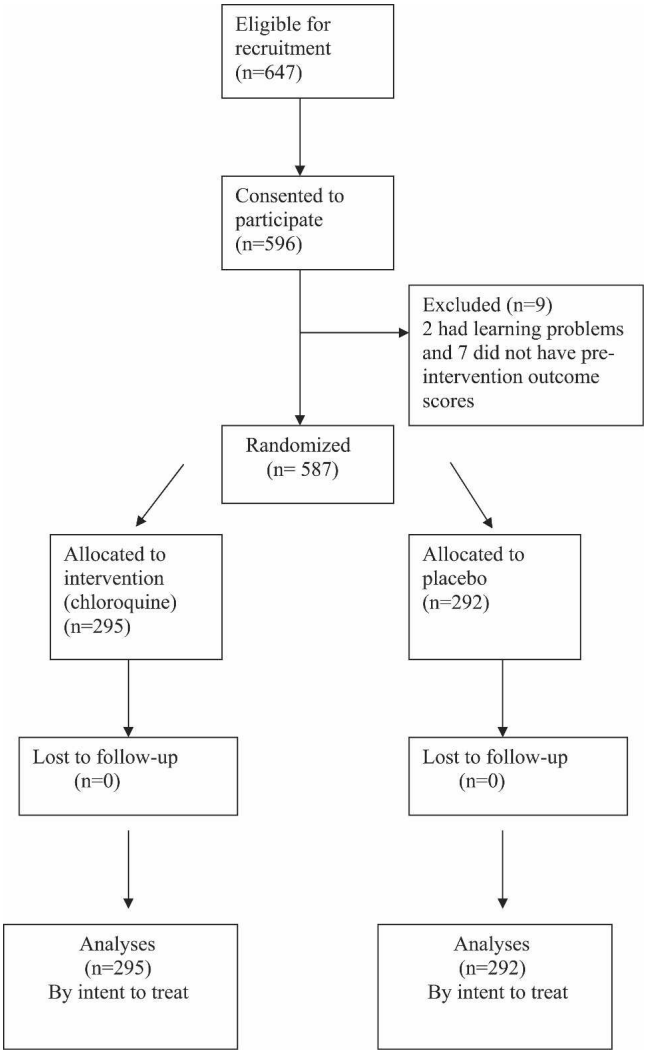

FIGURE 1. Flow chart of patient recruitment.

Malaria was diagnosed on detection of asexual parasites on blood smear examination by a trained senior technical officer of the Malaria Research Unit, University of Colombo and blood smears were routinely cross-checked. A stool sample of all children was microscopically examined for parasitic ova and cysts. The height and weight of each child were measured using standard procedures. Malarial infections were monitored throughout the study at malaria diagnosis and treatment centers in the area by passive case detection using microscopy that was provided free of charge. All children having malarial parasites on blood smear examination were treated with 300 mg of chloroquine phosphate base on days 1 and 2, and 150 mg of chloroquine phosphate base on day 3. In addition, children with a *P. falciparum* infection were administered 22.5 mg of primaquine as a stat dose on day 1, and children with a *P. vivax* infection were administered 7.5 mg of primaquine for 5 days.

Recording of absenteeism. School attendance of the children was obtained from school registers that are marked on a daily basis by the class teacher. When a child is absent from school, it is compulsory that a letter of excuse be sent by the parents indicating the reason for absenteeism. Prior to the study, the parents and guardians were educated by the prin-

cipal investigator to indicate on the letter the reason of absenteeism and, if the reason was because of illness to state the illness as indicated by the practitioner who provided treatment. The number of days absent and the reason for absenteeism were recorded during a seven-month period prior to starting the trial and during the intervention. Since the durations of the two periods were different, the number of days absent was calculated as a percentage of all school days during that period. Absenteeism because of malaria was cross-checked with records maintained at the malaria diagnosis and treatment centers and confirmed.

Assessment of educational attainment. All Government schools in Sri Lanka conduct three end-of-term examinations for each subject taught in each grade covering the syllabus of the term. The syllabus to be covered for a particular term is decided by the National Institute of Education, Sri Lanka and is common to all government schools in the country. The end-of-term examinations used to measure educational attainment were valid because only the subject matter taught in class was tested and the papers were prepared by the teachers of the relevant subject and were specific for a school. The average scores of the last two end-of-term examinations in mathematics and language for 1998 (pre-intervention) and 1999 (post-intervention) were used as indicators of educational attainment.

Socioeconomic stratification. The socioeconomic status of the family was assessed with respect to parents education, monthly family income, and based on the construction type of the house as previously described[22,23] by administering a structured questionnaire to a parent or guardian of the child.

Permission to conduct the study. Permission to conduct the study was obtained from the Ethical Review Committee of Faculty of Medicine, University of Colombo, the Zonal Educational Officers, and School Principals. Written informed consent was obtained from the parents of the children prior to their enrollment in the study.

Data analysis. The treatment code was deciphered at end of the trial. Anthropometric indices (weight-for-age, height-for-age, and weight-for-height) were obtained using Epi-Info software (Centers for Disease Control and Prevention, Atlanta, GA). Data analysis was done by intent to treat using *t*-tests to examine for differences between groups using Epi-Info software and SPSS software (SPSS Inc., Chicago, IL). Regression analysis and analysis of variance models were used to adjust for potential confounding variables.

RESULTS

Pre-intervention. The socioeconomic variables of the two groups of children were similar except for house type (Table 1). During the pre-intervention period, the mathematics and language scores, incidence of malaria and absenteeism because of malaria, health causes other than malaria and non-health causes, and total number of days absent in the chloroquine and placebo groups of children were similar (Table 2). Prior to the intervention, absenteeism from school in both groups of children were due to illnesses such as malaria, acute respiratory infections, viral fevers, and other non-health related reasons such as participation in social events and contingencies such as bad weather disrupting transport to school. There were no significant differences in the anthropometric indices or hemoglobin levels between the two groups of children at baseline in either boys or girls (Table 2).

TABLE 1
Sociodemographic status of the study population

Variable	Chloroquine group (n = 295) No.	%	Placebo group (n = 292) No.	%	χ^2	*P*
Sex						
Male	146	49.5	155	53.1	0.757	0.384
Female	149	50.5	137	46.9		
Age (years)						
6–9	147	49.8	147	50.3	0.188	0.910
9.1–12	137	46.4	136	46.6		
> 12	11	3.7	9	3.1		
Mother's education (grade)*						
None	7	2.4	12	4.1	3.825	0.281
1–5	101	34.2	106	36.3		
6–10	151	51.2	150	51.4		
> 10	36	12.2	24	8.2		
Father's education (grade)*						
None	13	4.4	18	6.2	6.09	0.107
1–5	95	32.2	117	40.1		
6–10	160	54.2	138	47.3		
> 10	27	9.2	19	6.5		
Monthly family income (Sri Lankan Rupees)†						
< 1,000	36	12.2	47	16.6	2.378	0.498
1,000–< 3,000	124	42.0	123	42.1		
3,000–< 5,000	115	39.0	101	34.6		
≥ 5,000	20	6.8	21	7.2		
House type‡						
Good	70	20.8	52	17.8	9.131	0.01
Moderate	155	51.1	139	47.6		
Poor	70	29.1	101	34.6		

* Grade of formal school education.
† One U.S.$ = 72 Sri Lankan Rupees.
‡ See Materials and Methods for classification of house type.

Post-intervention. Significant differences were observed between the two groups of children in both mathematics and language scores, with the scores being higher by approximately 26% in each of the subjects in children who received chloroquine. No significant differences were observed in the anthropometric indices between the two groups of children except for weight-for-age among girls ($P = 0.033$). The hemoglobin levels of both males ($P = 0.012$) and females ($P < 0.001$) receiving chloroquine were higher than those of placebo children. None of the children reported visual disturbance or other adverse effects after taking chloroquine.

During the nine months of intervention, the malaria incidence rate adjusted for 12 months in the chloroquine group was reduced to less than half (61.6%) of that in the placebo group (129.2%) ($P < 0.001$). Both total school absenteeism, as well as that due to malaria, were significantly reduced in the chloroquine group compared with that in the placebo group (Table 3). School absenteeism due to non-malarial illnesses and non-health reasons either before or during the intervention were similar in the two groups (Tables 2 and 3).

The performance in mathematics and language of children of both groups were analyzed in relation to 1) the number of malaria infections they experienced, 2) the total number of chloroquine tablets they had taken as a prophylactic, and 3) the extent of their school absenteeism due to malaria, and for comparison, due to non-malarial illnesses and non-health reasons (Table 4). Mathematics and language scores of children in the two treatment groups were significantly associated with

TABLE 2
Pre-intervention outcome measures of the two groups of children*

Variable	Chloroquine (n = 295)		Placebo (n = 292)		t	P
	Mean (95% CI)	SD	Mean (95% CI)	SD		
Mathematics scores						
	51.81 (29.24–54.3)	22.52	53.75 (51.12–56.38)	22.87	–1.034	0.301
Language scores						
	51.11 (48.44–53.78)	23.32	53.12 (50.43–55.81)	23.32	–1.044	0.297
Malaria incidence rate (% per year)						
	44.16		49.32		$\chi^2 = 0.67$	0.414
Total absenteeism, no. of days (%)						
Before (Jun–Dec 1998)	21.9 (19.0) (0–46.9)	12.8	22.6 (19.0) (0–48.5)	13.2	–0.634	0.526
Absenteeism due to malaria, no. of days (%)						
Before (Jun–Dec 1998)	5.8 (5.0) (0–22.9)	8.7	7.1 (6.0) (0–24.4)	8.8	–1.695	0.091
Absenteeism due to health causes other than malaria, no. of days (%)						
Before (Jun–Dec 1998)	6.7 (6.0) (0–18.3)	5.9	6.4 (6.0) (0–17.9)	5.9	0.574	0.566
Absenteeism due to non-health causes, no. of days (%)						
Before (Jun–Dec 1998)	9.4 (8.0) (0–23.55)	7.2	9.1 (8.0) (0–22.9)	7.1	0.488	0.654
Weight-for-age Z-score						
Males	–1.989 (1.85–2.12)	0.76	–2.118 (0.69–3.53)	0.84	1.317	0.189
Females	–1.739 (1.62–1.85)	0.69	–1.840 (1.71–1.97)	0.71	1.162	0.246
Height-for-age Z-score						
Males	–1.461 (1.34–1.93)	0.86	–1.520 (1.35–1.70)	1.06	0.499	0.618
Females	–1.140 (1.02–1.26)	0.71	–1.273 (1.15–1.52)	0.90	1.322	0.187
Weight-for-height Z-score						
Males	–1.589 (1.45–1.73)	0.81	–1.773 (1.62–3.6)	0.87	1.787	0.075
Females	–1.531 (1.37–1.69)	0.95	–1.590 (1.44–1.73)	0.81	0.532	0.595
Hemoglobin level (g/dL)						
Males	11.4 (11.2–11.6)	0.92	11.6 (11.4–11.7)	0.84	–1.661	0.098
Females	11.4 (11.2–11.6)	0.97	11.5 (11.2–11.6)	0.83	–0.716	0.475

* CI = confidence interval.

1) the number of malarial attacks they experienced and 2) absenteeism due to malaria. The performance decreased with increasing number of malarial attacks and increasing absenteeism due to malaria. In children who were absent because of non-malarial illnesses, particularly in the chloroquine group, there was a tendency for the performance to increase rather than decrease with increasing absenteeism. Except for this, there was no consistent association between scores and absenteeism due to reasons other than a malarial infection (Table 4).

The performances of children in both mathematics and language were associated with the total number of chloroquine tablets taken ($P < 0.001$), with children who had taken more than 22 tablets performing best (Table 4). Absenteeism due to malaria was significantly less in children who had taken more than 13 chloroquine tablets compared with those who had taken less, and was least among those who had taken more than 22 tablets (Table 5).

Mathematics and language scores, after controlling for confounding variables, were significantly associated with 1) receiving chloroquine prophylaxis and 2) absenteeism due to malaria (Table 6). Apart from this, the number of malarial infections was a significant predictor of language scores, and height-for-age was a significant predictor of mathematics scores (Table 6). The adjusted relative risks for better performance at the examinations were as follows: taking chloroquine prophylaxis increased mathematics and language scores by 5%; being absent less than 12 days due to malaria increased mathematics and language scores by more than 33% compared with being absent for more than 30 days; and experiencing no attacks of malaria increased language scores by 11%. Absenteeism due to causes other than malaria, including non-malarial illnesses, did not affect performance in either mathematics or language. The prevalence of geohelminth infections was low (2%)[24] and was similar in both groups pre-intervention and post-intervention.

DISCUSSION

This study demonstrates that malarial prophylaxis not only reduced the incidence of malaria but increased school performance relative to the placebo group. It also reduced school

TABLE 3
Post-intervention outcome measures of the two groups of children*

Variable	Chloroquine (n = 295)		Placebo (n = 292)		t	*P*
	Mean (95% CI)	SD	Mean (95% CI)	SD		
Mathematics scores						
	58.69 (56.42–60.96)	19.86	45.92 (43.45–48.39)	21.60	7.452	< 0.001
Language scores						
	52.74 (50.37–55.11)	20.75	40.79 (38.24–43.34)	22.21	6.7324	< 0.001
Malaria incidence rate (% per year)	61.6		129.22		χ^2 = 200.29	< 0.001
Total absenteeism, no. of days (%)						
During (Mar–Nov 1999)	33.6 (21.0) (6.4–60.8)	13.9	39.7 (24.0) (5.7–73.5)	17.3	–4.659	< 0.001
Absenteeism due to malaria, no. of days (%)						
During (Mar–Nov 1999)	4.8 (3.0) (0–24.2)	9.9	12.4 (8.0) (0–42.9)	15.2	–7.233	< 0.001
Absenteeism due to health causes other than malaria, no. of days (%)						
During (Mar–Nov 1999)	16.6 (10.0) (0–35.2)	9.5	15.6 (10.0) (0–35.1)	9.9	1.133	0.258
Absenteeism due to non-health causes, no. of days (%)						
During (Mar–Nov 1999)	12.3 (8.0) (0–25.6)	6.8	11.7 (7.0) (0–25.4)	7.0	0.977	0.329
Weight-for-age Z-scores						
Males	–2.018 (1.90–2.13)	0.65	–2.130 (2.02–2.24)	0.60	1.388	0.167
Females	–1.956 (1.82–2.09)	0.73	–2.148 (2.03–2.26)	0.62	2.149	0.033
Height-for-age Z-scores						
Males	–1.244 (1.07–1.42)	0.97	–1.379 (1.22–1.53)	0.91	1.132	0.267
Females	–1.147 (0.98–2.46)	0.92	–1.332 (1.17–1.49)	0.86	1.566	0.119
Weight-for-height Z-scores						
Males	–1.952 (1.81–2.09)	0.79	–2.014 (1.95–2.26)	0.78	0.606	0.545
Females	–1.960 (1.79–2.13)	0.94	–2.103 (1.98–2.22)	0.83	1.221	0.223
Hemoglobin levels (g/dL)						
Males	11.6 (11.4–11.7)	1.14	11.3 (11.1–11.4)	1.10	2.525	0.012
Females	11.8 (11.6–11.9)	0.93	11.3 (11.1–11.5)	1.08	4.510	< 0.001

* CI = confidence interval.

absenteeism. Among the children who received chloroquine during the study period of nine months, the number of malarial infections decreased by 55%. Since children in each class were randomized to the chloroquine and placebo arms, the differences observed in examination scores were, in fact, true differences and not due to differences in subject matter taught in different classes. The scores for both subjects in the placebo group at the end of the intervention were approximately 27% lower than in the chloroquine group.

The examination scores in the placebo group were significantly poorer post-intervention than pre-intervention. This is probably due to these children experiencing more attacks of malaria in the intervention period during which there was an increase in malaria transmission in the area. In this group, the incidence of malaria (corrected for 12 months) during the intervention period was higher (129% versus 49%) than it had been in the preceding six months of observation.

Since chloroquine prophylaxis reduced school absenteeism, the impact of the intervention on school performance could have been due to improving school attendance as a result of reducing the incidence of malaria, which by itself, is a major cause of school absenteeism. School performance correlated significantly and inversely only with malaria-specific absenteeism. Absenteeism due to other causes, whether due to illnesses other than malaria or causes unrelated to health, was not associated with lowered school performance. Conversely, school performance was better in children who were absent more because of non-malarial illness. Children who were absent more frequently because of other diseases were least frequently absent because of malaria (Table 4), which suggests that risk factors for malaria and those for other illnesses were different, and possibly, mutually exclusive. Thus, it was the experience of malaria *per se*, and not the associated absenteeism, that led to poorer school performance among children who received the placebo.

In high-transmission areas, Trape and others reported a daily absence rate due to malaria of 0.3%, which represented 5% of all causes of absence.[7,8] The number of school days lost was less than one day per child per year. In areas of low seasonal transmission, the average daily absence rate due to malaria was 0.2%, which represented less than 5% of all causes of absenteeism, and the number of school days lost was

TABLE 4
Mathematics and language scores of children by selected variables (at the end of the intervention trial)*

	Chloroquine						Placebo					
	Mathematics			Language			Mathematics			Language		
Variable	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD
Number of malaria attacks†												
0	200	63.18	17.30	200	59.33	18.65	140	57.29	17.67	140	53.74	19.04
1	66	54.34	18.70	66	44.73	14.67	66	45.32	18.48	66	42.11	16.12
2	29	33.26	17.47	29	25.52	17.91	86	27.87	16.82	86	23.70	10.90
F	40.56			54.49			74.37			121.37		
P	< 0.001			< 0.001			< 0.001			< 0.001		
Absenteeism due to malaria (days)												
0	220	63.57	17.39	220	58.42	18.95	152	56.88	18.10	152	53.39	18.79
1–12	30	62.68	15.36	30	49.36	13.14	22	56.10	12.17	22	54.49	16.55
13–29	30	33.48	10.58	30	33.18	9.22	62	36.61	16.87	62	30.58	7.02
≥ 30	15	29.58	12.56	15	15.16	4.94	56	22.49	12.89	56	12.47	5.73
F	46.29			44.97			68.75			119.71		
P	< 0.001			< 0.001			< 0.001			< 0.001		
Absenteeism due to non-malarial illnesses (days)												
0	8	55.69	21.29	8	35.63	15.93	16	35.08	18.02	16	24.03	16.01
1–12	101	54.43	20.74	101	47.02	18.86	97	43.52	21.79	97	38.83	22.15
13–29	159	60.59	18.94	159	55.93	20.64	153	49.41	20.23	153	43.53	21.78
≥ 30	27	64.30	19.46	27	60.37	22.46	26	41.10	27.02	26	42.35	24.05
F		2.86			7.28			3.59			4.24	
P		0.037			< 0.001				0.014		0.006	
Absenteeism due to non-health causes (days)												
0	4	44.38	30.62	4	30.13	26.90	6	16.42	10.22	6	17.17	10.93
1–12	153	58.18	20.44	153	52.09	20.81	148	49.52	21.13	148	42.67	23.16
13–29	135	59.85	18.62	135	54.11	19.98	135	43.49	21.19	135	39.85	21.14
≥ 30	3	51.50	32.04	3	54.00	36.72	3	37.00	25.72	3	38.00	11.95
F		1.01		1.85				6.15			2.76	
P		0.389		0.139				< 0.001			0.042	
Chloroquine tablets taken												
≥ 22	227	63.26	18.14	227	57.98	18.52		NA			NA	
14–21	35	51.55	16.92	35	42.85	14.91		NA			NA	
1–13	33	34.79	14.24	33	27.15	17.82		NA			NA	
0		NA			NA		292	45.92	21.60	292	40.79	22.21
F		15.36			18.27							
P		< 0.001			< 0.001							

* NA = not applicable.
† Number of malaria attacks experienced by the children during the period of intervention.

0.2–1 day per child per year. In this study, absenteeism due to malaria before prophylaxis was 5–7% of the school days. In children receiving prophylaxis, the percentage of days absent due to malaria remained the same for the chloroquine group but increased in the placebo group because of the greater number of malarial attacks during this period. Children are usually absent from school for 5.4 days after an attack of malaria, as has been reported elsewhere.[15]

During the intervention, total absenteeism was increased compared with the pre-intervention period. Absenteeism due to malaria increased in the placebo group because there was an epidemic of malaria during the period of intervention, which led to a greater number of attacks in this group and resulted in a greater number of days absent from school. The number of days absent because of health causes other than malaria and non-health causes was also higher during the intervention. This could have been because of changes in the weather patterns and children staying away from school for greater periods because of a severe drought during the intervention.

Chloroquine prophylaxis had a significant impact on both the number of malaria infections and malaria-related school absenteeism among the children, a finding that is consistent with the low incidence of chloroquine-resistant malaria (20–30%) reported in this area.[19,20] In Sri Lanka, *P. vivax* accounts for 70–80% of all malarial infections for which the treatment of choice is chloroquine as recommended by the National Malaria Control Program. The guidelines recommend that all malarial infections, irrespective of the species, be treated with a three-day course of chloroquine and a second-line drug used only if the infection is severe or there is

TABLE 5
Malaria attacks and absenteeism in children in relation to the number of chloroquine tablets taken

Chloroquine tablets taken (n)	No. (%) of children with malaria attacks	Mean (SD) no. of days absent due to		
		Malaria	Non-malarial illness	Non-health causes
> 22 (n = 227)	52 (22.9)	1.53 (6.21)	17.66 (9.46)	12.81 (6.53)
14–21 (n = 35)	31 (88.5)	10.57 (6.70)	12.94 (8.93)	10.00 (6.65)
1–13 (n = 33)	54 (163.6)	20.96 (13.85)	12.75 (8.32)	11.18 (8.57)
0* (n = 292)	238 (81.5)	12.42 (15.18)	15.64 (9.96)	11.73 (7.01)
F		108.06	7.025	3.089
P		< 0.001	0.001	0.047

* Placebo group.

TABLE 6

Analysis of variance using mathematics and language scores of school examinations as the dependent variable*

Independent variable	Mathematics score β	Mathematics score *P*	Language scores β	Language scores *P*
Intercept	16.264		24.154	
Drug†	5.413	0.001	4.167	0.008
Absenteeism due to malaria‡		< 0.001		< 0.001
0	33.191	< 0.001	33.720	< 0.001
1–12	33.721	< 0.001	37.235	< 0.001
13–29	10.399	0.003	16.682	< 0.001
Absenteeism due to non-malarial illnesses§		0.835		0.099
0	–2.146	0.668	–7.816	0.110
1–12	–1.772	0.534	–5.714	0.040
13–29	–0.354	0.896	–2.672	0.314
Absenteeism due to non-health causes¶		0.050		0.386
0	5.303	0.599	5.506	0.575
1–12	9.418	0.204	7.112	0.325
13–29	5.347	0.471	4.718	0.509
Number of malarial attacks#		0.624		0.022
0	2.506	0.585	10.999	0.014
1	–0.710	0.843	2.694	0.440
Weight for age**				
Normal	0.556	0.771	2.458	0.187
Height for age††				
Normal	5.647	0.006	–0.208	0.917
Weight for height‡‡				
Normal	–1.181	0.500	–3.339	0.051
Hemoglobin level§§	–0.277	0.700	–1.210	0.085

* β-regression coefficient.
† Reference group is the placebo group.
‡ Reference group is absenteeism more than 29 days.
§ Reference group is absenteeism more than 29 days.
¶ Reference group is absenteeism more than 29 days.
# Reference group is more than 1 attack.
** Reference group is underweight children.
†† Reference group is stunted children.
‡‡ Reference group is underweight children.
§§ Reference group is hemoglobin < 12 g/dL.

microscopic evidence of asexual parasitemia within 28 days of treatment with chloroquine. Although one-third of the children who were receiving chloroquine prophylaxis developed malaria, it was probably not because of chloroquine being the prophylactic agent but the result of other considerations such as relapses in *P. vivax* malaria and compliance.

Taking chloroquine prophylaxis was an even more powerful predictor of examination scores than the number of malarial infections that were experienced, which suggests that the effect of chloroquine taken as a prophylactic may have, in addition, to reducing the incidence of malaria, alleviated the impact of breakthrough infections.

The potential effects of malaria on cognitive development, performance, and motivation can be divided into two groups: the debilitating effects resulting from brain injury due to an acute episode of severe and complicated malaria; and the potential impact of performance mediated through the effects of chronic infection, repeated illness, anemia, and undernutrition.[6] In malaria-endemic countries in Africa, evidence suggests that brain injury as a consequence of cerebral malaria in early childhood may have an effect on child's cognitive and learning ability. Residual neurologic sequelae have shown to hinder the developmental progress of 1–5% of children infected early in life.[25]

Repeated attacks of malaria appear to affect physical growth of children as shown by an improvement in weight-for-age of female children, and higher hemoglobin levels in both sexes in the chloroquine group compared with the placebo group. Height-for age, an indicator of long-term nutritional status, was a significant predictor of mathematics scores. Retardation of physical growth and impairment of school performance may be parallel consequences of malaria or they may be causally related to each other.

In this study, the impairment of educational attainment was demonstrated in children with uncomplicated infections that occur frequently and repeatedly, and are generally forgotten after the event. Each infection lasted no longer than 3–5 days before they were effectively treated. In contrast, the more rare severe forms may leave residual neurologic effects.

The findings of this study have significant implications for policy makers and health care providers in particular and human development planners in general. In the light of these findings, it may be necessary to review and reassess the burden of malaria.

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REFERENCES

1. Clark SE, Brooker S, Njagi JK, Njau E, Estambale B, Muchiri E, Magnussein P, 2004. Malaria morbidity amongst school children living in two areas of contrasting transmission in western Kenya. *Am J Trop Med Hyg 71:* 732–738.
2. Luxemburger C, Perera WA, Delmas G, Pruja C, Pecoul B, Moren A, 1994. Permethrin-impregnated bed nets for prevention of malaria in schoolchildren on the Thai-Burmese Border. *Trans R Soc Trop Med Hyg 88:* 155–159.
3. Snow RW, 1997. Relationship between severe malaria in children and level of *Plasmodium falciparum* in Africa. *Lancet 349:* 1650–1654.
4. Brooker S, Guyatt H, Omumbo J, Shretta R, Drake L, Ouma J, 2000. Situation analysis of malaria in school-aged children in Kenya-what can be done? *Parasitol Today 16:* 183–186.
5. Bundy DAP, Lwin S, Osika JS, McLaughlin J, Pannenborg CO, 2000. What should schools do about malaria? *Parasitol Today 16:* 181–182.
6. Holding PA, Snow RW, 2001. Impact of *Plasmodium falc*iparum

malaria on performance and learning: review of evidence. *Am J Trop Med Hyg 64:* 68–75.
7. Trape JF, Zoulani A, Quinet MC, 1987. Assessment of incidence and prevalence of clinical malaria in semi-immune children exposed to intense and perennial transmission. *Am J Epidemiol 126:* 193–201.
8. Trape JE, Lefebvre-Zante E, Legros F, Druilhe P, Rogier C, Bourganali H, Salem G, 1993. Malaria morbidity among children exposed to low seasonal transmission in Dakar, Senegal and its implications for malaria control in tropical Africa. *Am J Trop Med Hyg 48:* 748–756.
9. United Nations Educational, Scientific and Cultural Organization, 2002. *Focusing Resources on Effective School Health*. Available from http://portal.unesco.org/education/en/ev.php-url_id=24006&url_do=do_topic&url_section=201.html
10. Colbourne M, 1955. The effect of malaria suppression in a group of Accra schoolchildren. *Trans R Soc Trop Med Hyg 49:* 356–369.
11. Boivin M, Giordani B, Ndanga K, Maky M, Menzeki M, Ngunu N, Muamba K, 1993. Effects of treatment for intestinal parasites and malaria on cognitive abilities of schoolchildren in Zaire, Africa. *Health Psychol 12:* 220–226.
12. Al Serouri AW, Grantham-McGregor SM, Greenwood B, Costello A, 2000. Impact of asymptomatic malaria parasitaemia on cognitive function and school achievement of school children in the Yemen Republic. *Parasitology 121:* 3337–3345.
13. Fernando D, Wickremasinghe R, Mendis KN, Wickremasinghe AR, 2003. Cognitive performance at school entry of children living in malaria endemic areas of Sri Lanka. *Trans R Soc Trop Med Hyg 97:* 161–165.
14. Fernando SD, Gunawardena DM, Bandara MR, de Silva D, Mendis KN, 2003. The impact of repeated malaria attacks on school performance of children. *Am J Trop Med Hyg 69:* 582–588.
15. Fernando D, de Silva D, Wickremasinghe R, 2003. Short-term impact of an acute attack of malaria on the cognitive performance of schoolchildren living in a malaria-endemic area of Sri Lanka. *Trans R Soc Trop Med Hyg 97:* 633–639.
16. Boivin M, 2002. Effects of early cerebral malaria on cognitive ability in Senegalese children. *J Dev Behav Pediatr 23:* 1–12.
17. Muntendam AH, Jaffar S, Bleichrodt N, van Hensbroek MB, 1996. Absence of neuropsychological sequelae following cerebral malaria in Gambian children. *Trans R Soc Trop Med Hyg 90:* 391–394.
18. Holding PA, Stevenson J, Peshu N, Marsh K, 1999. Cognitive sequelae of severe malaria with impaired consciousness. *Trans R Soc Trop Med Hyg 93:* 529–534.
19. Mendis KN, Carter R, 1995. Clinical disease and pathogenesis in malaria. *Parasit Today 11 (Suppl):* 1–6.
20. Handunnetti SM, Gunawardena DM, Pathirana PPSL, Ekanayake K, Weerasinghe CS, Mendis KN, 1996. Features of recrudescent chloroquine resistant *Plasmodium falciparum* infections confer a survival advantage on parasites, and have implications for disease control. *Trans R Soc Trop Med Hyg 90:* 563–567.
21. Fleck SL, Moody AH, 1993. *Diagnostic Techniques in Medical Parasitology*. 11th Edition. London: Butterworth-Heinemann.
22. Gamage-Mendis AC, Carter R, Mendis C, De Zoysa APK, Herath PRJ, Mendis KN, 1991. Malaria infections are clustered within an endemic population: risk of malaria associated with house construction type. *Am J Trop Med Hyg 45:* 77–85.
23. Gunawardena DM, Wickremasinghe AR, Muthuwatta L, Weerasingha S, Rajakaruna J, Senanayaka T, Kotta PK, Attanayake N, Carter R, Mendis KN, 1998. Malaria risk factors in an endemic region, and the impact and cost implications of risk factor-based interventions. *Am J Trop Med Hyg 58:* 533–542.
24. Fernando SD, Paranavitane SR, Rajakaruna J, Weerasinghe S, de Silva D, Wickremasinghe AR, 2000. The health and nutritional status of school children in two rural communities in Sri Lanka. *Trop Med Int Health 5:* 450–452.
25. Snow RW, Craig M, Deichmann U, Marsh K, 1999. Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. *Bull World Health Organ 77:* 624–640.